EXHIBIT 66

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Environmental Chemicals and Autism: A Scoping Review of the Human and Animal Research

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Background: Estimates of autism prevalence have increased dramatically over the past two decades. Evidence suggests environmental factors may contribute to the etiology of the disorder.

Objectives: This scoping review aimed to identify and categorize primary research and reviews on the association between prenatal and early postnatal exposure to environmental chemicals and the development of autism in epidemiological studies and rodent models of autism.

Methods: PubMed was searched through 8 February 2018. Included studies assessed exposure to environmental chemicals prior to 2 months of age in humans or 14 d in rodents. Rodent studies were considered relevant if they included at least one measurement of reciprocal social communicative behavior or repetitive and stereotyped behavior. Study details are presented in interactive displays using Tableau Public.

Results: The search returned 21,603 unique studies, of which 54 epidemiological studies, 46 experimental rodent studies, and 50 reviews were deemed relevant, covering 152 chemical exposures. The most frequently studied exposures in humans were particulate matter ($n = 14$), mercury ($n = 14$), nonspecific air pollution ($n = 10$), and lead ($n = 10$). In rodent studies, the most frequently studied exposures were chlorpyrifos ($n = 9$), mercury ($n = 6$), and lead ($n = 4$).

Discussion: Although research is growing rapidly, wide variability exists in study design and conduct, exposures investigated, and outcomes assessed. Conclusions focus on recommendations to guide development of best practices in epidemiology and toxicology, including greater harmonization across these fields of research to more quickly and efficiently identify chemicals of concern. In particular, we recommend chlorpyrifos, lead, and polychlorinated biphenyls (PCBs) be systematically reviewed in order to assess their relationship with the development of autism. There is a pressing need to move forward quickly and efficiently to understand environmental influences on autism in order to answer current regulatory questions and inform treatment and prevention efforts. https://doi.org/10.1289/EHP4386

Introduction

Autism and autism spectrum disorder comprise a broad array of conditions that impact an individual's social communication and behavior. The Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association 2013) has three main diagnostic criteria for autism: *a*) persistent deficits in social communication and social interaction across multiple contexts; *b*) restricted, repetitive patterns of behavior, interests, or activities; and *c*) the presence of symptoms in the early developmental period, although they may not become apparent until social demands exceed the individual's capacities (American Psychiatric Association 2013). Individuals with autism may express or experience these to varying degrees, resulting in a wide range of abilities from extremely gifted to severely challenged (American Psychiatric Association 2013; Centers for Disease Control and Prevention 2017a). Autism can have profound impacts on families and individuals, and also has widespread social and economic effects. In the United States, costs associated with autism are estimated at $11.5–60.9 billion annually due primarily to medical care, special education, and lost parental productivity (Buescher et al. 2014; Lavelle et al. 2014).

The prevalence of autism has increased from 1 in 150 in 2002 to 1 in 59 in 2014 (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2002 Principal Investigators 2007; Baio et al. 2018; Centers for Disease Control and Prevention 2017b). Although genetics are an important risk factor, they would not account for the dramatic rise in prevalence during this span in time, nor do changes in diagnostic criteria (Hertz-Picciotto and Delwiche 2009; Hertz-Picciotto et al. 2018b; King and Bearman 2009). Growing evidence suggests environmental factors and gene–environment interactions contribute to the etiology of the disorder (Frazier et al. 2014; Hallmayer et al. 2011). Some autism-related genes may be targeted by environmental pollutants, including pesticides, heavy metals, bisphenol A (BPA), phthalates, and many other chemicals in food, cosmetics, or household products (Carter and Blizard 2016). Further, evidence suggests that autism diagnosis is associated with variants in genes involved in the elimination of toxic chemicals from the body, which potentially results in a higher body burden of toxic chemicals (Rossignol et al. 2014). Investigating the contribution of environmental chemicals to autism offers an opportunity for intervention by reducing such exposures.

The early developmental period, and specifically the prenatal period, is a sensitive time when the developing brain is particularly susceptible to disruptions from environmental chemicals. This is supported by recent evidence indicating that subtle signs of autism can be detected as early as 9 months (Christensen et al. 2016a). Furthermore, autism disproportionately impacts males relative to females with a rate of diagnosis 3 to 4.5 times higher in males (Christensen et al. 2016b; Zablotsky et al. 2017), suggesting the developing endocrine system may be etiologically important (Baron-Cohen 2002). This is supported by studies comparing the length of the index finger to the ring finger, which is an established marker of fetal testosterone concentrations. Such studies have found that a decreased second digit-to-fourth digit ratio, indicating increased fetal testosterone exposure, is associated with an autism spectrum disorder diagnosis (Teatero and Netley 2013). The role and potential mechanisms of environmental endocrine disruptors in the etiology of autism has been discussed in earlier reviews (Moosa et al. 2018; Schwartzer et al. 2013).

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Animal models can support the epidemiological evidence reporting associations between environmental chemical exposures and autism. Animal models, for example, allow for the investigation of the complex neurobiological events that occur during early development that may be etiologically important for autism. In addition, due to animals' shorter lifespans, studies conducted in animal models may allow for more rapid assessment of a wide variety of environmental chemicals. Ideally, animal models accurately mimic the observed clinical phenotype, can be induced by the same biological or genetic mechanisms known to contribute to the etiology of autism in children, and have a similar response to treatments that prevent or treat autism in children (Crawley 2012). To the first point, significant progress has been made to outline specific rodent behavioral tests that address the two core behavioral features of a DSM diagnosis in children: persistent deficits in reciprocal social communication and restricted, repetitive patterns of behavior, interests, or activities (American Psychiatric Association 2013; Bey and Jiang 2014; Chang et al. 2017; Crawley 2012). The mouse and rat have been the best described and most utilized animal species to model autism to date. Recognizing the important contribution that animal models have, this scoping review considers the evidence that environmental chemical exposures are associated with autism in rodents alongside that in humans, which, to our knowledge, has not been done in previous reviews on the topic (e.g., Ng et al. 2017; Rossignol et al. 2014).

As a scoping review, the goal was to identify and categorize the peer-reviewed literature on the association between prenatal and early postnatal exposure to environmental chemicals and the development of autism in epidemiological studies and rodent models of autism. It was not the goal to draw conclusions about specific chemicals and their hazards. Specifically, we aimed to identify environmental chemical exposures during early life stages that could be further explored via systematic review. We also made recommendations to address research gaps, guide best practices, and prioritize future research.

Methods

A protocol for conducting this scoping review was prepared *a priori* but was not made publicly available, as there was no known venue for publication of protocols for scoping reviews at the time. A literature search strategy was crafted for PubMed and executed on 2 November 2016. Search strings were developed to address relevant populations, comparisons, and outcomes [three of the four components of a PECO (populations, exposures, comparators, outcomes) statement] (Table 1). The complete search logic is available in Excel Table S1. A combination of medical subject headings and free text words were used for the following concepts: autism spectrum disorder, prenatal or developmental life stages, human or rodent. There were no restrictions on exposures, language, or publication date. A search update was performed in PubMed on 8 February 2018 using the same search logic. During data extraction, reference lists of included studies were also hand screened to identify any additional studies that were not retrieved by the literature search.

Results of the PubMed search were uploaded to Sciome Workbench for Interactive computer-Facilitated Text-mining (SWIFT, Beta Test version) Active Screener (Sciome), a text mining and machine learning program. In this program, users are first presented with random studies to screen, and the program adaptively learns from the choices made by the users. Thus, as screening progresses, the remaining unreviewed studies are automatically prioritized, and the most relevant studies are presented for screening first, with the purpose of allowing screening to be stopped at a predefined estimated recovery rate for relevant studies.

Table 1. PECO statement.

PECO element	Evidence
Population	Human populations or rodent models of autism spectrum disorder.
Exposure	Exposure occurring during prenatal or early life period. Exposure should begin prior to 2 months of age for humans and postnatal day 14 for rats and mice. Exposure can be either gestational (i.e., via maternal exposure) or directly to the offspring. Only environmental chemical exposures are included (e.g., air pollution, pesticides, flame retardants, heavy metals, etc.).
Comparators	Comparison group with lower exposure or no exposure.
Outcome	Autism spectrum disorder or indicators of autism spectrum disorder. Rodent studies need to report at least one reciprocal social communicative behavior or one repetitive and stereotyped behavior.

Note: PECO, populations, exposures, comparators, outcome.

Title and abstract screening was performed in SWIFT Active Screener by two reviewers (K.E.P. and A.L.B) until an estimated recall of 90% was achieved (i.e., the text mining and machine learning algorithms of SWIFT Active Screener estimated that at least 90% of the relevant studies were identified). The decision to cease screening upon reaching an estimated recall of 90% was determined *a priori* based on methods recommended by the U.S. National Toxicology Program as appropriate for scoping reviews (A.A. Rooney, personal communication). Further, we hand searched reference lists to capture important studies that might have been missed in the screening process. Discrepancies between reviewers were tracked within SWIFT Active Screener and resolved through discussion.

The title and abstract screening of potentially relevant primary studies and reviews performed in SWIFT Active Screener was very broad. For the initial screening, reviewers asked, "Does this reference discuss prenatal or very early life exposures and autism spectrum disorder in humans or rodent models?" There were no limitations on the types of exposure in this level. When it was unclear if a study met the inclusion criteria based on review of the title and abstract, it was moved forward to the next screening stage and later confirmed during full-text review.

Studies included after title and abstract screening in SWIFT Active Screener were then uploaded to DistillerSR (Evidence Partners) for initial tagging by publication type (primary research or review), evidence stream (epidemiological study or experimental rodent study), and type of exposure (air pollution, alcohol, assisted reproduction, drugs of abuse, endogenous hormones, environmental chemicals, folic acid, heavy metals, infant feeding, medication/pharmaceutical, minerals/trace elements, research compounds, smoking, vaccines/immunoglobulins, valproic acid, vitamin D, other/not sure).

Studies tagged as air pollution, environmental chemicals, metals, and those where it was unclear what the exposure was from the title and abstract screening (tagged as "other/not sure") were reviewed at the full-text level. Full-text review of studies was carried out in DistillerSR. Studies had to be available in English language to be included at the stage of full-text review. For both epidemiological and experimental rodent studies to be included, there had to be exposure to environmental chemicals at an early developmental age. As this is a scoping review intended to cast a wide net, exposures that could possibly be proxy measurements of environmental chemical exposures were also included. Given that significant neurodevelopment occurs postnatally in rodents, exposure had to occur on or before postnatal day (PND) 14 to be included in this scoping review. This is a time approximately equivalent to 2 months of age in humans based on various

neurodevelopmental events (Clancy et al. 2007; Workman et al. 2013). Thus, epidemiological studies had to assess environmental exposures at or before 2 months of age to be included in this scoping review. All epidemiological studies that reported an outcome of autism diagnosis, regardless of how a diagnosis was defined, were included. Rodent studies had to report at least one reciprocal social communicative behavior or one repetitive and stereotyped behavior to be included. Table 2 provides specific examples of rodent outcomes and how they were categorized for analysis. The outcomes and their classification as reciprocal social communicative behaviors or repetitive and stereotyped behaviors are based on those recommended in Bey and Jiang (2014); Chang et al. (2017); Crawley (2012), and are meant to reflect the diagnostic requirements in humans as outlined in the DSM-5 (American Psychiatric Association 2013). Reviews were included if they addressed developmental exposure to environmental chemicals and autism in humans, or autism-related behaviors in rodents.

Data extraction from full-text documents was carried out in DistillerSR. Bibliographic citation information was recorded for all included studies. The following information was recorded for epidemiological studies: study type, name of study if provided, geographic location, overall sample size, sex of included participants, how autism was diagnosed, the age range of diagnosis, the year of birth, what the exposure was, if it was an occupational or a general population exposure, how the exposure was measured, and age when exposure was assessed. Initially, the specific exposures that were assessed in each study were extracted and listed. Upon the completion of data extraction, it became necessary to broadly classify the long list of exposures that had been captured. It should be noted that some chemicals may be classified in more than one broad category. For example, all studies on mercury, regardless of its source, are found in the broad category "metals & semi-metals," but only those studies where it was investigated as an air pollutant are also found in the broad category "air pollutants." Likewise, it became necessary to broadly categorize how autism was diagnosed. After consultation with experts in the field, we broadly categorized studies as: using specific diagnostic tools, using specific screening tools, and/or stating that children met either the DSM or International Statistical Classification of Diseases and Related Health Problems (ICD) criteria. It should be noted that diagnostic tools and screening tools are used by practitioners to reach a DSM or ICD diagnosis, but stating that a DSM or ICD diagnosis was given does not indicate which specific diagnostic or screening tools were used to reach that conclusion. Further, not all diagnostic and screening tools may be comparable (Randall et al. 2018).

The following information was recorded for rodent studies: the strain and species, the environmental exposure, age of exposure (categorized as gestational, postnatal, or both, which is referred to as "developmental"), route of exposure, whether or not the outcome occurred spontaneously or was induced (for example, by apomorphine or amphetamine), the timing of outcome assessment [categorized as neonatal (0–14 d), juvenile (15–40 d), adult (41+ d)], and the outcome. Comorbidities and mechanistic outcomes were also recorded if noted within the included studies (Table 2). During full-text review, the included reviews were characterized as narrative, systematic, scoping, or meta-analytic reviews, as per how the authors identified the publications. Data on the evidence stream (epidemiological or experimental rodent) and exposures studied were also extracted. All extracted information was exported from DistillerSR to Microsoft Excel and was subsequently visualized using Tableau Desktop Professional Edition (version 2018.3.1; Tableau, https://public.tableau.com/profile/the.endocrine.disruption.exchange#!/).

Results

The PubMed search retrieved 18,242 studies (Figure 1). After duplicate removal, 18,218 studies were uploaded to SWIFT Active Screener for title and abstract screening. The literature update retrieved an additional 3,359 studies, 11 of which were duplicates from the original search. The studies retrieved from the update were processed identically to the initial search. An estimated recall of 90% was achieved when 4,000 studies had been screened in SWIFT Active Screener. Likewise, estimated recall of 90% was achieved when 808 studies of the search update had been screened. Hand searching the bibliographies of included references resulted in an additional 37 studies to screen. In total, 1,127 studies were considered relevant after title and abstract screening and moved to DistillerSR for further categorization. Full text was reviewed for the 316 studies that were tagged as including an exposure to an environmental chemical, air pollutants, or metals, and that appeared relevant based on the title and abstract. Reasons for exclusion during full-text review are provided in Excel Table S2.

After full-text review, 150 studies were included: 54 epidemiological studies, 46 rodent studies, and 50 reviews (Figure 1). It should be noted that the direction of association (positive, negative, or not associated) of any particular exposure with autism was not captured in this scoping review. Overall, the rate of publication has been steadily increasing in the last 10 y, with a dramatic increase in epidemiological studies after 2012 (Figure 2). The number of reviews in 2016 ($n = 16$) equaled the number from the prior 5 y combined.

Extracted data from epidemiological and rodent studies is available in an interactive format in Figures S1 and S2 (see Supplemental Materials for more information on accessing and navigating the supplemental figures). In these interactive figures, the data can be filtered by environmental exposure and/or outcome. The epidemiological data can be additionally filtered by study type, and the rodent data can be additionally filtered by the timing of exposure or outcome assessment. Extracted data can also be viewed in Excel Table S3 (epidemiological data), Excel Table S4 (experimental rodent data), and Excel Table S5 (reviews). Results for epidemiological studies, experimental rodent studies, and reviews are presented and discussed below.

Epidemiological Studies

Fifty-four epidemiological studies were identified (Figure 3, Excel Table S3). Fifty studies investigated general population

Table 2. Experimental rodent outcomes.

Animal outcome categories	Specific examples of rodent outcomes
Reciprocal social communicative behaviors[a]	Three-chambered test, open field test with social component, play behaviors measurements, ultrasonic vocalizations, nest seeking response, social choice, social discrimination, other measurements of social behaviors other than aggression
Repetitive and stereotyped behaviors[a]	Classic stereotyped behaviors such as gnawing, circling, or rearing; repetitive behaviors measured by maze apparatus such as T, Y, or Morris water mazes; other stereotypical behavioral measurements
Comorbidities	Anxiety measurements such as elevated plus maze, light dark box, prepulse inhibition, elevated food test, or zero maze; other comorbid behaviors
Mechanistic outcomes	Neuropathology, neuropsychological functioning, neurochemical alterations

[a]Inclusion criteria.

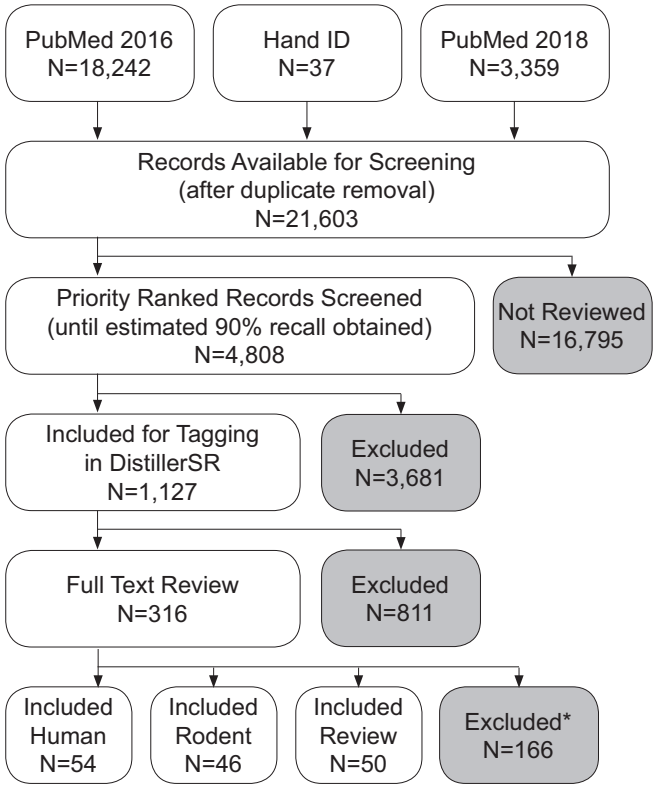


Figure 1. Flowchart of studies through the review process. This describes the number of studies evaluated at each step of the review process. "Hand ID" are the studies identified by scanning reference lists of included studies. Priority-ranked studies were screened at the title and abstract level in Sciome Workbench for Interactive computer-Facilitated Text-mining (SWIFT) Active Screener. Studies were excluded if they did not pertain to prenatal or very early life exposures and autism in humans or rodent models. At the full-text level, studies were excluded if there was not exposure to environmental chemicals prior to 2 months of age in humans or 14 d in rodents. *Note: Reasons for exclusion at the full-text level can be found in Excel Table S2.

exposures, and five investigated occupational exposures. Most studies used a case–control study design ($n = 39$), including 20 population-based studies and 10 nested studies. Cohort ($n = 7$), prospective cohort ($n = 7$), and ecological ($n = 1$) study designs were also used (Figure 4). Eleven of the epidemiological studies were from the Childhood Autism Risks from Genetics and Environment (CHARGE) project, a large population-based case–control study in California (Excel Table S3). The majority of the studies from CHARGE investigated the role of air pollutants ($n = 7$), but pesticides ($n = 3$), metals ($n = 2$), and occupational exposures ($n = 1$) have also been studied in this project.

The included studies represent children born from 1967 to 2010. Studies were conducted in 15 countries, but most were located within the United States (Figure 4), with 23 studies (43% of all epidemiological studies) conducted in California (Excel Table S3). Findings from these studies may or may not be generalizable to the general population, given the variability in

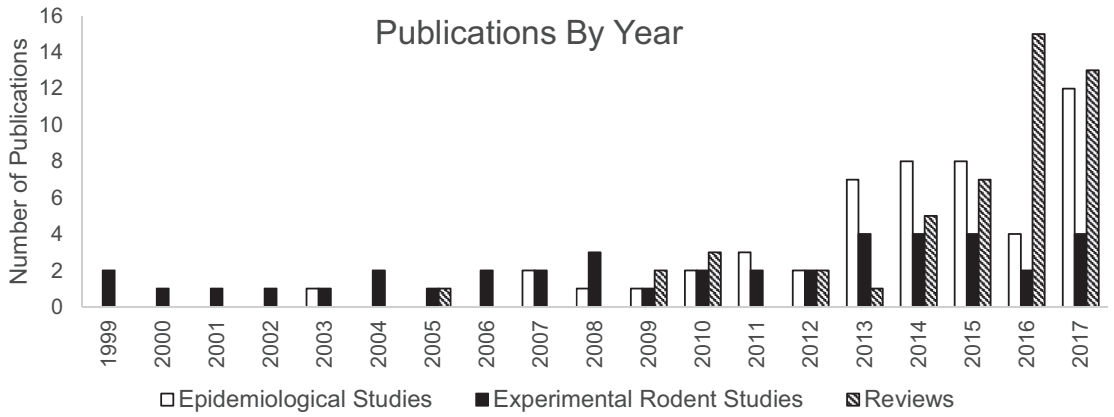


Figure 2. Number of studies published by year and type (1999–2017). The number of studies in each evidence stream are shown by year of publication. Note: Five experimental rodent studies published before 1999 are not shown in this figure. One paper was published in each of the following years: 1974, 1979, 1984, 1985, and 1995.

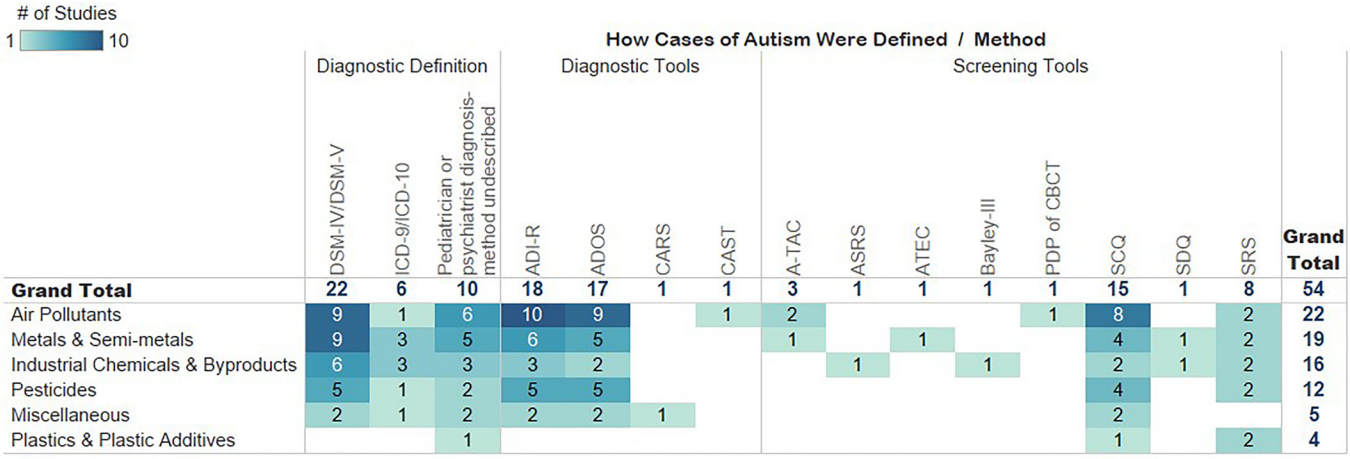


Figure 3. Heat map of included epidemiological studies by exposure (in rows) and how autism was determined within the study (in columns). Numbers within cells indicate the number of studies for a given exposure and method of autism determination. Empty cells indicate a lack of studies. An interactive version of this figure is available at https://public.tableau.com/profile/the.endocrine.disruption.exchange#!/vizhome/Fig3_Enviornmentalchemicalsandautism-epidemiologicaldata/Interactive. For clarity, the different methods of autism determination were collapsed into the following broad categories: used specific diagnostic tools, used specific screening tools, and/or stated that children met either the DSM or ICD criteria. It should be noted that diagnostic tools and screening tools are used by practitioners to reach a DSM or ICD diagnosis, but stating that a DSM or ICD diagnosis was given does not indicate which specific tools were used to reach that conclusion. The 142 specific exposures assessed in the included studies were also collapsed into six broad categories for improved clarity. The categories for types of exposures can be fully expanded in the interactive version of the figure. Additional study information can be found in the interactive Figure S1 and in Excel Table S3. Note: A-TAC: autism tics, ADHD, and other comorbidities inventory; ADIR-R, Autism Diagnostic Interview–Revised; ADOS, Autism Diagnostic Observation Schedules; ASRS, Autism Spectrum Rating Scales; ATEC, Autism Treatment Evaluation Checklist; CARS, Childhood Autism Rating Scale; CAST, Childhood Autism Spectrum Test; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Statistical Classification of Diseases and Related Health Problems; PDP of CBCT, Pervasive Developmental Problems subscale of the Child Behavior Checklist for Toddlers; SCQ, Social Communication Questionnaire; SDQ, Strengths and Difficulties Questionnaire; SRS, Social Responsiveness Scale.

exposure to environmental chemicals across different geographical locations and during different time periods.

One hundred forty-two chemical exposures were catalogued and organized into six broader exposure categories (Figure 3, Figure S1, Excel Table S3). In some studies, exposures were described only in general terms (e.g., metals, pesticides, air pollutants). In others, specific chemicals or chemical groups were investigated [e.g., BPA, chlorpyrifos, polychlorinated biphenyls (PCBs)]. In some studies, both the general exposures and the individual chemicals were analyzed. On average, each paper explored six exposures (median = 4).

The broad category of air pollutants has been the most studied to date ($n = 22$ studies; Figure S1). Air pollutant studies ranged from general "air pollution" to one or more individual chemicals, spanning 56 chemicals across all air pollutant studies. Of these, 11 were metals or semimetals studied as air pollutants. The next-largest broad category of exposure studied was metals and semimetals with $n = 19$ studies spanning 18 specific exposures. Industrial chemicals and by-products followed with $n = 16$ studies spanning 20 specific exposures, and pesticides with $n = 12$ studies spanning 40 specific exposures. The 40 specific pesticide exposures included 27 individual pesticides and 12 pesticide classes (e.g., described by study authors as "pyrethroids"), as well as the general term "pesticides."

Specific exposures can be viewed by expanding the exposures display in the interactive Figure S1, and from there, the specific studies associated with each exposure can also be easily obtained. Note that as described in the "Methods" section, some specific exposures may appear in more than one broad category. For example, studies that evaluated lead or mercury are always displayed in the metals and semimetals broad category, and additionally appear in the air pollutants broad category when they were considered in the context of air pollution.

Under the broad category of air pollutants ($n = 22$), several specific air pollutants have been evaluated. The most studied were particulate matter ($n = 14$), nonspecific "air pollution" (mostly as near-roadway or traffic-related air pollution; $n = 10$), nitrogen dioxide ($n = 8$), ozone ($n = 6$), lead ($n = 6$), nitrogen oxides ($n = 5$), manganese ($n = 5$), and cadmium ($n = 5$). PCBs are the most studied industrial chemicals and by-products ($n = 8$), though per- and polyfluoroalkyl substances and polybrominated diphenyl ethers (PBDEs) have been evaluated in $n = 4$ studies each. Mercury ($n = 14$), lead ($n = 10$), manganese ($n = 8$), chromium ($n = 6$), cadmium ($n = 6$), nickel ($n = 5$), nonspecific "metals" ($n = 5$), and arsenic ($n = 5$) have been the most studied metals and semimetals to date. As noted, some of these metals have been studied in the context of air pollution as well as from other sources (for example, mercury from dental amalgams). With the exception of organophosphates ($n = 4$), dichlorodiphenyldichloroethylene ($n = 4$), pyrethroids ($n = 3$), chlorpyrifos ($n = 3$), and trans-nonachlor ($n = 3$), most pesticides have only been evaluated in one or two papers each. Of the plastics and plastic additives, BPA has been studied the most ($n = 4$), with the phthalates and phthalate metabolites each being studied only once or twice each. Of all the 142 specific exposures catalogued, only 22% ($n = 31$) have been investigated in at least one prospective study.

Environmental exposures were determined by a variety of measurements. Details on how and when exposure was assessed can be found in Excel Table S3 and by hovering over the study details in Figure S1. In some cases, there was direct measurement in a biological matrix (e.g., blood, breast milk, and urine); in other cases, the exposure was determined based on modeling data, taking into consideration maternal residence and factors such as local or regional air quality monitoring data, or known dates of pesticide application. The latter measurements are less sensitive and specific and rely upon several assumptions that could introduce artifacts capable of impacting the outcome of the study. There is also the possibility for lack of specificity in terms of exposure timing. Some of the exposure measurements may be considered proxies for prenatal

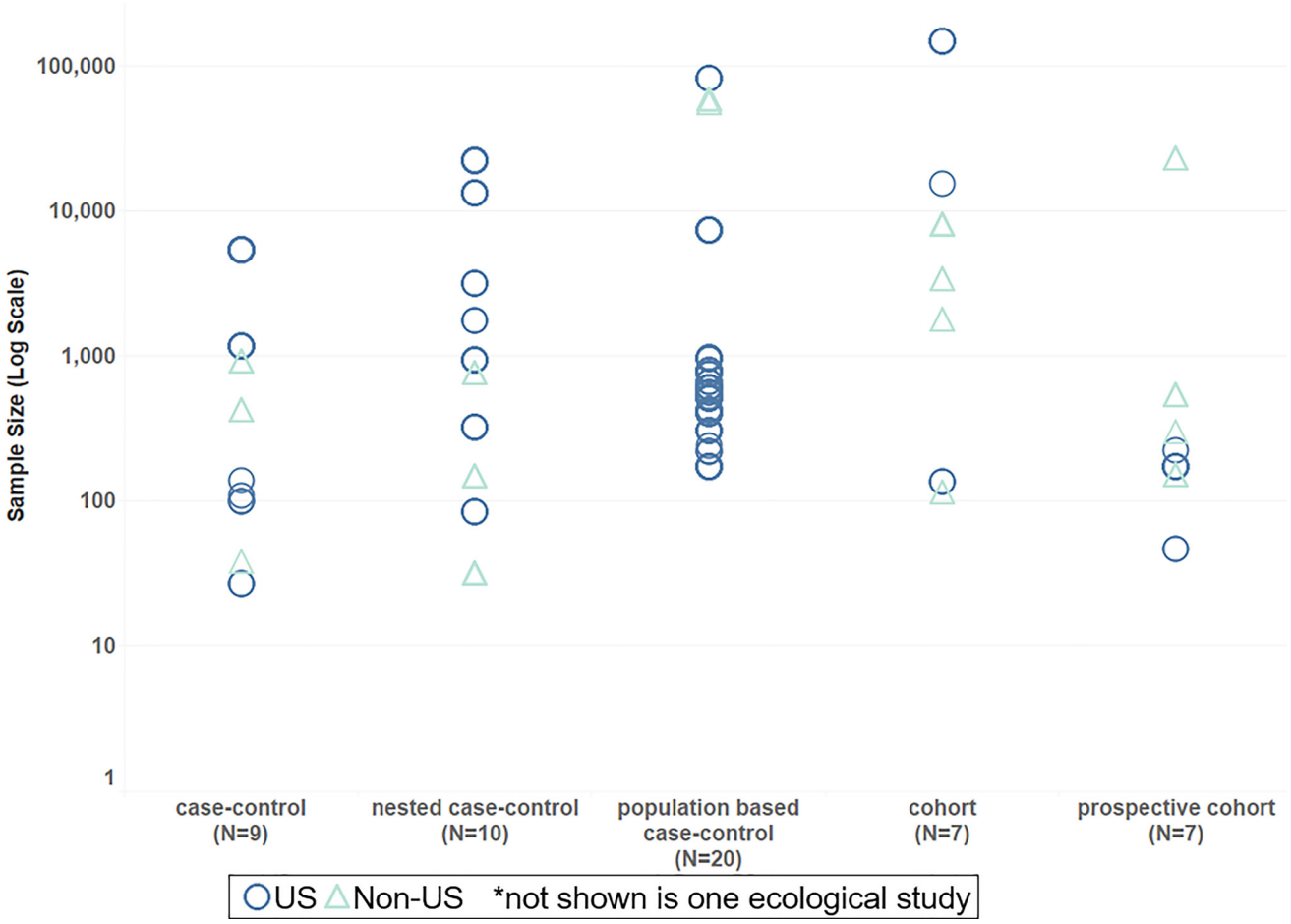
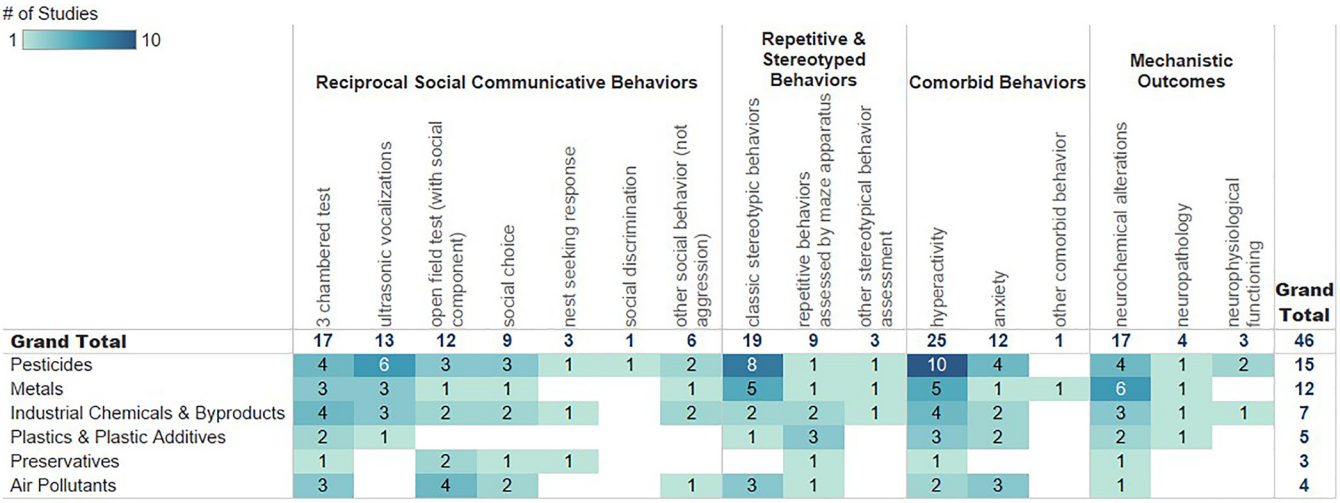


Figure 4. Sample size by epidemiological study type. Epidemiological studies are displayed in the scatterplot based on their study design on the *x*-axis (case–control, nested case–control, population-based case–control, cohort, or prospective cohort) and on the number of study participants on the *y*-axis (log scale). Studies conducted in the United States are shown as blue circles. Studies conducted outside of the United States are shown as light-teal triangles.

exposure (e.g., hair from first baby haircut, baby teeth, and some of the modeling data), and it is not clear if these truly represent early developmental vs. infant or early childhood exposures.

Studies differed in how autism cases were diagnosed and/or defined (Figure 3; Figure S1). The DSM and the ICD criteria are the two most widely used manuals for defining autism. The DSM



	Reciprocal Social Communicative Behaviors							Repetitive & Stereotyped Behaviors			Comorbid Behaviors			Mechanistic Outcomes			
	3 chambered test	ultrasonic vocalizations	open field test (with social component)	social choice	nest seeking response	social discrimination	other social behavior (not aggression)	classic stereotypic behaviors	repetitive behaviors assessed by maze apparatus	other stereotypical behavior assessment	hyperactivity	anxiety	other comorbid behavior	neurochemical alterations	neuropathology	neurophysiological functioning	Grand Total
Grand Total	17	13	12	9	3	1	6	19	9	3	25	12	1	17	4	3	46
Pesticides	4	6	3	3	1	1	2	8	1	1	10	4		4	1	2	15
Metals	3	3	1	1			1	5	1	1	5	1	1	6	1		12
Industrial Chemicals & Byproducts	4	3	2	2	1		2	2	2	1	4	2		3	1	1	7
Plastics & Plastic Additives	2	1						1	3		3	2		2	1		5
Preservatives	1		2	1	1				1		1			1			3
Air Pollutants	3		4	2			1	3	1		2	3		1			4

Figure 5. Heat map of included rodent studies by exposure (in rows) and types of rodent outcomes (in columns). Numbers within cells indicate the number of studies for a given exposure and outcome. Empty cells indicate a lack of studies. An interactive version of this figure is available at https://public.tableau.com/profile/the.endocrine.disruption.exchange#!/vizhome/SupplementalFigure2_Environmentalchemicalsandautism-rodentdata/Interactive. For clarity, the different outcomes have been collapsed to the four types of outcomes that were captured in this report. Additional study information can be found in the interactive Figure S2 and in Excel Table S4.

was updated from DSM-IV(American Psychiatric Association 1994) to DSM-V (American Psychiatric Association 2013) in 2013, and the ICD was updated from ICD-9 (Centers for Disease Control and Prevention 2013) to ICD-10 (WHO 2016) in 2015, and both versions were used by the studies included in this review. Twenty-two studies reportedly used the DSM criteria, and six used the ICD criteria. The specific evaluative measures administered by trained professionals for reaching a diagnosis based on the DSM or ICD manuals are referred to as diagnostic tools. The specific diagnostic tools used were reported in 23 studies (Figure S1; Excel Table S3). In comparison, screening tools are quick methods to identify someone who may have autism and who should be referred for more in-depth diagnostic testing (Children's Hospital of Philadelphia 2016). Screening tools are also used in the research setting to confirm controls are properly classified. Screening tools were used in 26 studies (Figure S1, Excel Table S3), indicating that many studies either do not thoroughly screen controls to ensure they are classified appropriately, or do not report it.

Of the 39 case–control studies, nearly all stated that cases received a DSM-IV or DSM-V diagnosis ($n = 17$), an ICD-9 or ICD-10 diagnosis ($n = 5$), or a diagnosis from a psychiatrist or physician (with no criteria provided) ($n = 10$), but most did not specify which specific screening or diagnostic tools were used to reach the diagnosis. Further, many of the case–control studies relied on previous diagnosis of autism as obtained from medical/administrative records, as opposed to performing diagnosis on the individual children enrolled in the studies. The exception is that the 11 reports from the population based case–control CHARGE study reported only the specific screening (Social Communication Questionnaire) and diagnostic tests used [Autism Diagnostic Interview-Revised (ADI-R) and Autism Diagnostic Observation Schedule (ADOS)], without specifying that case children met the DSM or ICD criteria, though that is implied. In contrast, the cohort studies relied mainly on screening tools, with the Social Responsiveness Scale (SRS) used most frequently ($n = 6$). The three largest cohort studies, however, did not use a screening tool (Gong et al. 2017; Kalkbrenner et al. 2014; von Ehrenstein et al. 2014). Instead, DSM-IV cases were identified by examining records from records-based surveillance programs. Whether it is appropriate to include and/or combine data from studies using different diagnostic and screening tools for autism should be addressed in future reviews.

Half of the studies did not report the age of autism diagnosis. Of those that did ($n = 27$), the range of age at diagnosis across the studies was from 0.3 to 12 y of age. Studies in which children are diagnosed at younger ages may miss cases that, for various reasons, are not diagnosed until the children are older. On the other hand, studies that include children diagnosed at later, preteen ages may be susceptible to misdiagnosis with other phenotypically similar disorders such as attention deficit hyperactivity disorder (ADHD) (Bal et al. 2019; Grzadzinski et al. 2016; Hommer and Swedo 2015). In either case, the field would benefit from better reporting of the age of diagnosis.

Experimental Rodent Studies

Forty-six studies met the inclusion criteria for rodent studies [i.e., the study had to report assessment of at least one reciprocal social communicative behavior or repetitive and stereotyped behavior (Table 2), and exposure had to occur prior to PND 14]. It should be noted that it was not required that studies deem the behaviors to be altered in a way that suggests an autism-like phenotype; rather, we only required the behavior to have been studied. Exposures occurred either gestationally ($n = 16$), postnatally ($n = 8$), or developmentally (exposure occurring during both pregnancy and lactation; $n = 26$). In Figure S2, these different exposure periods are represented by different colors and can also be found by hovering over the study details. Two studies evaluated the impact of different exposure timing scenarios on the behavioral outcomes in order to more clearly define the critical period of exposure (Venerosi et al. 2006; Zaidi et al. 1985). Animals were exposed to the chemicals via inhalation, subcutaneously (by injection or implantation of osmotic minipump or silastic capsule), by intraperitoneal injection, or orally (via feed or diet, drinking water or gavage).

There were 25 unique exposures captured (Figure 5, Figure S2, Excel Table S4). Pesticides and metals were the most explored with chlorpyrifos ($n = 9$), mercury ($n = 6$), and lead ($n = 4$) being the specific chemicals most studied. PCBs and particulate matter were each investigated in three studies. The remaining exposures were studied in one ($n = 13$) or two ($n = 7$) studies each.

In humans, an autism diagnosis is based on the presence of persistent deficits in social communication and social interaction and restricted, repetitive patterns of behavior, interests, or activities (American Psychiatric Association 2013). Thirty-one rodent studies reported reciprocal social communicative behaviors, and 28 studies reported repetitive and stereotyped behaviors (Figure S2). A challenge in using animals to study autism is assessing the model's face validity, or in other words, determining if the behavioral features are at least conceptually analogous to core diagnostic symptoms in humans. To this end, 13 studies reported on both types of behaviors in the same study and therefore may have stronger face validity. Arsenic, butyl paraben, cadmium, chlorpyrifos, di(2-ethylhexyl) phthalate, lead, manganese, mercury, ozone, particulate matter, PBDEs, PCBs, and trihalomethanes and perchloroethylene mixture were the only exposures in which reciprocal social communicative behaviors and repetitive and stereotyped behaviors were reported in the same study. Of these, only chlorpyrifos and particulate matter were reported in more than one study with both types of behaviors. Assessing both types of behaviors within a study would better reflect human diagnostic criteria.

Tests for reciprocal social communicative behavior assess how a rodent interacts with and/or communicates with another individual in a social setting, and may represent the persistent deficits in social communication and social interaction diagnostic of autism in humans (Roullet and Crawley 2011). The most commonly reported tests for reciprocal social communicative behavior were the three-chambered test ($n = 17$), ultrasonic vocalizations ($n = 13$), and the open field with social component test ($n = 12$) (Figure S2, Excel Table S4). The three-chambered test and open field test with a social component specifically assess aspects of sociability (Bey and Jiang 2014). Assessment of ultrasonic vocalizations specifically assesses communication behavior. Ultrasonic vocalizations are often evaluated by removing a neonatal pup from the dam and littermates, but intentional communication may be evaluated in juvenile or adult animals (Bey and Jiang 2014; Roullet and Crawley 2011). Assessment of repetitive and stereotyped behaviors in rodents represents the restricted, repetitive patterns of behavior, interests, or activities that are diagnostic of autism in humans (Crawley 2012). Assessment of classic stereotyped and repetitive behaviors (e.g., gnawing, circling, rearing) was reported in 19 studies and was the most common assessment of repetitive and stereotyped behaviors. The dopamine agonist apomorphine or the stimulant amphetamine was used to induce repetitive behaviors in rodents in nine of the 19 stereotypy studies. Data suggests induced and spontaneous stereotypies may be mediated by different mechanisms, although there is, as of yet, no clear guidance as to which assessment is more directly applicable in rodent models of autism

(Lewis et al. 2007; Presti et al. 2002). It should be noted that the animal evidence may be underestimated in this scoping review because we did not include search terms for each specific behavioral test.

In Figure S2, the different outcome assessment periods are represented by different shapes and can also be found by hovering over the study details. The timing of the outcome assessment was largely dependent on the outcome being measured. Some outcomes, such as ultrasonic vocalizations, can be evaluated for both pups and adults, although they need to be interpreted differently (Roullet and Crawley 2011). Eighteen studies evaluated end points in neonates (14 d old or younger) (Figure S2). End points measured at this time were primarily ultrasonic vocalizations and nest-seeking response. Twenty-one studies evaluated end points in juveniles (15–40 d old), and 36 studies evaluated end points in adults (41+ d old). Combinations of exposure and outcome timing can be explored in Figure S2.

Anxiety and hyperactivity are associated features supporting diagnosis of autism (American Psychiatric Association 2013; Bey and Jiang 2014). Thirty-one studies reported at least one comorbid behavior, with most ($n=25$) reporting a measurement of neonatal, juvenile, or adult hyperactivity, and some ($n=12$) reporting a measurement of juvenile or adult anxiety. Reporting of comorbid behaviors can further support the face validity of rodent models when the phenotype observed is analogous to human clinical presentation.

Likewise, mechanistic end points in rodent studies can support the validity of the model, for example, if molecular effects are the same as those observed in humans with autism spectrum disorders. A major advantage to using rodent models is that mechanistic end points, such as changes in neural cell populations, can more easily be studied than in humans. Nearly half of the rodent studies ($n=21$) included further investigation of at least one mechanistic end point, with the most common being neurochemical alterations ($n=17$) such as differences in dopamine or serotonin levels. Fewer studies ($n=4$) reported changes in neural structures or architecture, such as alterations in cell number or cell structure. Three studies reported alterations in neurophysiological functioning (acetylcholinesterase activity). De Felice et al. (2016) and Sadowski et al. (2014) published follow-up studies with mechanistic outcomes.

The experimental rodent studies were split fairly evenly between rat ($n=22$) and mouse ($n=24$) model systems. While there are many similarities, there are more options for exploring the role of genetics when using mice due to the availability of a wider variety of genetically modified mouse models than rat models. This is apparent by the lack of genetically modified strains of rat and the use of genetically modified strains of mice in the included studies. Ellenbroek and Youn (2016) discuss notable species differences as they pertain to models of neuropsychiatric disorders. These include functional differences in brain structure and differences in social structure that in turn affect social behavior (Ellenbroek and Youn 2016). They conclude that rats may be the preferred model for assessing social behaviors, as mice display less social interaction and receptiveness. It should also be noted that strain differences are likely to exist within each species as well (Spearow et al. 1999). While our search of animal models of autism was limited to rat and mouse models, other animal models exist and should be considered in future work on this topic. For example, primates and rodent models other than mice and rats, [e.g., *Microtus* (vole) and *Peromyscus* (deer mouse)] have been used to study environmental chemicals (Patisaul et al. 2018). Although they may not be as well characterized or utilized as rat and mouse models for studying autism, they have unique advantages (Watson and Platt 2012). For example, the vole is more social than either the rat or the mouse (Beery and Kaufer 2015), and the mechanism underlying their prosocial traits is well characterized, making them an excellent animal model for studying the effects of environmental chemicals on neurodevelopmental disorders like autism (Patisaul et al. 2018).

Reviews

Fifty reviews were identified, covering 57 exposures (Excel Table S5). As in the primary literature, air pollution, mercury, and pesticides were the most frequently discussed exposures in the reviews. Of the various review types, systematic reviews and meta-analyses are generally regarded as the best suited for establishing the strength of the evidence between environmental exposures and autism (Gopalakrishnan and Ganeshkumar 2013; Mandrioli and Silbergeld 2016; Woodruff and Sutton 2014). Nine systematic reviews (as identified by the review authors) and three meta-analyses have been conducted since 2014; they included only human evidence. Note that we did not evaluate the quality of the systematic reviews to ascertain whether they were indeed systematic according to current standards such as ROSES [RepOrting standards for Systematic Evidence Syntheses (Haddaway et al. 2017)]. Only mercury (from air pollution) (Yoshimasu et al. 2014), particulate matter (Flores-Pajot et al. 2016; Lam et al. 2016), nitrogen dioxide (Flores-Pajot et al. 2016), and ozone (Flores-Pajot et al. 2016) have been evaluated by meta-analysis. Systematic reviews of the epidemiological evidence have been conducted on particulate matter (Lam et al. 2016; Morales-Suárez-Varela et al. 2017), air pollutants (Flores-Pajot et al. 2016; Fordyce et al. 2018; Lam et al. 2016; Rossignol et al. 2014), chromium and nickel (McDermott et al. 2015), mercury (from air pollution) (Yoshimasu et al. 2014), neonicotinoid pesticides (Cimino et al. 2016), and phthalate esters (Jeddi et al. 2016). Though significant effects were noted for mercury, and there was limited evidence that developmental exposure to air pollutants was associated with autism, overall, the systematic reviews highlighted the need for more and better observational human studies. Authors of the systematic reviews largely declared that there was not enough evidence, or the evidence was too heterogeneous, to declare strong support for an association between the reviewed exposures and autism.

The remaining reviews were narrative and addressed human epidemiological studies ($n=47$) and rodent studies ($n=12$). Some were more general (e.g., Fluegge 2016; Heyer and Meredith 2017), for example, discussing autism and other neurological diseases and disorders (e.g., ADHD), and others were more narrowly focused on autism (e.g., Lyall et al. 2017; Ye et al. 2017). Yet other reviews drew mechanistic links between environmental exposures and autism and used the primary literature to support their proposed hypotheses (e.g., Moosa et al. 2018). Most reviews discussed five or fewer environmental chemical exposures.

Discussion

The aims of this scoping review were to identify research gaps, make recommendations to help guide the field and prioritize future research, and propose specific topics that we deemed ready for systematic review. In this review, we identified 152 exposures across the epidemiological and experimental rodent studies. Importantly, this surveys only a small fraction of the chemicals manufactured or processed, which is estimated to be upwards of 85,000 in the United States (U.S. EPA 2016).

Epidemiological Studies

When assessing a body of evidence, particularly in a systematic review with meta-analysis, a major challenge is combining

studies that used very different methods. In this review, the 54 epidemiological studies varied widely in terms of study design, specific exposures assessed, how and when exposures were evaluated, and how autism cases were defined. We recommend the following in order to reduce this heterogeneity and improve research methods in this field of study:

Autism diagnosis. Based on our experience conducting this scoping review, the field would benefit from more thorough reporting in the primary research of how autism cases and controls are defined, specifically which diagnostic and/or screening tools are used to reach a DSM or ICD diagnosis. There are numerous tools available to screen and diagnose autism, some more specific and sensitive than others (Falkmer et al. 2013; Randall et al. 2018), and whenever possible, we recommend researchers use the most rigorous methods of diagnosing autism [e.g., ADOS and ADI-R (Randall et al. 2018)]. Further, in our opinion, attention should be paid to appropriately screening participants to minimize cases being inappropriately classified as controls. Additionally, the age of autism diagnosis should be better reported, as it is important in evaluating the likelihood of an accurate diagnosis. These issues are particularly problematic in studies that rely solely on record review for DSM or ICD diagnosis.

Exposure assessment. Exposure assessment methods and timing varied widely between chemicals and even for the same chemical. The reliance in the past on less sensitive and precise measures of exposure levels and timing [e.g., those based on data modeled from historical Toxic Release Inventory data (Lam et al. 2016) or baby's first haircut] allowed for the early exploration of associations with autism, but in our opinion, will be less useful moving forward. More sensitive and direct exposure assessment methods that determine individual levels of exposure are now available. For example, biological samples, personal exposure monitoring systems, and exposomic analyses may provide more accurate and comprehensive exposure information (Turner et al. 2018; Vineis et al. 2017). In addition, for chemicals for which exposure levels are known to fluctuate over time [e.g., pesticides (Arcury et al. 2009; Li et al. 2014)] or that are rapidly metabolized [e.g., BPA (Thayer et al. 2015; Ye et al. 2011)], studies should include exposure assessments at multiple time points.

Study location. The geographical distribution of studies identified in this review was highly skewed toward the United States, and specifically California. It is known that environmental chemical exposures vary between time and place, due to different environmental chemical regulations (e.g., for pesticides), regional weather patterns (e.g., air pollution), differences in local industries (e.g., manufacturing), and other variables. Further, it is also known that autism diagnosis rates vary geographically, and this may be related to different environmental exposures across regions (Hoffman et al. 2017). It may be important to establish studies in more diverse locations to better understand the influence of environmental chemical exposures on autism.

Study design. There were only seven prospective studies identified in this scoping review. Prospective studies that enroll families during early pregnancy or even preconception, and track exposures through early postnatal life, provide the most direct evidence linking environmental exposures to autism. It may be helpful to establish studies similar to the Health Outcomes and Measures of the Environment (HOME) study, a prospective cohort study set in Cincinnati, Ohio (Braun et al. 2017), in diverse geographic locations. On the other hand, additional population based case–control studies similar to the CHARGE study in California (Hertz-Picciotto et al. 2006) would more quickly grow the evidence base for chemicals that currently only have one or two studies.

Experimental Rodent Studies

Although animal models will never fully mimic real-world exposures and the complex set of demographic, environmental, and social factors that go into a condition like autism, results from animal model studies can contribute valuable information to the body of evidence linking environmental chemicals to autism. In part, this is due to the ability to control the chemicals, doses, and timing of exposure in animal studies. Animal studies can also shed light on biological mechanisms critical to ensuring proper development, such as neurotransmitter and hormone signaling. Understanding these processes as they are related to autism may help identify opportunities for prevention or treatment. Further, for chemicals deemed to be associated with autism, animal studies will likely be necessary to satisfy current regulatory risk assessment methods that set safe levels of exposure (U.S. EPA 1998). Based on the 46 experimental rodent studies identified in this scoping review, we make the following recommendations:

Harmonized efforts. As the field moves forward, better harmonization between the chemicals that are studied in humans and those studied in animals is recommended. Many chemicals were only studied in one body of evidence or the other. It would be helpful for future animal studies to focus on addressing questions identified by epidemiological studies (e.g., regarding dose, timing, and mechanisms of action) to help identify causal relationships. For example, there are 22 epidemiological studies evaluating over 50 different components of air pollution, yet there are only four rodent studies. More research using rodent models could improve our understanding of causative chemicals in such complex mixtures. In addition, chemicals currently identified only in animal studies (e.g., butyl paraben, diethylhexyl phthalate, dichlorvos, fenvalerate, glufosinate ammonium, isobutyl paraben, propionic acid, and tungsten) should be evaluated for possible inclusion in epidemiological studies to better understand their relevance to humans.

Improved model characterization. Currently, resources are available that describe how different rodent behavioral assays contribute to the face validity of the model (Roullet and Crawley 2011). However, there has not been, as of yet, clear guidance on which specific behavioral tests or combinations of tests provide the most valid and reliable model of autism. Moving forward, we recommend that studies specifically aiming to model autism in animals should measure both reciprocal social communicative and stereotyped and repetitive behaviors. Measurements of comorbid behaviors and mechanistic outcomes should also be included in future studies in order to more fully characterize the phenotype. Furthermore, the utility of other animal models, including nonhuman primates and voles, should continue to be explored, as they may offer unique similarities to the human condition.

Reviews

We identified 50 reviews, including nine systematic reviews and three meta-analyses. The reviews varied greatly in their depth. None of the systematic reviews or meta-analyses in this field have incorporated evidence from animal models. One of the benefits of systematic review methods designed for environmental health research (Rooney et al. 2014; Woodruff and Sutton 2014) is that they provide specific guidance on how to integrate evidence across human and animal studies, as well as how to incorporate mechanistic evidence. As such, these frameworks allow stronger conclusions to be drawn about hazards posed by environmental chemicals. Other strengths of these systematic review frameworks are that they feature risk of bias evaluations, inclusion of positive and negative findings, and transparent decision-making in order to arrive at the most robust conclusions. Based

on our experience conducting this scoping review, we recommend the following:

Future systematic reviews. There is no clear guidance on what makes a topic ready for systematic review and meta-analysis. Although, technically, a systematic review can be conducted on a minimum of two studies, typically they include more, as they are designed to tease apart more complex research questions in environmental health. In conducting scoping reviews, we base our recommendations for systematic review on the number of studies we identify in the epidemiological and animal literature, the presence or absence of other literature reviews, insight gained during the scoping process, and other contextual factors. As a result of this scoping review of autism, we recommend the following chemicals for systematic review:

- Chlorpyrifos: We identified three epidemiological studies and nine experimental rodent studies that investigated the relationship between the pesticide chlorpyrifos and autism. The epidemiological studies (but not the rodent studies) were previously reviewed by Lam et al. (2016), indicating a trend towards a positive association. Notably, chlorpyrifos was one of the few chemicals we reviewed that included rodent studies with behaviors addressing both diagnostic criteria for autism. Chlorpyrifos's association with autism has not yet been evaluated by meta-analysis. Given current efforts to determine whether U.S. Environmental Protection Agency should regulate chlorpyrifos due to its effects on neurodevelopment (Hertz-Picciotto et al. 2018a; U.S. EPA 2017), we believe a systematic review considering both the epidemiological and experimental rodent evidence is warranted and timely.
- Lead: We identified ten epidemiological studies on lead, six of which were related to lead as an air pollutant (reviewed by Lam et al. with mixed results) (Lam et al. 2016). It may be fruitful to review lead again, adding the three epidemiological studies where lead was investigated as a biomarker of exposure (in baby teeth) and the four experimental rodent studies. Although efforts are underway to bring lead exposure to "near zero" levels (Bellinger et al. 2017), understanding specifically whether it contributes to the incidence of autism is an important question to address, as it may have relevance for treatment and prevention efforts.
- PCBs: Another potential candidate for systematic review is the group of industrial pollutants, PCBs. We identified eight epidemiological studies and three experimental rodent studies on PCBs. Although they have been largely regulated as hazardous chemicals, whether PCBs contribute to the etiology of autism in humans remains to be determined, as they have not yet been evaluated by systematic review or meta-analysis.

Search terms. It should be noted that the animal evidence in this scoping review may be underestimated because we did not include search terms for specific behavioral tests such as ultrasonic vocalizations or the three-chamber test. It is likely that these specific tests have been utilized in developmentally exposed animals outside of the context of autism, for example, in studies exploring effects of developmental chemical exposures on social behavior [e.g., Wolstenholme et al. (2011)] or in studies modeling other neurobehavioral disorders. Future reviews would benefit from the refinement of relevant literature search terms for specific animal behavioral tests. To some extent, this may occur as journals begin publishing protocols developed *a priori* for scoping and systematic reviews, which allows for input on the search strategy during peer review and also provides an opportunity for public review. Toward this end, all of the data evaluated in this scoping review are publicly available in easy-to-use, interactive figures that allow further exploration and analysis of the research that has been conducted to date.

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EXHIBIT 67

Pregnancy, Immunity, Schizophrenia, and Autism

by Paul H. Patterson

Opposite: A detail from *The Temptations of St. Anthony* by Hieronymus Bosch (d. 1516). The fantastic—in the strictest sense of the word—figures portrayed here are not unlike some hallucinations reported by schizophrenia sufferers. Courtesy of the Museu Nacional de Arte Antiga, Lisbon.

Can something as innocuous as the flu cause schizophrenia? Can a pregnant mom's sniffles have lifelong consequences for her unborn child? Does the brain's own immune system play a role in autism? The answers to these and related questions are indeed surprising, and may suggest new avenues for treatment or even prevention.

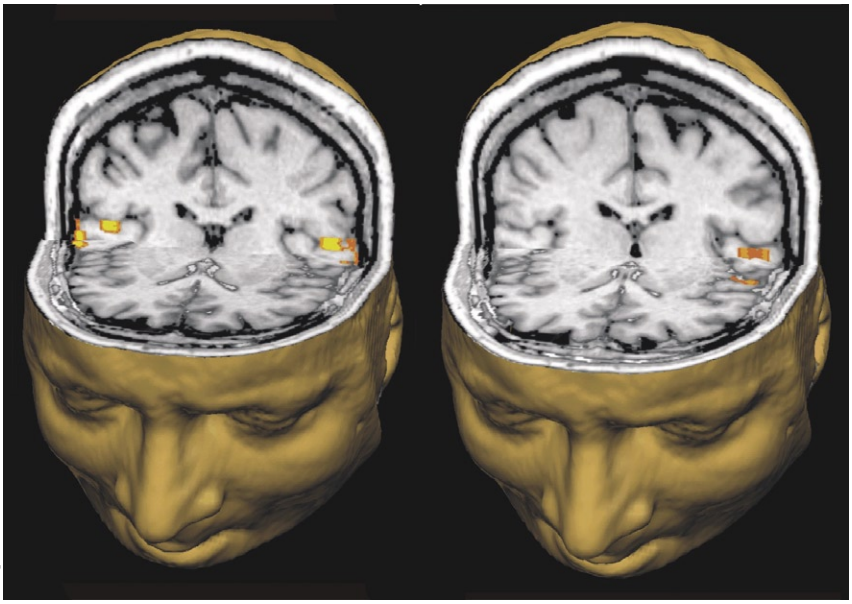
As we learn more about the connections between the brain and the immune system, we find that these seemingly independent networks of cells are, in fact, continually talking to each other. As an adult, the activation of your immune system causes many striking changes in your behavior—increased sleep, loss of appetite, less social interaction—and, of course, headaches. Conversely, stress in your life (as perceived by your brain) can influence immune function—the brain regulates immune organs, such as the spleen, via the autonomic nervous system.

Recent evidence shows that this brain-immune conversation actually starts during the development of the embryo, where the state of the mother's immune system can alter the growth of cells in the fetal brain. As we shall see, such alterations can lead to an increased risk of schizophrenia or autism in the offspring.

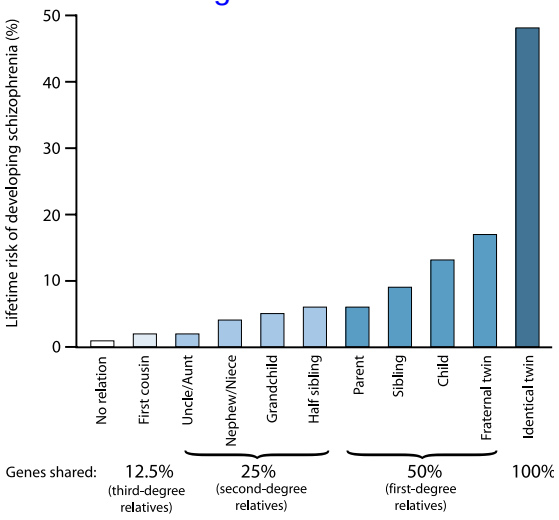
First let's consider schizophrenia, which is a progressive disorder whose initial psychotic symptoms usually appear in early adulthood. (For a gripping rendering of how psychotic episodes might appear to the sufferer, see Russell Crowe in *A Beautiful Mind*.) People with schizophrenia can be seemingly quite normal part of the time, and then have very severe problems, which is a huge difficulty for them—people have tended to blame the victim and wonder why the patient doesn't get him- or herself together and behave properly.

In the last decade or two, anatomical and functional differences between schizophrenic and typical brains have begun to emerge. Magnetic resonance imaging (MRI) scans of the brains of identical twins, one with schizophrenia and one without, have shown that in 90 percent of the cases the twin with schizophrenia has enlarged ventricles, which are butterfly-shaped, cerebrospinal-fluid-containing voids in the center of the brain. One explanation for this enlargement is that the gray matter surrounding the ventricles might have shrunk, meaning the brain has fewer or perhaps smaller neurons. Or the neurons might be more densely packed. An alternative hypothesis invokes an infection—encephalitis, for instance, will expand the ventricles. Schizophrenia does not result from a frank infection of the mature brain, but there are other indications, which I'll come back to, that infections might be involved very early on.

MRI shows anatomical details, but functional MRI, which tracks blood flow, shows brain activity. The more blood moving through a particular part of the brain, the more active it presumably is. In these renderings of functional MRI scans of a schizophrenic patient, the head at far left shows, in yellow, that the auditory cortex lit up when a



Heschl's gyrus is the brain's main sound-processing center. A real sound lights it up on both sides of the brain, as seen at far left in these 3-D renderings. The gyrus lights up spontaneously during an auditory hallucination (left), but only on the brain's dominant side.



Right: There is clearly a genetic predisposition to schizophrenia. This chart shows how your chances of developing the disease increase if you have a close relative with it—the more genes you share with the affected person, the higher your susceptibility. Adapted from *Schizophrenia Genesis: The Origins of Madness* by Irving I. Gottesman, W. H. Freeman and Company, New York, 1990.

Separated at birth, the Mallifert twins meet accidentally.

stereophonic sound was played through earphones. The other head shows the brain activity when the patient pushed a button to signal that he or she was "hearing voices." The hallucinations only appear in the dominant hemisphere, so in this right-handed patient, only the left hemisphere's auditory cortex lit up. It used to be said that the voices in their heads were imaginary, but since there is activity in the part of the brain that actually does process auditory information, they really exist, in a sense. Schizophrenics *are* hearing sounds, as far as their brains know, and it would be very interesting to discover what generates this activity spontaneously.

We know that schizophrenia begins in early development. Statistically, children who will later develop psychosis are more prone to disciplinary problems in school, tend to have lower IQs, and are more likely to be beset with emotional and social problems. The differences are too small to be useful for an early diagnosis, but they're there. There's also a surprising delay in the development of motor functions—sitting, standing, walking, and so on.

There's a genetic component to schizophrenia. The most important risk factor for predicting schizophrenia is having a sibling with the disorder. In the general population, the risk for schizophrenia is approximately 1 percent worldwide. If you have a schizophrenic cousin or uncle or aunt, the risk is doubled, which is not very significant. But if you have an identical twin with schizophrenia, the risk is about 50 percent that you will become schizophrenic as well. But it's not 100 percent, so it's not a classical, dominant genetic disease like Huntington's disease, where a single malfunctioning gene gives you the disorder. Rather, people think there are some six to 12 genes involved, each of which contributes a small amount of risk. In the last couple of years, a number of these genes have been identified, including neuregulin, dysbindin, and one called "Disrupted-in-Schizophrenia," or DISC1. Furthermore, each of these genes is well known from animal studies to be very important in early embryonic brain development.

There is also an environmental risk component. Being born in the winter or spring months, or being born and raised in an urban area both increase risk. This is consistent with an infectious hypothesis—we tend to get sick more often in the winter and spring, and we're more likely to sample other people's germs if we live in a crowded area.

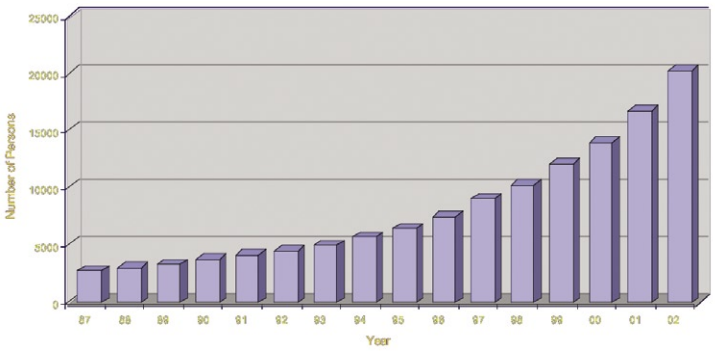
Another important environmental risk factor is maternal infection, which will be one of my major themes. Having a respiratory infection during the second trimester of pregnancy increases the risk for schizophrenia in one's offspring. In the year 2000, Alan Brown and his colleagues at Columbia University in New York studied the medical records of 12,000 pregnant women who belonged to the Kaiser HMO in the Oakland area. Brown found

that there was about a threefold increase in risk if the woman had a respiratory infection during the second trimester, confirming the conclusions of previous studies that had not had access to patient records. The researchers then analyzed frozen serum samples from those women, and found a similar, or even larger—up to sevenfold—increased risk if antiflu antibodies were present during the first half of pregnancy. Moreover, they found a statistically significant association with elevated levels of some members of a group of proteins called cytokines. Cytokines are produced by the white blood cells, and their levels in the blood increase when we get an infection. A calculation of the so-called attributable risk from this data led to the estimate that about 20 percent of the schizophrenia cases would not have occurred if flu exposure had been prevented.

This is a really dramatic piece of information, particularly given that the researchers had to completely ignore the genetic angle. (Even now, we cannot screen for the susceptibility genes that have since been identified.) Thus, the study presumably included a large number of people who will never get schizophrenia because they aren't genetically predisposed, yet it *still* found a three-to-sevenfold risk increase. The actual risk due to maternal infection is therefore likely to be much higher.

Alarmingly, cases of autism appear to be dramatically on the rise. However, it's not clear how much of this actually represents an increase in the incidence of autism, or an increase in the diagnosis of autism rather than, for instance, mental retardation.

Other studies of adult schizophrenic subjects have found cytokine imbalances and elevated levels of white cells in the blood. And antipsychotic drugs such as clozapine, which people take to treat hallucinations and disordered thoughts, are known from animal studies to modulate cytokine levels in the blood. So these drugs might not only be acting in the brain, but on some aspect of the immune system to achieve their effectiveness. I think this is a very interesting observation, but it hasn't made much of an impression on the research community yet, so the possibility hasn't really been investigated carefully.



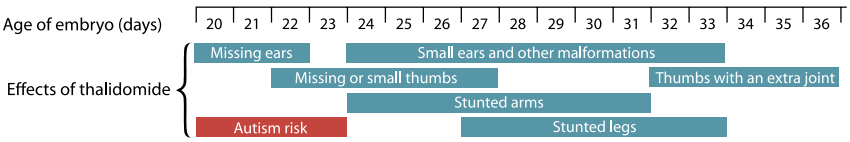
This chart shows how the annual number of people diagnosed with autism who were served by California's Department of Developmental Services began to skyrocket in the mid-1990s. Courtesy of the DDS.

A recent, very impressive paper by William Eaton and colleagues at Johns Hopkins University Medical School analyzed the remarkably comprehensive records of Denmark's health system, which tracks every Dane from the cradle to the grave. The investigators accessed the files on all 7,704 people who were diagnosed with schizophrenia between 1981 and 1998, including the details of every hospital visit those people ever made in their entire lives. It turns out that people who developed any of nine different autoimmune disorders—diseases in which the body's immune system begins attacking one's own cells—had a 45-percent increase in risk for developing schizophrenia.

So there is a link between the immune system and schizophrenia, but we don't know what it is. We know that a genetic predisposition to autoimmune disease exists—are the genes responsible for this predisposition somehow linked to the ones predisposing to schizophrenia? Or is there something about having an autoimmune disorder, such as the creation of antibodies against certain molecules, which increases risk for schizophrenia?

Now let's turn to autism, which was originally described by Leo Kanner at Johns Hopkins in 1943 as a type of schizophrenia. We don't think that way anymore, but there are some interesting similarities—particularly in the withdrawal of patients from the world around them. The hallmarks of autism are, of course, deficient social skills—patients don't read other people's emotions well or respond to them appropriately—and the lack of development of language. Heartbreakingly, about 30 percent of patients actually experience a regression in these areas that starts at about age three. Unlike schizophrenics, however, autistic children frequently display odd, repetitive gestures—banging their heads against the wall, or a flapping motion with the hands that is a classic symptom often used by teachers as a possible indication that a problem may exist. And autistics tend to fixate on objects and rituals. A patient might spend hours playing with a piece of string, for example, or eating her dinner in just the right way. There's also fear of new situations or objects, and oftentimes considerable problems with sensory stimuli—extreme sensitivity to noises, for example. Alarmingly, cases of autism appear to be dramatically on the rise. However, it's not clear how much of this actually represents an increase in the incidence of autism, or an increase in the diagnosis of autism rather than, for instance, mental retardation.

Like schizophrenia, there's a strong genetic component to autism—the single biggest risk factor is having a sibling with it. Autism is also a multi-



Fingers, toes, limbs, and organs all develop in the fetus according to a very strict timetable, and the types of birth defects seen in thalidomide babies correlate very precisely to when the mother-to-be took the drug. Some thalidomide babies are also autistic, revealing a window of vulnerability in early brain development. Autism data from K. Strömland et al. in *Developmental Medicine and Child Neurology*, April 1994; graphic after Patricia Rodier, *Scientific American*, February 2000.

genetic disorder, with six to 10 genes involved, and again, the genes that have been identified thus far (neuroligins 3 and 4, En-2, and Hox-a1) are very important in embryonic brain development. Furthermore, there are environmental risk factors for autism. Valproic acid, which is used to treat epilepsy, causes a dramatic increase in the risk of autism when taken by women before they know they're pregnant. This drug is still commonly prescribed, but people are beginning to get concerned about its use by pregnant women.

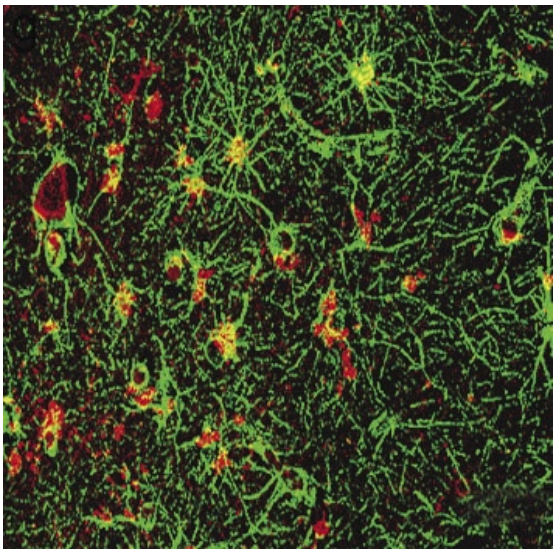
We have a valuable insight into the fetus's period of vulnerability, thanks to the thalidomide tragedy. Those of you who are old enough will remember the use of thalidomide as an anti-morning-sickness drug in the 1960s. Severe birth defects resulted, as did an increased incidence of autism. But what is key here is that the kind of physical abnormality one got—missing ears, stunted arms, stunted legs—was found to depend on how far along the pregnancy was. In other words, the child's deformity told us exactly when, sometimes to within a day or two, the mother took the drug. The window of risk for autism proved to be days 20 through 23 after conception—a very early stage in neural development. At this time, the neural tube is just closing, and the first neurons are just being born. A similar window of risk is found with valproic acid, and with an ulcer-preventing drug called misoprostol. We don't know the cause or causes of autism in most cases, but this window of vulnerability is clearly a very important clue to how the brain is altered in this disorder.

Again, as in schizophrenia, there's a maternal-infection risk factor. A review of the literature by Andrea and Roland Ciaranello at Stanford concluded that "the principal nongenetic cause of autism is prenatal viral infection." This was based primarily on studies of an epidemic of rubella, or German measles, in New England in 1964. On the order of 10 percent of the children born to infected mothers exhibited symptoms of autism, which is really an astronomical increase in risk. Of course, rubella is not common anymore, because we get vaccinated against it, but the point is that maternal infection can increase the risk for autism. Other infections have also been implicated—a paper just came out last week linking genital herpes infection with an increased risk for autism.

Without going into the details, the rates of autoimmune diseases and allergies are higher in families with autism, particularly in the mother. There are also reports of immune dysfunctions in the blood of autistic individuals. These various connections to the immune system are, of course, reminiscent of schizophrenia.

There is also very striking evidence of immune dysregulation in the brain itself. Just last year, a group led by Carlos Pardo at Johns Hopkins found what they're calling a "neural inflammation" in postmortem examination of brains of patients with autism who died between the ages of eight and 44 years. But these people weren't infected—they died of such things as drowning or heart attacks. The study found that the microglial cells, which act as the brain's own immune system, were activated. The study also found amazing increases of certain cytokines in the brain, and of others in the cerebrospinal fluid. This is a landmark paper, in my opinion. It presents the first evidence that there's an ongoing, permanent immune-system activation in the brains of autistic people. It's a subclinical state, because there's no overt infection. But it's there.

To try to untangle how the immune system is intertwined with the development of these diseases, we turned to an animal model. Animals are vital to



Vargas, et al. *Annals of Neurology*, vol. 57, no. 1, pp. 67–81, 2005. © 2004 American Neurological Association. Reprinted with permission of John Wiley & Sons, Inc.

In this cross section of the cerebellum of an autistic patient, the microglial cells have been activated, as shown by their absorption of a red dye that binds to an immune-system protein called HLA-DR.

medical progress. If you think a gene is important in a particular disease, you can introduce that gene into a mouse, and note whether it gets something like the human disease. You can also test bacteria, viruses, and environmental toxins. You can study pathogenesis—how the stages of the disease progress, and how it spreads from tissue to tissue—in animals much much easier than you could in humans. And you can, of course, test treatments. By law, you *have* to test drugs on animals first. It's also how we work out the details of new surgical procedures and explore the potential of new therapies, such as those involving stem cells. Without the animal studies that preceded them, such common but highly complex procedures as bone marrow, kidney, and heart transplants would not be available today.

That's all well and good, but what about animal models of mental illness? How do you psychoanalyze a mouse? How can you tell if it's hallucinating? (I think we can, but that's a topic for a future Watson lecture.) And how do we even *model* a disease like autism, which is supposed to be uniquely human? How can you measure an autistic mouse's impaired language skills when—sorry, Walt—they aren't capable of speech in the first place? Or at least not speech that we can understand—they do communicate via alarm and distress calls, and there is even some speculation that they can recognize other mice by their voices. But that, again, is another story.

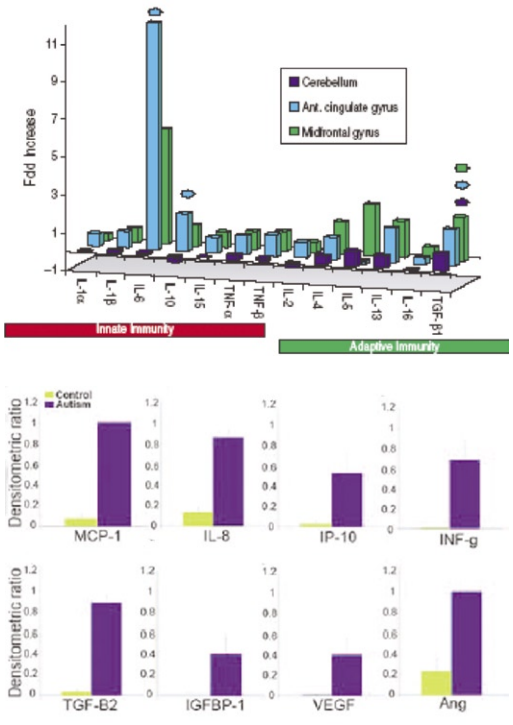
Fortunately, that isn't what we really do with animal models. We don't mimic the *whole* disease in any model—we mimic *features* of the disease. This might be the kinds of neurons that die. It might be some change in the electrical properties of the neurons, or some molecular change such as the cytokine levels. Or it could be the tremors and shuffling gait of Parkinson's disease. In fact, the mouse models of Alzheimer's and Huntington's diseases that are in routine use in labs around the world do not display some of the diseases' key features. The neurons that typically die in human patients somehow survive, for example. So a model doesn't have to be perfect to be extremely useful, even when testing potential human therapies.

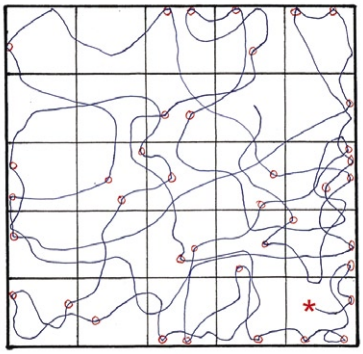
Our laboratory is exploring a model of maternal infection. We give a pregnant mouse the flu by touching a pipette containing a solution of the human influenza virus to her nose, which she then inhales. The mouse gets lethargic, stops grooming herself, hunches in the corner of the cage, and in a few days recovers and behaves normally again. In due time she gives birth, and we study the pups, both as infants and adults. We watch their behavior, and then examine their pathology—what their brains look like.

What types of mouse behavior might be relevant for schizophrenia or autism? People often use what's called an open field test to study anxiety under mildly stressful conditions. The mouse is placed in an enclosure with a camera overhead and grid

A handy guide to deciphering mouse psychology.

Top: Elevated cytokine levels were found in three different parts of the brains of autistic patients. The flat gray rectangle at the bottom of the graph shows the corresponding levels in typical brains. Bottom: Cytokine levels in the cerebrospinal fluid of autistic (purple) and unaffected (yellow) subjects.



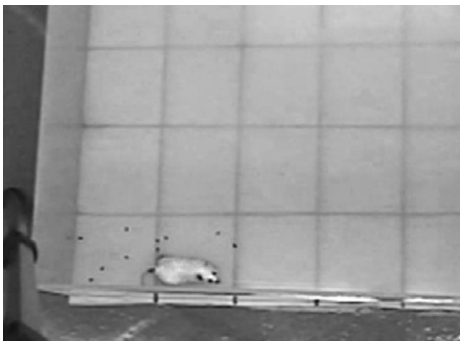


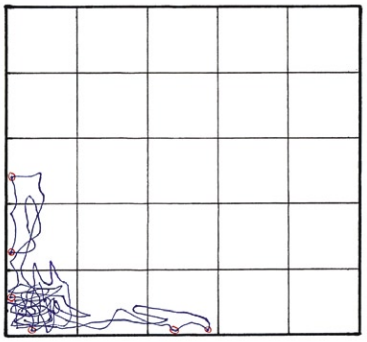
The path followed by a control mouse exploring an unfamiliar place. The asterisk marks where the mouse was placed in the box, and the red circles show where the mouse stood up on its hind legs for a better whiff of its surroundings.

lines on the floor so we can track where the animal moves. A normal mouse usually spends a lot of time creeping along the edges of the box at first, because it's afraid that it's dangerous to go out into the middle—which, obviously, it might be. But it will eventually inspect most of the box, pausing frequently in the process to rear up on its hind legs and sniff the air. Our normal mice, which we call control mice, are born to "sham-infected" mothers who were given a sterile saline solution without the virus. These mice do exactly the same thing—they are timid at first, but they're soon traipsing all over the box.

Below is an example of an adult mouse who was born to a flu-infected mother, and you can tell immediately from the fecal pellets that it hasn't moved beyond its corner very much at all. We would interpret this as excessively fearful behavior, given the mildly stressful nature of the situation, and we can quantitate it by simply measuring the amount of time spent in the center squares of the box. This mouse enters the center many fewer times, and it rears and sniffs much less often as well.

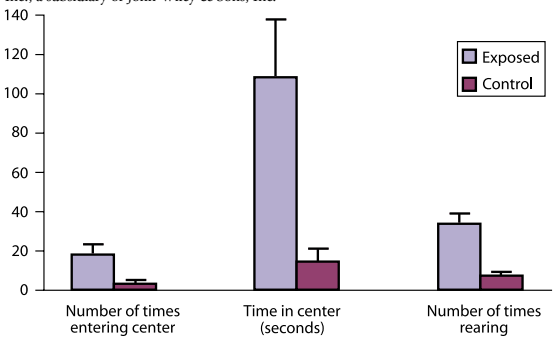
By contrast, a mouse whose mother got the flu tends to stay hunkered down in the corner where it was placed.





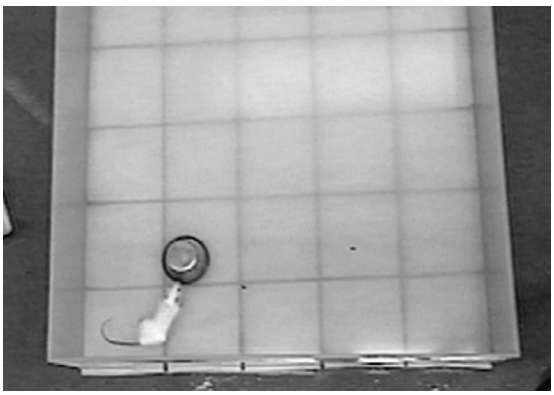
The so-called novel-object test is also relevant. Remember, autistic children are often afraid of unfamiliar things. So when we put something strange and new in the field, say a coffee cup, the control mouse carefully investigates it, touching and sniffing it from all sides, whereas our mouse born to an infected mother is very reluctant to go anywhere near it. In fact, this mouse turns its head away and acts as if the object isn't there. We measure the time lapse before the mouse first touches the object, which we call the latency to first contact, and we count how often contacts are made. Again, the differences are dramatic. The "autistic" mouse waits much longer, and touches the object far fewer times.

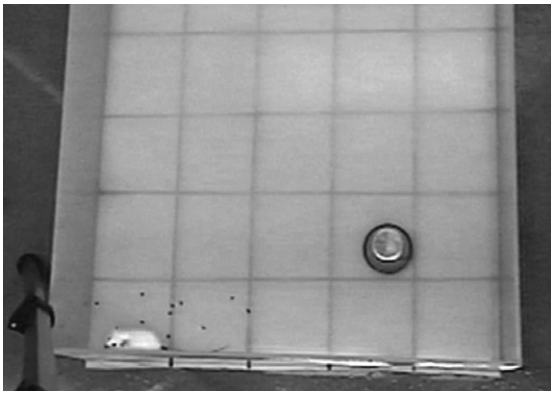
We also do simple social interaction tests. We put two mice who don't know each other in the box, and ask how long it takes them to make physical contact, and how often they do so. And not surprisingly, pairs of mice born to infected mothers make contact less than half as often and have more than four times the latency. So clearly they're not socializing properly. Grad student Steve Smith is now following up on that observation by



Mice whose mothers were given the flu virus ventured into the great empty middle of the box much less often (left) and spent much less time there overall (center). They also reared up to sniff less often (right).

At least rodents don't run up bar tabs—biology staff member Limin Shi puts a pair of mice in a three-room box designed to test their social skills.



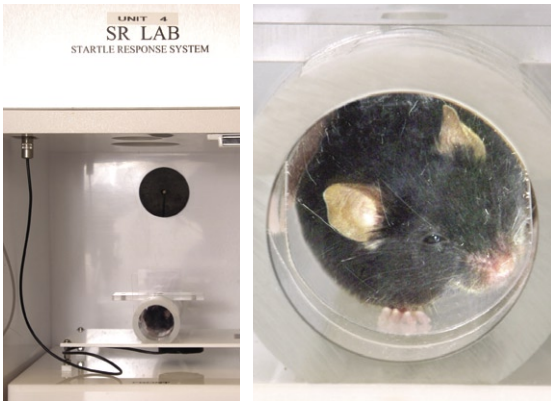


Top: A normal mouse inspects an unfamiliar object with avid curiosity.

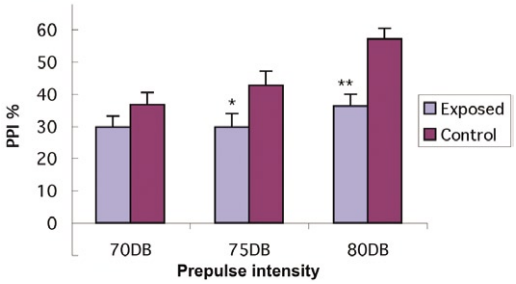
Bottom: An "autistic" mouse ignores it, seeming to act on the theory that if it can't see the object, the object doesn't exist.

using a box divided into three rooms. We put our test mouse in the middle room, and then we put an unfamiliar mouse in one of the side rooms. We leave the room on the opposite side empty in some tests, and in others we put a cage mate of our test mouse in there. Then we sit back and watch where our test mouse goes. Normal mice like novelty, and almost always go to the strange mouse, even when there is a familiar mouse in the other room. Preliminary results with our "autistic" mice, however, show that they prefer to remain in the central chamber regardless of who else is in the box with them.

Another pertinent test is the startle response, which is a lot like sneaking up behind someone with an inflated paper bag and popping it. We put the mouse in a tube inside a soundproof box, and underneath that tube is a motion sensor. There's a speaker in the box, and when a loud sound is played, the mouse is startled, and we measure how high it jumps. But if we precede the loud sound with a softer sound that doesn't startle the mouse—called a prepulse—it doesn't jump so much. This is called prepulse inhibition, or PPI, and when the same type of test is done in people, a striking deficit is observed in schizophrenic and autistic subjects. In other words, they get startled just as much regardless of whether they got a prepulse or not. The loud noise surprises them every time. We think this relates to the attention-deficit issues. On the next page is a plot of the amount of the mice's PPI versus prepulse intensity. As we increase the prepulse intensity, we get a bigger inhibition across the board, but our "autistic" mice have a PPI deficit at every intensity.



Right: The mouse-startling machine. The mouse sits in its comfy burrow—a plastic tube, seen end-on in these pictures, that in turn sits on a platform with a motion sensor (the black unit connected to the black cable) on its underside.



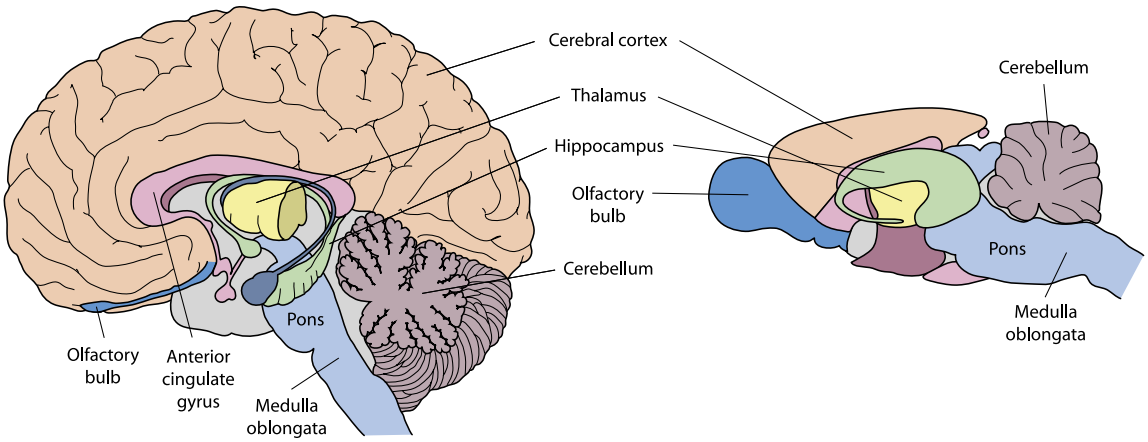
Far right: Regardless of how loud the prepulse was (the numbers are in decibels), the "autistic" mouse was always more startled—that is, had a lower prepulse inhibition (PPI) than a control mouse.

Adapted from Shi, et al., *The Journal of Neuroscience*, vol. 23, no. 1, pp. 297–302, January 1, 2003. © 2002 Society for Neuroscience. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

The PPI is thought to be a measure of sensory-motor gating—the connection between the filtering of incoming sensory information and the creation of motor outputs to the muscles—which is likely to be related to attention deficits and distractibility. In fact, a PPI deficit is also found in attention deficient disorder. Importantly, those antipsychotic drugs mentioned earlier can restore the PPI in schizophrenic subjects, whereas psychomimetic drugs—hallucinatory drugs—disrupt PPI. We have shown the same thing to be true in our mice.

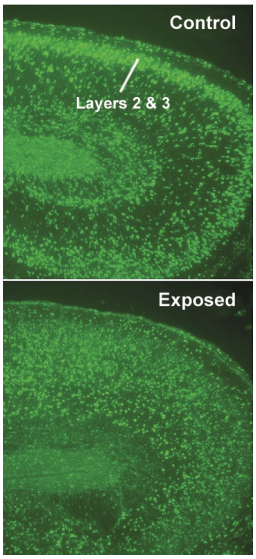
We presume that these behavioral abnormalities are based in brain pathology—changes in the nerve cells, or in their connections. In fact, postmortem examinations of at least some brains of schizophrenia patients have shown nerve cells that are not in their appropriate locations. So recently, biology staff member Limin Shi, postdoc Natalia Malkova, and Steve Smith have been looking at fetal brain development in the mice. For this analysis, the pregnant mice are given the flu at mid-pregnancy, day 9.5 of gestation, which corresponds to the period of very early brain development in humans. In other words, it's similar to the thalidomide window of autism vulnerability. However, because fetal mice develop so fast, the illness also extends through the period corresponding to that second-trimester stage in humans when maternal infections lead to an increased risk of schizophrenia. Five days into the infection, a dye that marks newly formed neurons is injected into the mice, and they give birth six days after that. At right is the brain of a normal pup. The green neurons have taken up the dye, and most of them have migrated out to what neuroanatomists call layers 2 and 3 of the cerebral cortex. This is similar to how a normal newborn human brain would look, too. But this layer is barely present in the pups from infected mothers. Something has gone very wrong, because the green cells have wandered off all over instead of forming the normal, tightly packed layers. We plan to repeat the experiment but let the pups grow to adulthood to see if this disorganization persists, and whether it looks similar to what was found in those few human schizophrenia examples.

Another human pathology occurs in the cerebellum. The cerebellum has lobes, called lobules, which look like a cauliflower in cross section, and contain neurons called Purkinje cells that are pres-



The human (right) and mouse (far right) brains, not to scale.

A 20-month-old child participates in Pierce and Courchesne's current set of exploration studies. The tape grid on the floor helps the researchers map the child's movements. Photo courtesy of Karen Pierce.



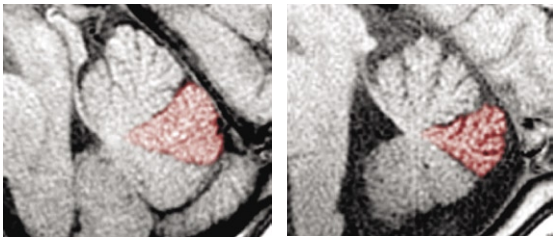
Neurons from an early stage of brain development have been labeled with a fluorescent green dye. These neurons form clearly visible layers in a healthy newborn mouse brain (top), but when the mother was infected in midpregnancy (bottom), the neurons are scattered almost at random.

ent in all mammalian species. Some 90 percent of postmortem autism samples show a substantial reduction in the number of Purkinje cells in lobules VI and VII. In some cases there are even misplaced Purkinje cells. And MRI studies of living autistic subjects reveal that lobules VI and VII are underdeveloped.

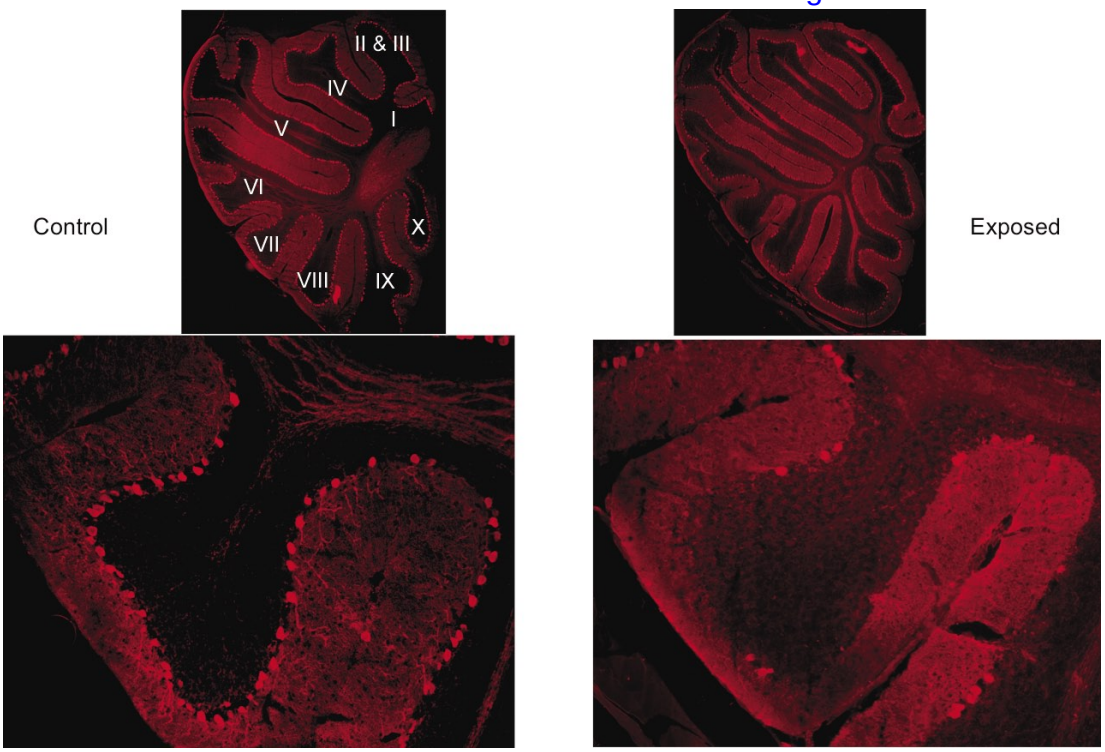
There is a fascinating correlation between abnormalities in lobules VI and VII and children's exploratory behavior. In 2001, Karen Pierce and Eric Courchesne at UC San Diego did a study where they put a child (aged three to eight) in a room with a lot of brightly colored boxes and other intriguing objects, and counted how many of them the child played with in eight minutes. The control kids, on average, explored about 10 of the 14 items. But the autistic children tended to fixate on a few objects to the exclusion of all others—in one extreme example, the child got no further than the very first item it encountered. All of these children had previously had MRI scans as part of another study, and a dramatic correlation popped out—the smaller the autistic child's lobules VI and VII, the fewer objects the child showed interest in.

Because our "autistic" mice were similarly immune to the allure of an unknown object, we wanted to see if they had the same cerebellar abnormality. Treating the cerebellum with a dye that just stains Purkinje cells reveals a consistent difference in these mice, as you will see on the next page. In addition, we occasionally see what we think are misplaced Purkinje cells. The cell bodies are supposed to line up in a neat row along the boundary between the red and the black zones, and not dawdle in the dark interior. We think that this misplacement must have occurred in embryonic development.

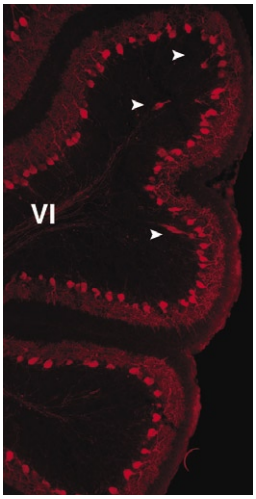
Now let's consider the mechanism for how this works, which is where the animal model comes in very handy indeed. Does the virus actually infect the fetal brain itself, or is it working indirectly through the mother's immune system? We think



An MRI scan of a control child's cerebellum (left) and an autistic child's (right), with lobules VI and VII shaded red.



Control and "autistic" mouse cerebellums stained with a dye that binds to Purkinje cells. The bottom two images are close-ups of lobule VII. The bright red globs are the Purkinje cell bodies, and the dark voids are actually chock-full with other types of cells. The right-hand image—an extreme example from an adult mouse born to an infected mother—shows almost no Purkinje cells.



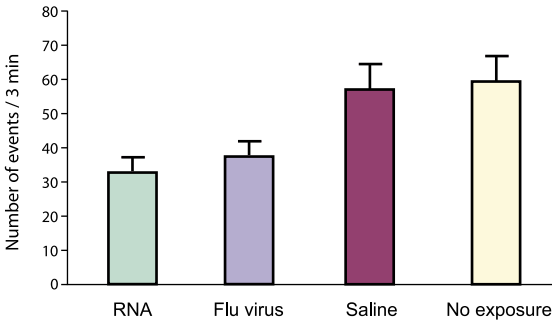
Errant Purkinje cells (white arrowheads) in the middle of lobule VI.

it's the latter, because we can't find the virus in the offspring, either in the embryonic brain or at birth. That's not surprising because, after all, influenza is primarily a respiratory virus. It hardly ever gets out of the lungs, throat, and nose and into the rest of the body. When it does, you have viremia, which is a very serious disease.

Furthermore, we can evoke an immune response in the mother without using a virus, simply by injecting her with a piece of double-stranded RNA. Mammals don't make double-stranded RNA but many viruses do, so the immune system knows that when it sees double-stranded RNA, it needs to swing into action. It starts secreting cytokines and in general mounting a vigorous antiviral response, even though there's no infection. Tellingly, the offspring of mothers whose immune systems have been artificially activated in this way display the same PPI deficit that we saw before. So we don't need the virus; activation of the maternal immune system is sufficient to alter the behavior of the offspring.

A second example of "autistic" behavior brought on by maternal immune activation was discovered by Natalia Malkova. Anecdotal evidence suggests that autistic human infants may be less bonded with their mothers. When Natalia removes the mother mouse from the family cage, it normally induces considerable crying in the control pups, although since mouse pups vocalize at ultrasonic frequencies, we have to use a special microphone to hear them. So Natalia counted how often the pups cried in three minutes, and the mice born to a double-stranded-RNA-exposed mother cried less than pups born to a normal mother.

We think that maternal immune activation alters brain circuits. Besides that dramatic abnormal layering Limin finds in the mouse cortex, and a loss of Purkinje cells that's been seen in the human cerebellum, there's that permanent, subclinical, altered immune state in the autistic brain—those increased cytokine levels. Are those cytokines an irrelevant, residual footprint—a fossil, if you will—of some earlier event, like a maternal infection? Or are they actually interacting with the brain in an ongoing fashion, with consequences visible in the patients' behavior? I favor the latter hypothesis.



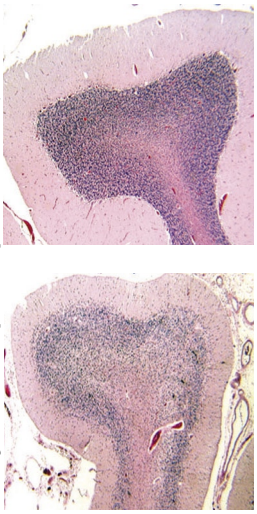
Mouse pups born to uninfected mothers (yellow bar) cried about 60 times in three minutes, or once every three seconds, when separated from Mom. So did control pups (purple) whose mothers had inhaled a sterile saline solution. Pups whose mothers' immune systems had been activated, either by a virus (lavender) or a piece of double-stranded RNA (green), cried much less often.

In some clinical trials where cancer patients were given cytokines in the hopes that these molecules would attack their tumors, dramatic differences in behavior and mood became apparent—up to severe depression, in the worst cases. And other researchers have found that high levels of cytokines in animals can alter learning and memory.

If this hypothesis is true, what would happen if we changed the brain's immune state? Antipsychotic drugs are known to suppress the immune system. Is that relevant to psychotic behavior? We are very interested in this possibility. In fact, Carlos Pardo of Johns Hopkins and I are organizing a meeting with the Cure Autism Now and Autism Speaks foundations to examine the possibility of immune intervention in autism. People take anti-inflammatory drugs such as aspirin to modulate their immune response all the time—is this a strategy worth exploring in this context?

We are just starting to explore the interactions between the immune system and the developing brain. Cytokines aren't the only possible conduit from a mother's infection to the fetus's developing brain—there are other changes brought about by corticosteroids, which are released following an infection or sickness, that also have effects on the fetus. And don't forget the genetic component—on what are those genes acting to increase the susceptibility? They might affect fetal brain development directly, or they might affect the brain's susceptibility to such other factors as cytokines, or the response of the placenta to the mother's immune activation, or they might even be acting in the mother, to affect her response to infection. We should be able to sort these possibilities out eventually, using this animal model.

Finally, I want to ask a question that's come up in the literature in the last few years—should we really be promoting universal maternal vaccination? The flu vaccine has been recommended routinely to pregnant women in the United States since 1957. The official policy of the Centers for Disease Control states that "administration of vaccines to women seeking prenatal care is an opportunity for preventative intervention that should not be wasted." Now you might say, "Well, of course, you don't want to get the flu if you're pregnant!" But remember that double-stranded RNA experiment—we activated the immune system, and it caused all these downstream effects on the fetus. And what does a vaccination do? It activates the immune system. That's the *point* of vaccination. In practice, not all pregnant women receive flu shots, and I think that universal vaccination of pregnant women could get us into a whole new set of problems. I'm hoping, therefore, that a way will be found to intervene somehow and repair the damage or reregulate the immune system. This mouse model is an excellent place to start. □



Vargas, et al. *Annals of Neurology*, vol. 57, no. 1, pp. 67–81, 2005, © 2004 American Neurological Association. Reprinted with permission of John Wiley & Sons, Inc.

Top: Purkinje cells (purple-blue dots) in a normal human cerebellum. Bottom: Nine of the 10 autistic brains analyzed showed patchy Purkinje cell loss.

Postdoc Natalia Malkova and friend.

Paul Patterson, the Biaggini Professor of Biological Sciences at Caltech and a research professor of neurobiological surgery at the Keck School of Medicine at USC, got his BA in biology at Grinnell College in Iowa in 1965, and his PhD from Johns Hopkins in 1970. He was a professor of neurobiology at the Harvard Medical School before coming to Caltech in 1983, following in the footsteps of his uncle, the late Professor of Geochemistry Clair Patterson. This article was adapted by Douglas Smith from a Watson lecture given May 17, 2005, at which Patterson was introduced by Caltech trustee Ted Jenkins (BS '65, MS '66), who has a schizophrenic son, and who with his wife, Ginger, underwrote the cost of the mice for the beginning of this work. Other support came from the late Ruben Mettler (BS '44, MS '47, PhD '49), the Cure Autism Now and Autism Speaks foundations, the Stanley Medical Research Institute, the McKnight Foundation, and the National Institute of Mental Health.

Mouse limos.

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Economic Burden of Childhood Autism Spectrum Disorders

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Abstract

OBJECTIVE: To estimate the associations between autism spectrum disorder (ASD) diagnoses and service use, caregiver time, and cost outcomes.

METHODS: We used national data from the Medical Expenditure Panel Survey linked to the National Health Interview Survey and a study-specific survey to estimate the annual utilization and costs for health care, school, ASD-related therapy, family-coordinated services, as well as caregiver time in children aged 3 to 17 years, with and without parent-reported ASD. Regression analyses estimated the association between ASD diagnosis and cost, controlling for child gender, age, race/ethnicity, insurance status, household income, country region and urban/rural classification, and non–ASD-related illnesses.

RESULTS: Children with parent-reported ASD had higher levels of health care office visits and prescription drug use compared with children without ASD ($P < .05$). A greater proportion of children in the ASD group used special educational services (76% vs 7% in the control group, $P < .05$). After adjusting for child demographic characteristics and non–ASD-associated illnesses, ASD was associated with $3020 (95% confidence interval [CI]: $1017–$4259) higher health care costs and $14 061 (95% CI: $4390–$24 302) higher aggregate non–health care costs, including $8610 (95% CI: $6595–$10 421) higher school costs. In adjusted analyses, parents who reported

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Dr Lavelle contributed to the conceptualization and design of the study, coordinated data collection, carried out all data analyses, drafted the manuscript, had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis; Drs Weinstein, Newhouse, Munir, and Prosser contributed to the conceptualization and design of the study and reviewed and revised the manuscript; Dr Kuhlthau contributed to the conceptualization and design of the study and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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that their child had ASD did not have significantly higher out-of-pocket costs or spend more time on caregiving activities compared with control parents.

CONCLUSIONS: The economic burden associated with ASD is substantial and can be measured across multiple sectors of our society. Previous analyses that focused on health care underestimated this economic burden, particularly for school systems.

Keywords

cost of illness; health economics; autism spectrum disorder

Over the past decade, the prevalence of autism spectrum disorder (ASD) diagnoses has increased considerably. The most recent data released from the Autism and Developmental Disabilities Network reveal a 78% increase in ASD prevalence between 2002 and 2008,[1] and data from the National Survey of Children's Health reveal that the prevalence of parent-reported ASD among children aged 6 to 17 years increased from 1.2% in 2007 to 2.0% in 2011–2012.[2] The increasing prevalence highlights a growing need for resources to provide care for this population of children. Studies have shown that families of children with ASD face high out-of-pocket costs.[3–9] To date, however, there has not been a comprehensive pediatric cost analysis of ASD in the United States. Previous analyses have mainly focused on health care,[8–13] despite evidence that costs incurred outside of the health care system may play a more important role in the total economic burden of ASD.[3,14]

In this study, we used data from 3 national sources to estimate the total economic costs associated with pediatric ASD and the out-of-pocket costs specifically borne by families. We compared the following sources of cost for children with and without parent-reported ASD: the annual utilization of health care, school, ASD-related therapy, family-coordinated services, and caregiver time.

METHODS

Study Samples

Study samples included children between the ages of 3 and 17 years with and without parent-reported ASD. To estimate annual health care utilization and costs, we linked observations from the cross-sectional Medical Expenditure Panel Survey (MEPS) to the Sample Child Core questionnaire in the National Health Interview Survey (NHIS).[15,16] The NHIS is administered each year to a new sample of US households with noninstitutionalized adults and children. General health data are collected from all members of the sampled households, and more detailed health information is collected on 1 child in the household for the Sample Child Core questionnaire. In this study, children with a positive response to the NHIS Sample Child Core question "Has a doctor or health care provider ever told you that [child's name] has autism?" were assigned to the ASD group. The control group was composed of children with a negative response. The MEPS collects more detailed health care utilization and expenditure data from a representative subset of households from the previous year's NHIS sample, and follows this sample subset over a 2-year period.

We used individual ID numbers to link 23 057 observations of children who had records in both the NHIS Sample Child Core from 2001 to 2007 and the MEPS from 2003 to 2008. These linkable observations were 19% of the total NHIS Child Core sample and 13% of the MEPS sample. Twelve children were eliminated from the linked sample for not having an indicator of ASD illness, and an additional 4161 children were eliminated for being outside of the 3- to 17-year age range when their MEPS data were collected, which left a final sample size of 18 884 (109 children with parent-reported ASD and 18 775 controls; Fig 1).

To estimate non–health care utilization and expenditures, a survey was administered to 2 groups of parents enrolled in a survey research panel managed by GfK Custom Research, LLC. This research panel is nationally representative; new panel members are currently recruited by mail by using probability sampling from a published address–based sample frame that covers ~98% of US households.[17] Of all households initially contacted to join the survey panel along with our study sample, 16% had at least 1 household member who was successfully recruited. Panel members are asked to complete online surveys 3 to 4 times per month. Those without previous Internet access are provided with a laptop computer and Internet service while on the panel; those with Internet access are given small monthly stipends in exchange for their participation.[18] All panel members are asked to complete a series of profile questions to determine their eligibility for specific surveys.

A total of 201 potential respondents for our ASD group were randomly sampled from all survey panel members who had previously indicated on their GfK profile survey that they were the caregiver of a child under 18 years with autism or Asperger's, and 204 potential respondents for our control group of parents of children without ASD were randomly selected from all parents on the panel who had a negative response to this profile question.

A link to a screener questionnaire was e-mailed to the 405 survey panel members during October 2011. Screener questions asked parents whether they had a child between the ages of 3 and 17 years, and whether any of their children in this age range had been diagnosed with ASD, including autism, Asperger's syndrome, or pervasive developmental disorder, not otherwise specified (PDD-NOS). Those in the ASD group who responded positively to both questions were then asked to complete a 25-minute online survey; those in the control group were asked to continue onto the survey if they had a child in this age range and no children in the range with ASD.

We received responses from 72% ($n = 145$) of parents in the ASD group and 67% ($n = 136$) of controls after 2 e-mail reminders. Compared with nonrespondents, respondents were more likely to have previous Internet access ($P < .01$) and a bachelor's degree or higher ($P = .04$), but other demographic characteristics were not statistically different.

Twenty-three respondents were excluded from the sample at the screening stage on the basis of age and diagnosis criteria, 8 from the ASD group and 15 from the control group, leaving a final sample size of 258 (137 ASD, 121 controls; Fig 1). This study was approved by the Harvard University Institutional Review Board. All data were deidentified, and no informed consent was required.

Outcomes and Study Variables

Our primary outcomes of interest were annual utilization and costs for health care, school services, ASD-related therapies, family-coordinated services, and caregiver time (full classification of each category available in Supplemental Table 5). We estimated total costs for each category and family out-of-pocket costs for all services.

We measured health care utilization for all categories reported in the MEPS data set including hospitalizations, office and emergency department visits, home health care, dental care visits, and prescription drug use. Total costs were assessed by using payments from all sources, including household and insurance payments; out-of-pocket costs were derived from household payments only.

School resource utilization was examined broadly by type of school (public, private day, residential, home, or other), classroom type (special, general education), and whether the child qualified for and used special education services through an Individualized Education Program. Children were categorized into 11 mutually exclusive school placements on the basis of their school type, special education use, and age. Previously published unit cost estimates for total annual education expenditures by school placement type were applied to these classifications to estimate the annual education costs at all public and residential schools, as well as private schools providing special education services (Supplemental Table 6).[19–22] Reported tuition expenditures from all sources were used to assess the total cost of educating children in private day schools without any special education services. Out-of-pocket costs for all school placements were based on the reported family tuition expenditures.

We used the parent survey to measure utilization and expenditures for ASD-related therapies that were not included in the MEPS data. These include treatments such as applied behavioral analysis, sensory integration, and communication therapies. All other resources used to care for children with parent-reported ASD are categorized as “family-coordinated services” for the purposes of this analysis. This is a broad category that includes items such as child care, legal services, and transportation. Costs for ASD-related therapies and family-coordinated services were based on reported expenditures by the family or other source excluding their school system (ie, insurance, Department of Developmental Services, charity, foundation, scholarship, fellowship). Out-of-pocket costs reflect family expenditures only.

Caregiving time was measured as the amount of time all caregivers in the household had reportedly spent on activities such as coordinating their child’s therapies, homework help, and travel to appointments and activities during the previous 12 months. Time costs were converted to a dollar value by multiplying the number of hours spent on each caregiving activity by the 2011 mean wage rate for all US workers ($23/hour).[23]

Our study survey and MEPS provided data on child demographic characteristics, health insurance coverage, geographic region, household income, and health conditions. In our survey we asked parents of children with ASD to report their child’s specific diagnosis (autism, Asperger’s syndrome, or PDD-NOS) and the severity of the child’s social

communication problems and restricted interests/repetitive behavior domains. A 3-level composite severity score (mild, moderate, severe) was derived on the basis of the reported severity levels on these 2 domains (Supplemental Fig 3).

Analyses

We compared demographic and clinical characteristics for the ASD and control groups by using χ^2 tests. We compared service utilization and caregiving hours for the ASD and control groups by using χ^2 tests for categorical measures and nonparametric Kolmogorov-Smirnov tests for continuous measures.[24] To estimate the association between ASD diagnosis and cost outcomes, we used generalized linear models (GLMs) with a log link function.[25] The GLM was used in combination with a logit model to create a 2-part model for cost categories with ≥50% zero-cost observations. For analyses of health care costs we used the generalized estimating equation extension of the GLM to account for the multiple observations per subject in the sample, and also evaluated a 2-part model in a sensitivity analysis.

In adjusted analyses we controlled for variables that had previously been identified as having an impact on costs, independent of health status.[9,26–29] These included child gender, age, race/ethnicity, insurance status, household income, geographic region, and urban/ rural classification. We also controlled for the presence of other illnesses that do not have an established association with ASD[30,31] and that were available in all data. These included allergies, arthritis, asthma, cerebral palsy, cystic fibrosis, diabetes, diarrhea/colitis, Down syndrome, hearing impairment, heart disease, muscular dystrophy, sickle cell anemia, and vision impairment. In sensitivity analyses we added an indicator variable for the presence of epilepsy or intellectual disability to our model, to evaluate the influence of controlling for these conditions with established associations with ASD.[32,33]

Confidence intervals (CIs) around all mean values and regression coefficients were estimated using nonparametric bootstrapping procedures.[34] The goodness of fit of each GLM was measured by using a test of concordance between the observed and predicted costs.[35] All cost data were updated to 2011 US dollars by using the Gross Domestic Product deflator.[36] To reduce the influence of outliers, costs derived from MEPS and the study survey were truncated at the 99th and 90th percentiles, respectively.

RESULTS

Study Samples

In both study samples, children with parent-reported ASD were significantly more likely than controls to be male, over the age of 5 years, and non-Hispanic white. Children with parent-reported ASD were also significantly more likely to have certain comorbid conditions, including allergies, attention-deficit/hyperactivity disorder, and intellectual disability ($P < .05$ for all; Table 1).

Resource Utilization

Ninety-two percent of children in the ASD group had used some form of health care during the year compared with 82% in the control group ($P = .01$). On average, children with parent-reported ASD had significantly higher levels of physician and nonphysician office visits and prescription drug use compared with children in the control group ($P < .05$ for all). Other health care service use did not differ significantly between the 2 groups (Table 2).

School placements differed significantly between the ASD and control groups. A greater proportion of children in the ASD group attended public school or were home schooled (85%) during the year compared with the control group (65%). Seventy-six percent of the children in the ASD group used special education services through an Individualized Education Program compared with 8% in the control group ($P < .05$ for all; Table 3). The use of special education services ranged from 73% for children with mild ASD to 91% for children with severe ASD, and was least likely among children with a specific diagnosis of Asperger's syndrome, although differences between subgroups were not statistically significant (Supplemental Tables 7 and 8).

Thirty-one percent of children with parent-reported ASD used some form of ASD-related therapy during the year, such as applied behavior analysis or sensory integration therapy. Compared with children in the control group, a significantly greater proportion of children in the ASD group used legal aid, private academic tutors, or private school observation services ($P < .05$ for all; results not shown). Total caregiving hours did not differ significantly between the groups.

Costs

Having ASD was significantly associated with $3020 (95% CI: $1017–$4259) higher health care costs after adjusting for demographic and non–ASD-associated illnesses in our primary analysis. Regression-adjusted school costs were $8610 (95% CI: $6595–$10 421) higher for children with ASD. Costs associated with ASD-related therapies and other family-coordinated services were not significantly higher in the ASD group, nor were caregiving time costs. When the 3 non–health care categories were examined in aggregate, however, their total cost was $14 061 (95% CI: $4390–$24 302) higher in the ASD group. Out-of-pocket costs were not significantly higher for the ASD group in any category (Table 4; full models for health care and aggregate non–health care costs are shown in Supplemental Tables 9 and 10). Concordance coefficients for all models ranged from 0.08 to 0.73 and were all significantly greater than zero, indicating a significant and positive correlation between observed and predicted costs.

In sensitivity analyses, the association between ASD and health care costs decreased to $2373 (95% CI: $902–$3695) when modeled by using a 2-part model. The association between ASD and out-of-pocket health care costs became significant in a 2-part model, with the ASD group having $154 (95% CI: $3–$344) higher costs compared with controls. Health care costs were no longer significantly higher in the ASD group when we controlled for the presence of epilepsy or intellectual disability. The association between ASD and aggregate

non–health care costs decreased to $10 508 (95% CI: $725–$20 586) when we controlled for these comorbidities.

In subgroup analyses, regression-adjusted aggregate non–health care costs were significantly higher for mild, moderate, and severe ASD, compared with no ASD, and increased with each severity level (Supplemental Table 11). A specific diagnosis of autism was associated with higher aggregate non–health care costs, but specific diagnoses of Asperger's syndrome and PDD-NOS were not (Supplemental Table 12). Each severity level and subtype of ASD significantly predicted higher school costs. The most severe level of ASD was significantly associated with $21 313 (95% CI: $6556–$39 473) higher caregiver time costs compared with a child without ASD (Fig 2). Similar to the overall group, this significant association did not persist among children with less severe levels of ASD, or among any of the 3 specific subtypes of ASD.

DISCUSSION

This is the first study to our knowledge to provide comprehensive estimates of the total economic burden of childhood ASD. Using 3 national data sets, we found that the additional costs of caring for a child with parent-reported ASD, including health care, education, ASD-related therapy, family-coordinated services, and caregiver time, totaled $17 081 per year. Applying these estimates to the projected 673 000 children aged 3 to 17 years in the United States with ASD,[37] the total societal costs of caring for this group of children were $11.5 billion in 2011.

Despite the literature's emphasis on estimating health care costs for this population of children, we find that these costs are not the main contributor to the overall economic burden of this disorder. Of the estimated $17 000 additional costs we found to be associated with childhood ASD annually, only 18% were attributable to the increased use of health care services, specifically office visits and prescriptions. Our estimated health care costs are within the range of previously derived estimates, which show additional costs for children with ASD ranging from $2191 to $11 590 per year (2011 US dollars).[8–13] Differences in data sources, comparison groups, and analytic methods contribute to the substantial variation in these results.

School services were the biggest contributor to costs associated with childhood ASD due to the increased use of special education services in this group. Although previous studies have estimated costs for children with ASD in special education,[19] this is the first study to estimate educational costs for all children with parent-reported ASD. The results highlight the economic burden placed on this sector and the need for policies to ensure that resources are available to school systems to provide needed services in the future. Under federal law, students with disabilities are entitled to special education and related services through age 21. Previous research has suggested that after this time the cost burden may shift to sectors that provide adult-based services.[3]

Previous studies on this topic are limited, particularly in the United States. A study of children with ASD in a Swedish municipality reported the additional annual cost associated

with this disorder to be ~€50 000 per child ($68 000 in 2011 US dollars),[38] and a study of children with ASD in the United Kingdom reported an additional annual per capita cost of ~ £25 000 ($44 063 in 2011 US dollars).[39,40] In the United States, Ganz[3] estimated the additional lifetime costs associated with ASD to be $3.2 million per person ($3.8 million in 2011), including the costs for health care, special education, child and adult care, respite services, supported employment, and lost productivity. Although these estimates indicate a greater economic burden than one would infer from our study, direct comparisons between studies are not possible due to different country settings and different time horizons of the analyses.

Previous studies have also found that parents of children with ASD endure substantial financial burdens, in the form of high out-of-pocket costs, and decreased workforce involvement.[3–9] In our study we did not find that parents of children with ASD in the overall group had higher out-of-pocket costs or spent more time on caregiving activities compared with parents of children without ASD. We did find that parents in the ASD group reported more time than those in the control group on several specific caregiving activities, such as coordinating their child's medical care and therapy and providing homework help, and reported less time on "general daily household caregiver activities." This shift from general to specific caregiving activities for parents of children with ASD is important to note, because it could have important implications for the care of other children in the household. More studies are needed to provide a better understanding of the financial impact of ASD on families and how it may be evolving over time, particularly as states continue to enact legislative mandates requiring private insurance companies to cover additional ASD-related services.[41] One study found that families of children with ASD living in states with ASD-specific parity laws were less likely to have health-related out-of-pocket expenditures compared with families living in states without mandates.[42]

We did find that having a child with the most severe level of ASD was associated with higher caregiving time costs. We accommodated social communication problems and restricted interest/repetitive behaviors domains in our composite assessment of severity, which is unique for this study. It is important to note that there is currently no universal tool used to assess the severity of children with ASD.[43] In light of the recent revision of the *Diagnostic and Statistical Manual of Mental Disorders (Diagnostic and Statistical Manual of Mental Disorders*, *Fifth Edition*), which collapses subtypes of ASD into 1 diagnosis,[44] these results emphasize the importance of a consistent measure of severity that can provide important categorizations of this broad disorder. Diagnoses of ASD under the *Diagnostic and Statistical Manual of Mental Disorders*, *Fifth Edition,* include level of severity assessments for social communication and restricted, repetitive behaviors. Such classifications could help to quickly identify families who may face increased caregiving demands.

Some limitations of the study must be noted. Due to the observational nature of our study we are not able to draw causative conclusions. Relatively small sample sizes may have limited our ability to detect important cost differences. Although our study benefited from national samples, these samples were different for our health care and non–health care analyses, and were not necessarily representative of the broader populations of families of children with

and without ASD. In particular, low recruitment rates for the panel used for our survey of non–health care utilization may have contributed to selection bias. Controlling for observed demographic variables in adjusted cost analyses allowed us to mitigate the impact of potential selection biases, but the impact of unmeasured confounding variables on our estimates is not known. We also controlled for comorbidities in our regression analyses that do not have an established association with ASD,[30,31] but if a causal association does exist between any of these conditions and ASD, then our adjusted results will underestimate the total costs attributable to ASD.

Linking MEPS data to the NHIS allowed us to identify children with parent-reported ASD who did not have any health care use, but identification through the NHIS has some limitations. Specifically, parents are asked report whether their child has ever been diagnosed with autism, not ASD, and diagnoses of Asperger's syndrome and PDD-NOS may be underreported. In addition, diagnoses of ASD do not necessarily remain stable over time.[1,37,45] If there was any misclassification between our ASD and control groups at the time of resource utilization, then our findings may be biased toward the null.

All diagnoses were ascertained via parent report; previous research has revealed that parent report of ASD is highly reliable when verified against professional diagnostic documentation,[46] but limited data are available about the reliability of parent report of specific diagnoses within the spectrum and misclassification may have occurred. Parent report was also used to document caregiver time and non–health care service utilization and expenditures over the previous 12 months. This time interval was chosen to include both the school year and summer time, 2 periods during which the intensity of services and time commitments may be different, but the long recall period may have led to underreporting.[47]

The results of this study reveal the current economic costs associated with caring for children with ASD, but they do not address how current investments may lead to a change in the future trajectory of services required. This study also does not indicate whether these costs reflect an optimal level of resources, or whether resources are being used efficiently, which highlights the need for cost-effectiveness analyses to provide guidance on how to improve the allocation of resources devoted to ASD.[48] And finally, this study addresses only the cost burden associated with ASD, and not the impact that ASD has on the health and well-being of family members; previous research has shown that children with ASD and their families have diminished health-related quality of life.[49]

CONCLUSIONS

There is a large economic burden associated with caring for a child with ASD, a substantial portion of which is borne by the educational system, principally the cost of special education services in public schools. These costs have been underrecognized. Families of children with the most severe level of symptoms also face large caregiving demands and severity measures may help highlight those in greatest need for support. Comprehensive policies are needed to ensure that funds are allocated to meet the needs of this population, and future cost-effectiveness analyses should inform how these funds are spent to ensure the best possible outcomes for children with ASD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

ASD	autism spectrum disorder
CI	confidence interval
GLM	generalized linear model
MEPS	Medical Expenditure Panel Survey
NHIS	National Health Interview Survey
PDD-NOS	pervasive developmental disorder, not otherwise specified

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WHAT'S KNOWN ON THIS SUBJECT:

Previous analyses have documented increased health care costs for children with autism spectrum disorders but have not provided comprehensive estimates of the total economic burden.

WHAT THIS STUDY ADDS:

There are substantial additional costs associated with caring for children with autism spectrum disorders, amounting to >$17 000 per child annually. Costs accrued outside of the health care system account for the majority of the financial burden.

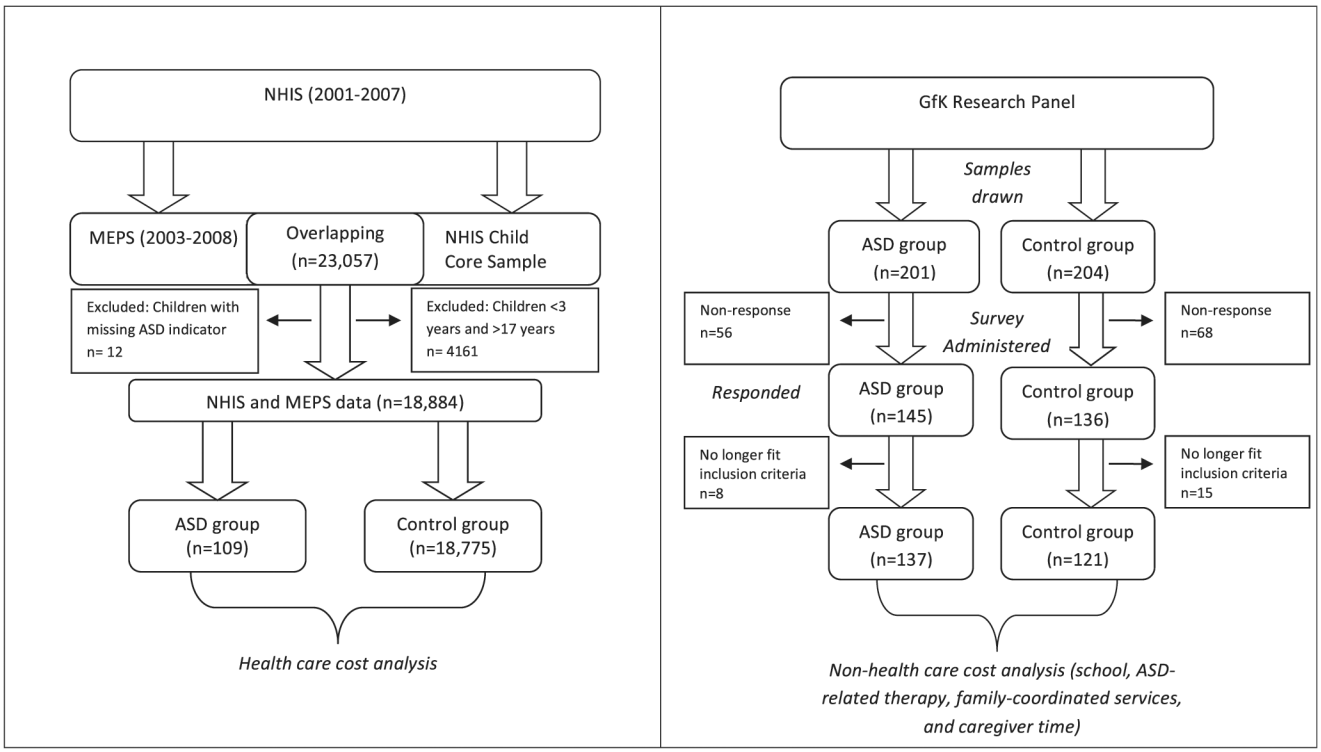


FIGURE 1.
Study inclusion flowcharts for health care and non–health care analyses.

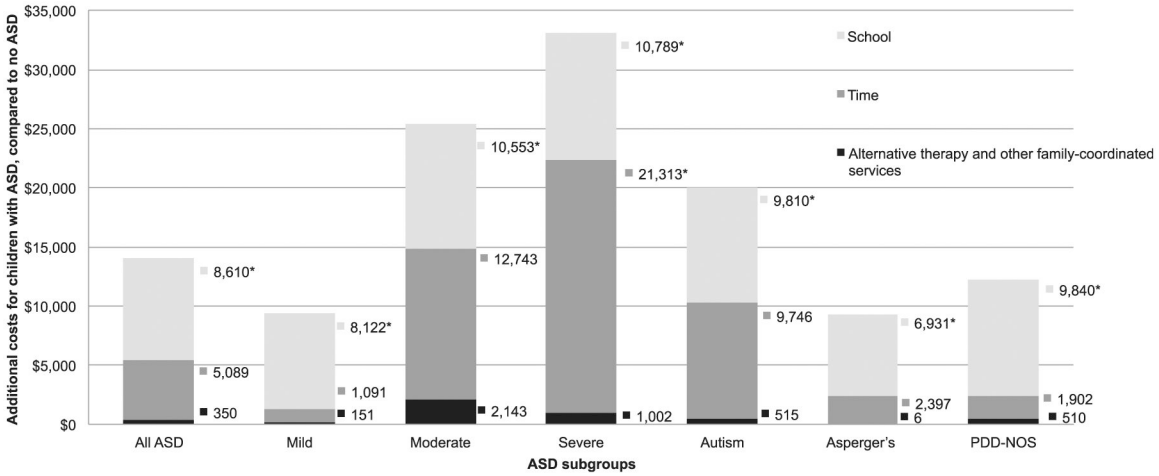


FIGURE 2.

Regression-adjusted differences in non–health care costs for children with ASD compared with children without ASD, by severity and diagnostic subgroups.

*Statistically significant difference compared to children without ASD ($P < .05$).

TABLE 1

Child Demographic and Clinical Characteristics

Characteristic	MEPS			Study Survey		
	ASD (*n* = 109), %	Control (*n* = 18 775), %	*P*	ASD (*n* = 137),%	Control (*n* = 121), %	*P*
Male	83.7	51.2	<.01	80.3	65.3	.01
Age			<.01			.01
3–5 years	9.2	22.7		8.0	21.7	
6–10 years	49.5	31.2		32.9	34.2	
11–13 years	21.1	18.8		24.1	18.3	
14–17 years	20.2	27.3		35.0	25.8	
Insurance			.01			.35
Any private	59.6	51.4		71.3	66.7	
Public only	37.6	40.7		25.7	26.7	
None	2.8	7.9		2.9	6.7	
Race/ethnicity			.02			<.01
White, non-Hispanic	60.6	41.2		82.5	68.6	
Black, non-Hispanic	11.0	18.6		4.4	10.7	
Hispanic	21.1	32.8		7.3	2.5	
Non-Hispanic, other	7.3	7.4		5.8	18.2	
Region			.88			.87
Northeast	18.4	14.9		20.4	21.5	
Midwest	18.4	19.0		23.4	19.0	
South	34.9	38.6		31.4	33.9	
West	28.4	27.5		24.8	25.6	
MSA						
Urban	91.7	83.1	.01	84.7	85.1	.92
Income (% of FPL)			.03			.85
≤100%	13.8	25.0		11.0	12.4	
100% to 199%	25.7	26.3		24.1	19.8	
200% to 299%	39.5	27.6		20.4	19.8	
≥300%	21.1	21.1		44.5	48.0	

Characteristic	MEPS			Study Survey		
	ASD (*n* = 109), %	Control (*n* = 18 775), %	*P*	ASD (*n* = 137), %	Control (*n* = 121), %	*P*
Comorbid health conditions						
Allergies[a]	44.0	25.1	<.01	51.1	18.2	<.01
Anxiety	NA[b]	NA	NA	34.3	5.0	<.01
Asthma	19.3	13.6	.27	10.2	9.9	.94
Attention-deficit/hyperactivity disorder	44.0	6.1	<.01	43.8	8.3	<.01
Bipolar	NA	NA	NA	3.7	1.7	.32
Cerebral palsy	1.8	1.8	.97	3.7	0.0	.03
Depression	NA	NA	NA	6.6	2.5	.12
Epilepsy	0.0	0.2	.63	7.3	0.0	<.01
Gastrointestinal	8.3	1.7	.06	8.8	0.8	<.01
Hearing problem	4.6	3.0	.49	2.9	0.8	.22
Heart disease[c]	5.5	1.5	.16	1.5	0.0	.18
Intellectual disability	15.6	0.5	<.01	18.3	0.0	<.01
Obsessive-compulsive disorder	NA	NA	NA	18.3	2.5	<.01
Sleep disorder	NA	NA	NA	10.2	2.5	.01
Vision problem	0.9	2.4	.1	5.8	0.8	.03

P values were calculated by using χ^2 tests. All comparisons are based on unweighted data. FPL, Federal Poverty Level; MSA, Metropolitan Statistical Area; NA, not available.

[a] Includes hay fever, respiratory allergy, food/digestive allergy, and eczema/skin allergy.

[b] Not available in the MEPS data set.

[c] Congenital or other.

TABLE 2

Health Care Utilization

Health Care Resource Category	ASD			Control			*P*
	Mean	95% CI	Median	Mean	95% CI	Median	
Nights in inpatient hospital	0.3	0.0–0.7	0.0	0.1	0.1–0.1	0.0	.1
Outpatient visits (total)	10.7	5.8–16.3	4.0	3.7	3.7–3.9	2.0	.04
Outpatient hospital[a]	0.3	0.0–0.6	0.0	0.1	0.1–0.2	0.0	.38
Physician office	5.2	2.8–7.6	2.0	1.8	1.7–1.9	1.0	.02
Nonphysician office[b]	3.1	1.9–5.5	0.0	0.7	0.7–0.8	0.0	<.01
Emergency department	0.1	0.1–0.2	0.0	0.2	0.2–0.2	0.0	.13
Home health care visits[c]	11.6	0.3–19.9	0.0	0.3	0.2–0.4	0.0	.12
Dental care visits	1.2	0.9–1.7	1.0	1.1	1.1–1.2	0.0	.82
Prescription medications with refills	11.4	7.4–16.3	3.0	2.6	2.5–2.7	0.0	<.01

95% CIs are bootstrapped by using a clustered variance to account for multiple observations per person.

[a] Physician and nonphysician visits.

[b] Includes chiropractors, midwives, nurses and nurse practitioners, optometrists, podiatrists, physician assistants, physical therapists, occupational therapists, psychologists, social workers, technicians, and receptionists/clerks/secretaries.

[c] Includes agency and nonagency home health care.

TABLE 3

School Resource Utilization

	ASD, %	Control, %	P
School type			<.01
Public, nonresidential	78.1	62.1	
Private, nonresidential	8.8	18.1	
Residential school	3.7	8.6	
Home school	6.6	2.6	
No school	0.7	6.9	
Other	2.2	1.7	
Classroom type[a]			<.01
General education only	50.8	93.5	
General and special education	37.1	4.4	
Special education only	12.1	1.1	
Other	0.0	1.1	
Educational accommodations			<.01
Individualized Education Program[b]	75.7	7.5	
504 Plan[c]	4.4	4.7	
None	19.9	87.9	

[a]Among those children enrolled in public, private, residential or other schools. Does not include children who are home schooled.

[b]Indicates eligibility for, and use of, special education services in public schools. It contains information regarding the child's present level of functioning, goals, and services to be provided.

[c]A 504 Plan is a document for children in public schools with physical or mental health disabilities who are not eligible for special education services. It lists special accommodations required by the child so that he or she may participate in the general classroom setting and educational programs.

TABLE 4

Summary of the Regression-Adjusted Difference in Costs for Children With ASD Compared With Children Without ASD

Category	Total costs,[a] $	95% CI	Out of pocket costs[a], $	95% CI
Health care	3020	1017 to 4259	182	−6 to 299
Total aggregate non–health care	14061	4390 to 24 302	−112	−715 to 749
School	8610	6595 to 10 421	−462	−3496 to 189
ASD-related therapy and other family-coordinated services	350	−76 to 972	81	−318 to 523
Time	5089	−1672 to 11 936	—	—

[a] Adjusted for child gender, age, race/ethnicity, insurance status, household income, geographic region, urban/rural classification, and the presence of a comorbidity not related to ASD.

EXHIBIT 69

New Research Finds Annual Cost of Autism Has More Than Tripled to $126 Billion in the U.S. and Reached £34 Billion in the U.K.

Lifetime Care of Individuals with Autism Highest for Those with Intellectual Disability $2.3 Million U.S. and £1.5 Million U.K.

New York, N.Y. (March 28, 2012) – Autism Speaks, the world's leading autism science and advocacy organization, today announced preliminary results of new research that estimates autism costs society a staggering $126 billion per year (U.S.) – a number that has more than tripled since 2006, and annually in the U.K. has reached more than £34 billion (equivalent to $54 billion U.S.).

The costs of providing care for each person with autism affected by intellectual disability through his or her lifespan are $2.3 million in the U.S. and £1.5 million ($2.4 million) in the U.K. The lifetime costs of caring for individuals who are not impacted by intellectual disability are $1.4 million in the U.S. and £917,000 in the U.K. (equivalent to $1.46 million).

The Autism Speaks-funded research, conducted by researchers Martin Knapp, Ph.D., of the London School of Economics, and David Mandell, Sc.D., of the University of Pennsylvania, will be presented at the international conference "Investing in our Future: The Economic Costs of Autism," hosted by Goldman Sachs in collaboration with the Child Development Centre and Autism Speaks, on March 31 in Hong Kong.

Drs. Knapp and Mandell compiled information from recent studies of autism costs from multiple sources to calculate the current cost of autism associated with the current CDC-reported prevalence that 1:110 children are diagnosed with an autism spectrum disorder (ASD). The cost of autism continues to grow with the rise in prevalence. While the latest prevalence estimates in the U.S. and U.K. are comparable, the primary difference in total costs of autism in the U.S. and U.K. are due to differences in total country population (five times larger in the U.S. than the U.K.). The research team found that the cost of autism in the U.S. alone is greater than the entire Gross Domestic Product (GDP) of 139 countries around the world.

Bob Wright, co-founder of Autism Speaks, said, "Autism is a global public health crisis. The costs are staggering and will continue to rise as prevalence continues to increase. We know that early diagnosis and treatment are critical, so it is imperative that the U.S. and governments around the world step up their commitment to helping people living with autism today. The investment we make now is essential to reducing the long-term costs of autism."

This research found that intellectual disability plays a major role in the cost of autism to individuals, families, and society as a whole. The costs of autism per year are nearly twice as high on average for children and adults with intellectual disability than for children and adults without intellectual disability, $2.3 million in the U.S. and £1.5 million in the U.K. ($2.4 million) for those individuals who are impacted by intellectual disability compared with more than $1.4 million in the U.S. and £917,000 ($1.46 million) in the U.K. for those who do not have intellectual disability.

A number of factors were considered by the researchers that contributed to the cost differential between U.S. and U.K. lifetime and total costs. The education and healthcare systems in the two countries offer different responses to the needs of people with autism and their families. Access to empirical data regarding healthcare and education costs differed between the two countries. It is also currently estimated that 45 percent of individuals with ASD in the U.S. and 55 percent of individuals with ASD in the U.K. have intellectual disabilities, defined as an IQ of 70 or less. Experts consistently point to early interventions as key to increasing language and IQ scores, and reducing life span costs.

Total costs to the U.S. were also based on adult prevalence of one-half of one percent, lower than currently estimated 1:110 prevalence of autism in children, derived from past CDC studies. The researchers point to adult prevalence as an area for additional study in the U.S.

The research also found that non-medical costs account for the greatest proportion of expenses. While direct medical costs, such as outpatient care, home care, and pharmacy, contribute significantly to overall expenses, non-medical costs, including intervention services and special education, child daycare, and especially residential placements and care for adults who age out of school and can no longer live at home with parents account for the largest proportion of autism costs.

“The burden on families affected by autism is enormous,” continued Autism Speaks President Mark Roithmayr. “The extraordinary cost further exacerbates that burden. The time and effort involved in coordinating the care and treatment plan across a large number of providers has reduced the ability of many families to earn a living. Too many families are still denied insurance coverage for essential treatments and services, and the economics add to overall emotional burden on families.”

Building on this preliminary research, Autism Speaks recently provided additional funding to Drs. Knapp and Mandell to support an additional year of study to examine how autism therapies reduce lifetime costs associated with autism. Their investigation will focus on both intensive preschool behavioral interventions and vocational interventions that support an individual’s independence during the transition to adulthood. Calculations will take into account costs related to healthcare, education, caregiving, housing, and employment.

As confirmed by this study, the majority of costs related to autism are incurred during adulthood, principally due to the cost of residential care as well as loss of productivity, underemployment and unemployment among adults with autism. Services for adults are both lacking and expensive.

In 2007, Michael L. Ganz, Ph.D. of the Harvard School of Public Health published research in the journal *Archives of Pediatric and Adolescent Medicine* which estimated that autism cost the United States more than $35 billion per year, and that the incremental cost of caring for an individual with autism over his or her lifetime due to their special needs was more than $3 million. Despite growing prevalence, autism currently receives less than five percent of the research funding of many less prevalent childhood diseases and disorders.

Dr. Mandell added, “We are paying for the costs of inaction and the costs of ‘inappropriate action.’ Social exclusion of individuals with autism and intellectual disability, and exclusion of higher-functioning individuals from employment opportunities are increasing the burden not only on these individuals and their families, but on society as a whole.”

Dr. Mandell and his colleagues recently published findings in *Pediatrics* that mothers of children with ASD are less likely to work, work fewer hours per week and earn substantially less. Typically the primary caregiver, mothers are called upon to serve as their child’s case manager and advocate, and on average, earn 56 percent less than mothers of children with no health limitations. They earn 35 percent less than mothers of children with another health limitation. They are 6 percent less likely to be employed, and they work an average of seven hours less per week.

Dr. Knapp, Professor of Social Policy at the London School of Economics and Political Science and a preeminent expert on health economics explained that the economic burden of autism varies widely across different parts of society from the individuals with ASD, their families, the communities they live in, businesses in those communities, to the government agencies which provide healthcare, education, welfare benefits, social care, and housing. “There is an immediate need for better coordination across public agencies and levels of government from local to national in the way that society structures its service delivery system; too often responses to the needs of individuals and families are piecemeal and less helpful than they could be,” he concluded.

This research was wholly funded by Autism Speaks. The World Health Organization (WHO), through its partnership with Autism Speaks, is serving in an advisory capacity and providing technical support for the cost of autism analysis.

About Autism

Autism, or autism spectrum disorder, refers to a broad range of conditions characterized by challenges with social skills, repetitive behaviors, speech and nonverbal communication. We now know that there is not one autism but many subtypes, and each person with autism can have unique strengths and challenges. A combination of genetic and environmental factors influence the development of autism, and autism often is accompanied by medical issues such as GI disorders, seizures and sleep disturbances. Autism affects an estimated 1 in 59 children.

About Autism Speaks

Autism Speaks is dedicated to promoting solutions, across the spectrum and throughout the life span, for the needs of individuals with autism and their families. We do this through advocacy and support; increasing understanding and acceptance of people with autism spectrum disorder; and advancing research into causes and better interventions for autism spectrum disorder and related conditions.

EXHIBIT 70

Attention-deficit hyperactivity disorder | definition of attention-deficit hyperactivity disorder by Medical dictionary

https://medical-dictionary.thefreedictionary.com/attention-deficit+hyperactivity+disorder

←

attention-deficit hyperactivity disorder

Also found in: **Dictionary**, **Thesaurus**, **Encyclopedia**, **Wikipedia**.
Related to attention-deficit hyperactivity disorder: **ADD**

attention-deficit hyperactivity disorder ,ADHD

A persistent pattern of inattention, hyperactivity and impulsivity, or both, occurring more frequently and severely than is typical in those at a comparable level of development. ADHD is the most commonly reported neurobehavioral disorder of childhood. The illness may begin in early childhood but may not be diagnosed until after the symptoms have been present for many years. The prevalence is estimated to be 3% to 5% in children; 4% in adults.

Symptoms

Signs may be minimal or absent when the person is under strict control or is engaged in esp. interesting or challenging situations. They are more likely to occur in group situations. Although behaviors vary widely, affected people typically exhibit motor restlessness, impulsivity, and difficulty concentrating on a single task or chore. They tend to do more poorly in school than one might predict based on assessments of their intelligence alone. While characteristics of ADHD are found in many people at one time or another, a key feature of ADHD is the excessive or unusual pattern of behavior outside normal bounds of exuberance or excitement. The findings must be severe enough to be maladaptive and inconsistent with specified levels of development, and last at least six months.

Diagnosis

CAUTION!

ADHD may sometimes be confused with other disorders.

The disorder is difficult to diagnose in children under age 5. It is important to distinguish ADHD from age-appropriate behavior in active children and from disorders such as mental retardation, primary learning disabilities, alteration of mood, anxiety, petit mal seizures, or personality changes caused by illness, family stress, or drugs. The criteria determined by the American Psychiatric Association include specific limits concerning the duration and severity of symptoms of inattention and hyperactivity-impulsivity. The findings must be severe enough to be maladaptive and inconsistent with specified levels of development.

Treatment

In both children and adults, the domestic, school, social, and occupational environments are evaluated to determine contributing factors and their relative importance. Standard treatment includes behavioral and psychological therapy, environmental changes, and medication. Medications commonly used to treat ADHD include methylphenidate, dextroamphetamine, atomoxetine, and pemoline. These agents, with the exception of atomoxetine, are central nervous system (CNS) stimulants. Adverse reactions to CNS stimulants include decreased appetite, difficulty sleeping, anxiety, stomach ache, headache, jitteriness, and social withdrawal (the latter in children).

Behavior therapy for patients with ADHD includes positive reinforcement, time-out, response cost (loss of rewards or privileges for problem behaviors) and token economy (a combination of positive reinforcement and response cost). Combinations of drug therapy and behavioral therapies, or drug therapies alone, appear to have a more beneficial effect than behavioral therapy, psychotherapy, or parent skills training alone.

Attention-deficit hyperactivity disorder (ADHD)

A condition in which a person (usually a child) has an unusually high activity level and a short attention span. People with the disorder may act impulsively and may have learning and behavioral problems.

Mentioned in: **Central Nervous System Stimulants**

EXHIBIT 71

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Attention-Deficit / Hyperactivity Disorder (ADHD)

Data and Statistics About ADHD

CDC uses datasets from parent surveys and healthcare claims to understand diagnosis and treatment patterns for attention-deficit/hyperactivity disorder (ADHD). Estimates for diagnosis and treatment can vary depending on the source. This page includes ADHD data from different sources.

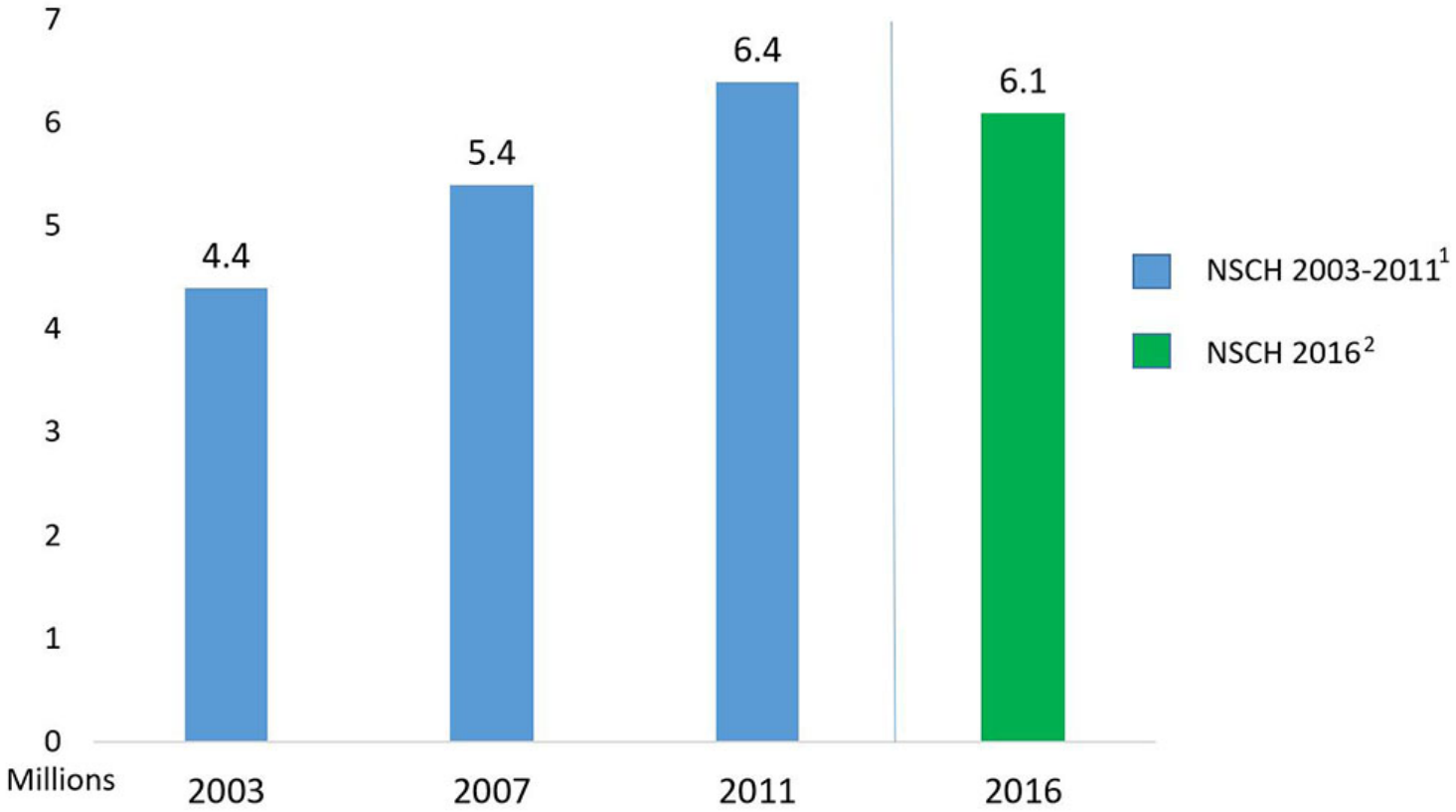
Facts about ADHD

Millions of US children have been diagnosed with ADHD

- The estimated number of children ever diagnosed with ADHD, according to a national 2016 parent survey,[1] is 6.1 million (9.4%). This number includes:
  - 388,000 children aged 2–5 years
  - 4 million children aged 6–11 years
  - 3 million children aged 12–17 years
- Boys are more likely to be diagnosed with ADHD than girls (12.9% compared to 5.6%).[1]

The number of US children ever diagnosed with ADHD has changed over time

Estimated number of US children who ever had a diagnosis of ADHD



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View text version

About this chart:
[1] **NSCH 2003-2011:** National Survey of Children's Health, telephone survey data; estimate includes children 4-17 years of age [Read key findings]
[2] **NSCH 2016:** Redesigned as an online and mail survey, estimate includes children 2-17 years of age [Read key findings]

Because the 2016 NSCH survey used different methods, estimates are not directly comparable with estimates based on previous NSCH data. Because of an increased focus on ADHD in younger children, age ranges were expanded to include children 2-17 years of age.

For more information:

- ADHD diagnosis throughout the years
- State-based information about ADHD diagnosis (2003-2012)

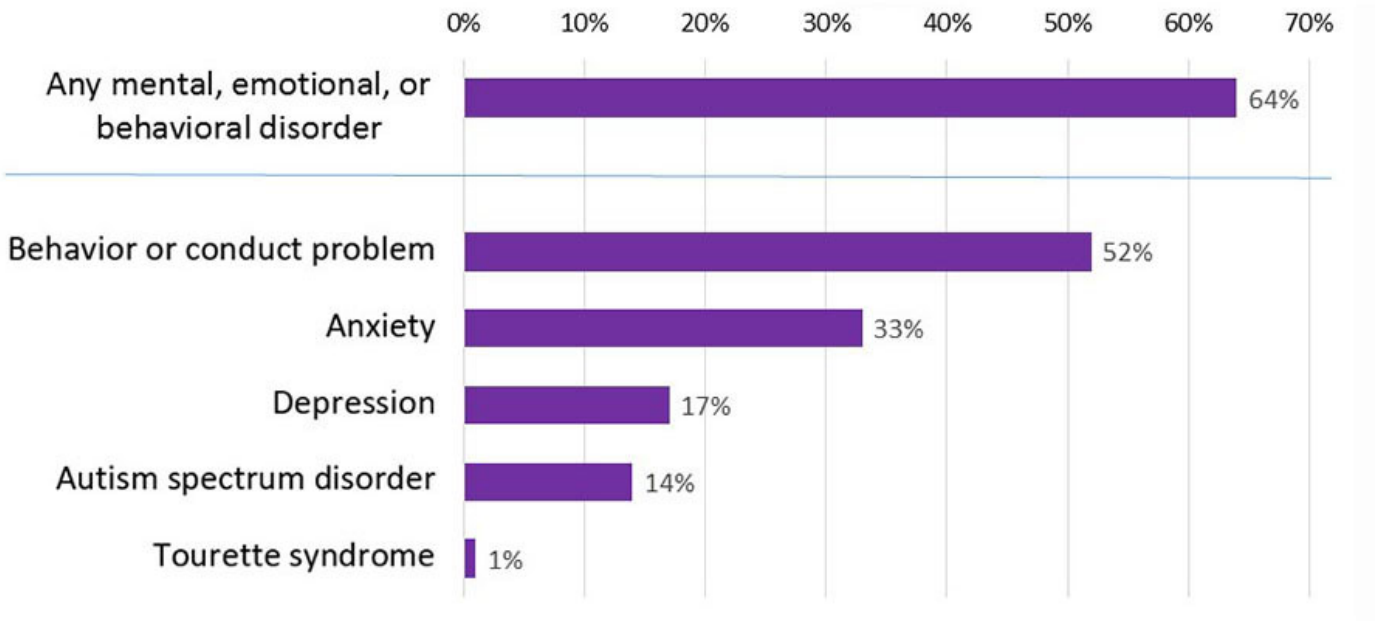
Many children with ADHD also have other disorders

According to a national 2016 parent survey,[1] 6 in 10 children with ADHD had at least one other mental, emotional, or behavioral disorder:

- About 5 in 10 children with ADHD had a behavior or conduct problem.
- About 3 in 10 children with ADHD had anxiety.

Other conditions affecting children with ADHD: depression, autism spectrum disorder, and Tourette Syndrome.

Percentage of children with ADHD and another disorder[1]



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Treatment for ADHD

About 3 in 4 US children with current ADHD receive treatment

A national parent survey from 2016[1] reported on medication and behavioral treatment for children 2–17 years of age with current ADHD:

Did you know?

Treatment for ADHD can include behavior therapy and medication. For children 6 years of age and older, the American Academy of Pediatrics (AAP) recommends behavior therapy and medication, preferably both together. For children under 6 years of age behavior therapy is recommended as the first line of treatment.

Read more about recommendations

were taking ADHD medication
- Ages 2–5: 18%
- Ages 6–11: 69%
- Ages 12–17: 62%

- 47% received behavioral treatment
  - Ages 2–5: 60%
  - Ages 6–11: 51%
  - Ages 12–17: 42%

- Altogether, 77% were receiving treatment. Of these children:
  - About 30% were treated with medication alone.
  - About 15% received behavioral treatment alone.
  - About 32% children with ADHD received both medication treatment and behavioral treatment.

- About 23% children with ADHD were receiving neither medication treatment nor behavioral treatment.

It is not known what type of behavioral treatment these children received.

Read more about these findings

Most children with ADHD receive some types of services

A more in-depth national survey[2] from 2014 reported on treatment and services that children with ADHD had received at some point prior to the survey. This survey was conducted with parents of children 4–17 years of age who had ever been diagnosed with ADHD.

- Almost 9 out of 10 children had received school support, which includes school accommodations and help in the classroom.
- About 6 out of 10 children had received some type of behavioral treatment or skills training:
  - 3 out of 10 received parent-delivered behavior therapy (/ncbddd/adhd/behavior-therapy.html).
  - 4 out of 10 received social skills training.
  - 3 out of 10 received peer interventions.
  - 2 out of 10 received cognitive behavioral therapy.

Read more about these findings

Read more about different types of therapy

Recommendations for treatment of ADHD

State-based Information about ADHD medication treatment (2007-2012)

Healthcare claims data show treatment gaps

In addition to parent-reported data, healthcare claims from Medicaid or employer-sponsored insurance provide another way to understand treatment patterns. A study[3] looking at the healthcare claims data for young US children found:

- During 2008–2011, children ages 2–5 years covered by Medicaid were twice as likely to receive clinical care for ADHD compared with similar-aged children covered by commercial employer-sponsored insurance.
- About 3 in 4 children ages 2–5 years who had clinical care for ADHD recorded in their healthcare claims from 2008–2014 received ADHD medication, and fewer than half received any form of psychological services.

It is not known what types of psychological services these children received, or whether these children received behavioral treatments that were not entered into the healthcare claims data.

Read more about these findings

References

1. Danielson ML, Bitsko RH, Ghandour RM, Holbrook JR, Kogan MD, Blumberg SJ. Prevalence of parent-reported ADHD diagnosis and associated treatment among U.S. children and adolescents, 2016. Journal of Clinical Child and Adolescent Psychology. 2018, 47:2, 199-212.
2. Danielson ML, Visser SN, Chronis-Tuscano A, DuPaul GJ. A national description of treatment among U.S. children and adolescents with ADHD. Journal of Pediatrics. 2018, 192, 240–246.e1.
3. Visser, SN Danielson ML, Wolraich ML, Fox M, Grosse SD, Valle LA, Holbrook JR, Claussen AH, Peacock, P. Vital signs: National and state-specific patterns of attention deficit/hyperactivity disorder treatment among insured children aged 2–5 years — United States, 2008–2014. Morbidity and Mortality Weekly Report (MMWR); 2016,65, 443–450.

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Page last reviewed: October 15, 2019

Content source: National Center on Birth Defects and Developmental Disabilities

EXHIBIT 72

COVID-19 is an emerging, rapidly evolving situation.

Get the latest public health information from CDC: https://www.coronavirus.gov
Get the latest research information from NIH: https://www.nih.gov/coronavirus

The National Institute of Mental Health: www.nimh.nih.gov

Attention-Deficit/Hyperactivity Disorder (ADHD)

Definition

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common childhood disorders and can continue through adolescence and into adulthood. Symptoms include difficulty staying focused and paying attention, difficulty controlling behavior, and hyperactivity (over-activity).

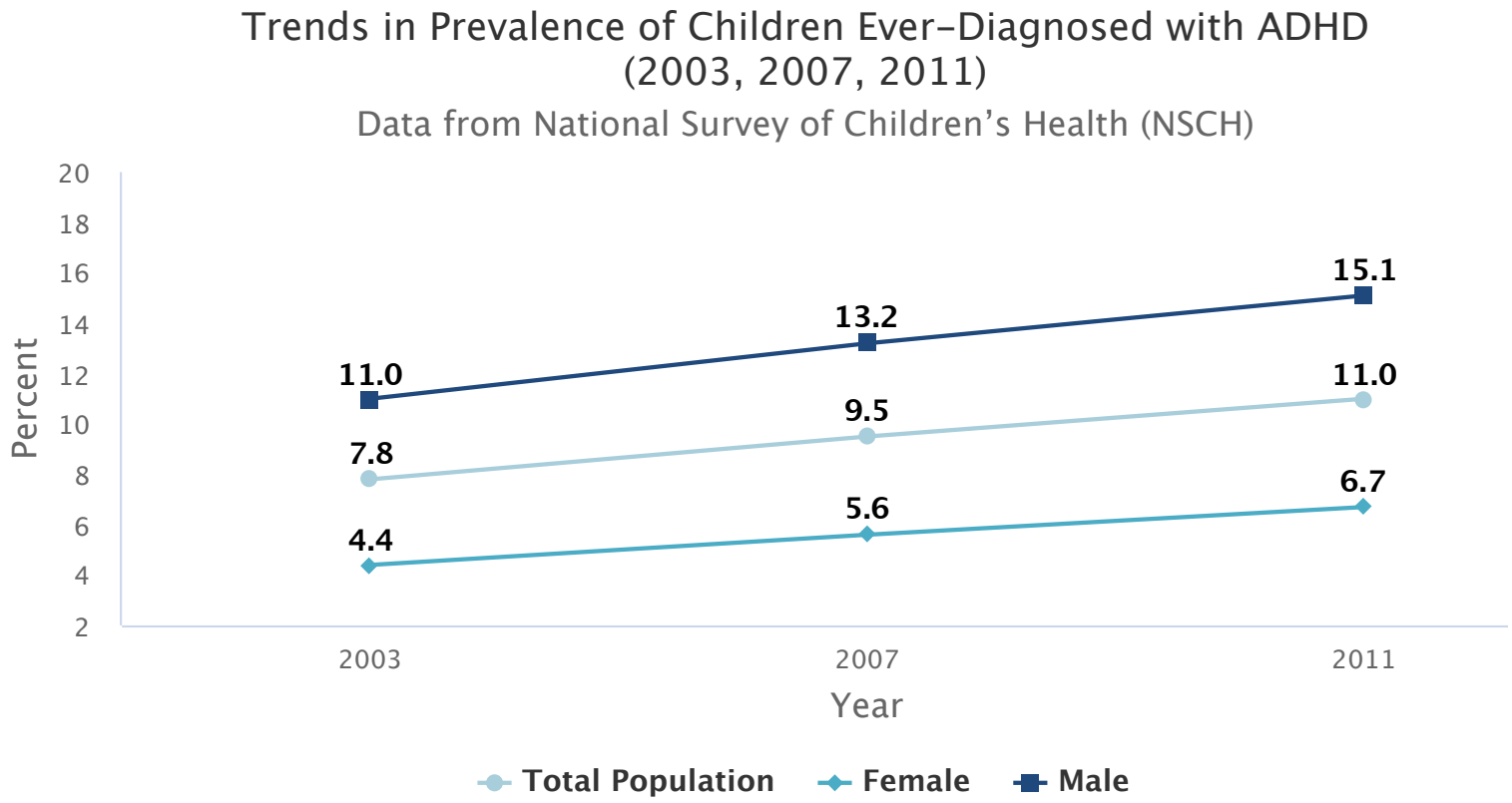
Additional information about ADHD can be found on the NIMH Health Topics page on Attention-Deficit/Hyperactivity Disorder (www.nimh.nih.gov//health/topics/attention-deficit-hyperactivity-disorder-adhd/index.shtml).

Trends in Prevalence of ADHD Diagnosis Among Children

Based on parent-report data from National Survey of Children's Health (NSCH), Figure 1 shows the trends in prevalence of U.S. children aged 4-17 ever diagnosed with ADHD by a health care provider.[1]

- The prevalence of children ever diagnosed with ADHD increased by 42% between 2003 (7.8%) and 2011 (11.0%).
- Males had a consistently higher prevalence of ADHD than females from 2003 to 2011.

Figure 1



Age of Onset

Based on data from the NSCH, the median age of onset for children with current ADHD was 6 years.[1]
More severe cases of ADHD in children, as described by parents, were diagnosed earlier.

- The median age of diagnosis for **severe** ADHD was 4 years.
- The median age of diagnosis for **moderate** ADHD was 6 years.
- The median age of diagnosis for **mild** ADHD was 7 years.

Approximately one-third of children diagnosed with ADHD retain the diagnosis into adulthood.[2]

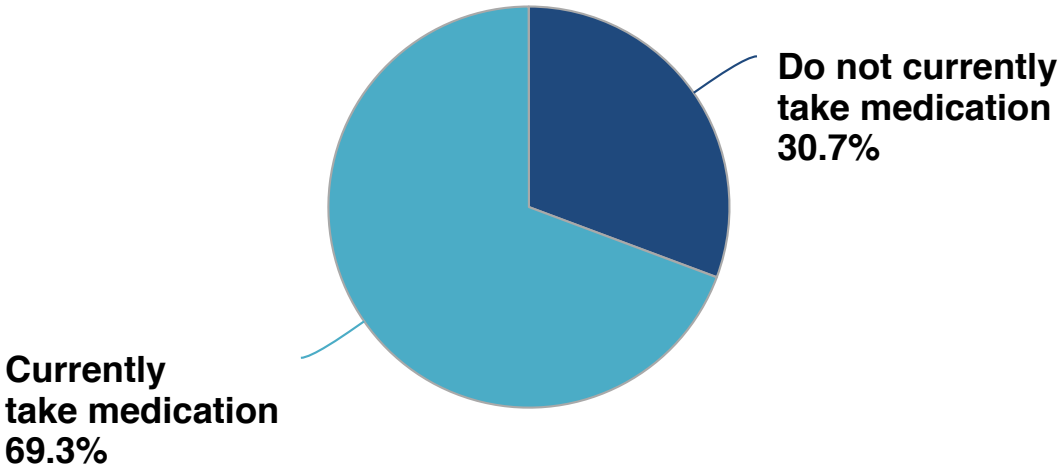
Treatment for ADHD in Children

Medication can be used to effectively treat ADHD symptoms of impulsivity, inattention, and hyperactivity, and is the single most effective treatment for reducing ADHD symptoms.[1]
Figure 2 is based on data from the NSCH and shows medication use among children with ADHD in 2011. An estimated 69.3% of children with a current diagnosis of ADHD received medication for ADHD. Medication use increased 4% overall from 2007 to 2011, particularly among male teens.[1]

Figure 2

Medication Use Among Children Currently Diagnosed with ADHD (2011)

Data from National Survey of Children's Health (NSCH)



Prevalence of ADHD Among Adolescents

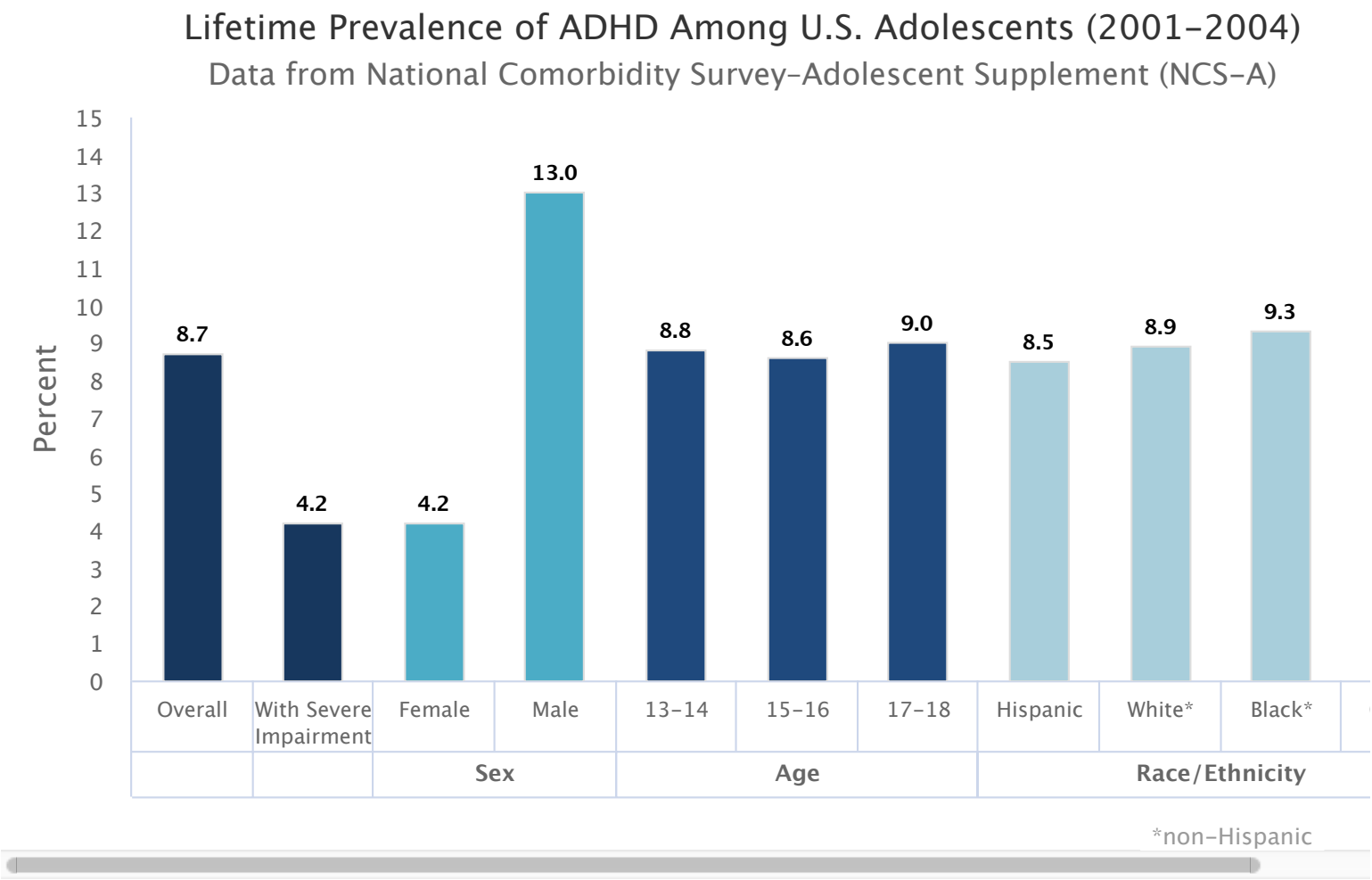
Based on diagnostic interview data from National Comorbidity Survey–Adolescent Supplement (NCS-A), Figure 3 shows the lifetime prevalence of ADHD among U.S. adolescents aged 13 to 18 years.[3,4]

The lifetime prevalence of ADHD was 8.7%.

Nearly half of all cases showed severe impairment (4.2%). Impairment criteria were based on the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).

ADHD affected three times as many males (13.0%) as females (4.2%).

Figure 3



Prevalence of ADHD Among Adults

Based on diagnostic interview data from the National Comorbidity Survey Replication (NCS-R), Figure 4 shows the estimated prevalence of adults aged 18 to 44 years with a current diagnosis of ADHD.[5]

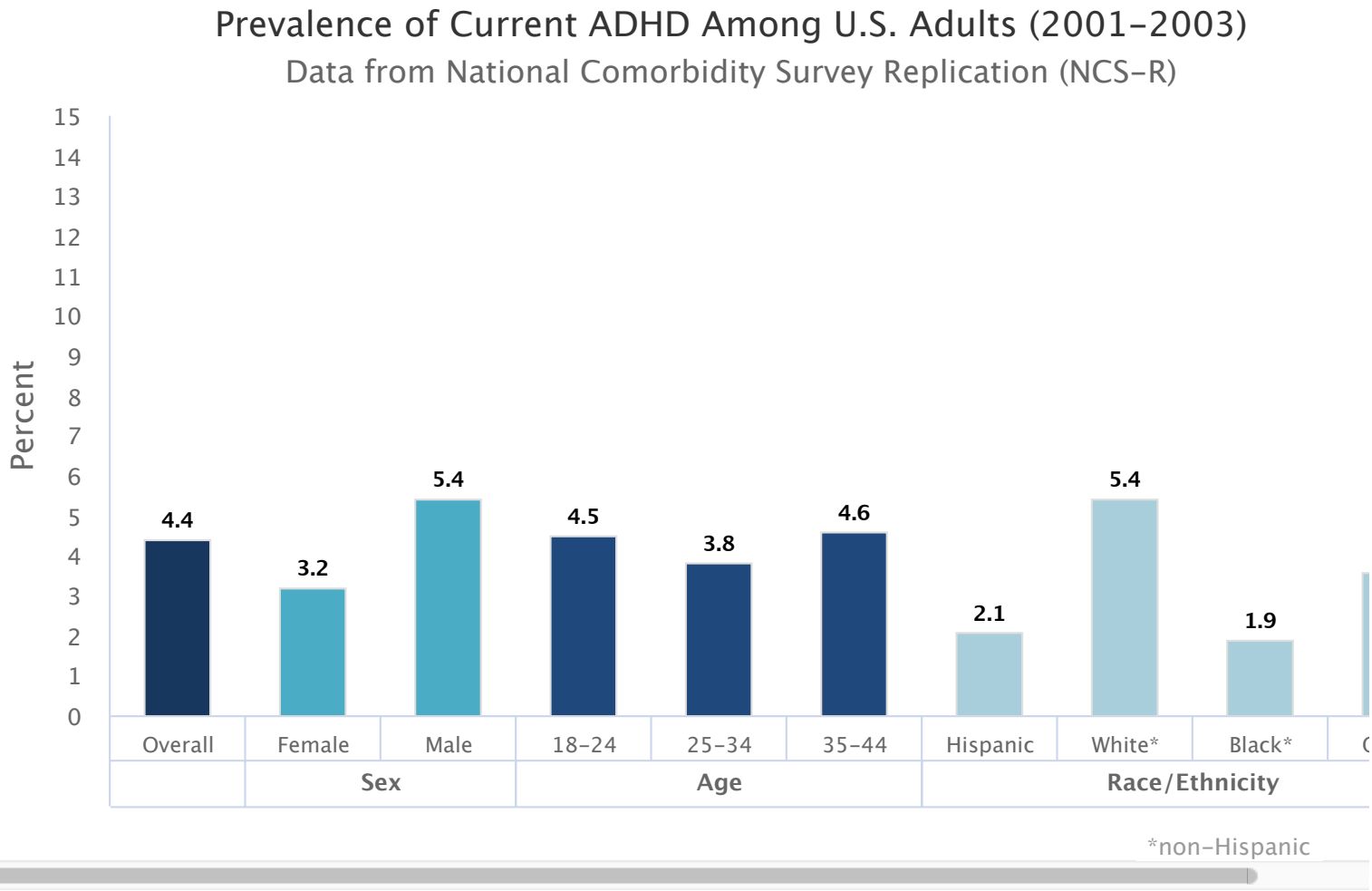
The overall prevalence of current adult ADHD is 4.4%.

Prevalence was higher for males (5.4%) versus females (3.2%).

The non-Hispanic white group (5.4%) had a higher prevalence than all other race/ethnicity groups.

The estimated lifetime prevalence of ADHD in U.S. adults aged 18 to 44 years was 8.1%.[6]

Figure 4



Data Sources

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Statistical Methods and Measurement Caveats

This webpage presents data from three sources.

National Survey of Children's Health (NSCH)

The CDC's NSCH is a national cross-sectional telephone survey of children's physical and mental health, conducted in 2003, 2007, and 2011. The NSCH was led by the National Center for Health Statistics at the Centers for Disease Control and Prevention under the direction and sponsorship of the Maternal and Child Health Bureau, Health Resources and Services Administration (HRSA). The survey provides parent-reported data for children/adolescents with ADHD aged 4 to 17 years. Between February 2011 and June 2012, 95,677 interviews were completed. Landline and cell-phone interview completion rates were 54.1% and 41.2% respectively, with a 23.0% overall response rate.
For more information, see PMID: 24342384 and CDC's NSCH FAQ page.

National Comorbidity Survey Adolescent Supplement (NCS-A)

Diagnostic Assessment and Population:

The NCS-A was carried out under a cooperative agreement sponsored by NIMH to meet a request from Congress to provide national data on the prevalence and correlates of mental disorders among U.S. youth. The NCS-A was a nationally representative, face-to-face survey of 10,123 adolescents aged 13 to 18 years in the continental United States. ADHD was assessed in a subsample of 8,470 adolescents. The survey was based on a dual-frame design that included 904 adolescent residents of the households that participated in the adult U.S. National Comorbidity Survey Replication and 9,244 adolescent students selected from a nationally representative sample of 320 schools. The survey was fielded between February 2001 and January 2004. DSM-IV mental disorders were assessed using a modified version of the fully structured World Health Organization Composite International Diagnostic Interview.

Survey Non-response:

The overall adolescent non-response rate was 24.4%. This is made up of non-response rates of 14.1% in the household sample, 18.2% in the un-blinded school sample, and 77.7% in the blinded school sample. Non-response was largely due to refusal (21.3%), which in the household and un-blinded school samples came largely from parents rather than adolescents (72.3% and 81.0%, respectively). The refusals in the blinded school sample, in comparison, came almost entirely (98.1%) from parents failing to return the signed consent postcard.
For more information, see PMID: 19507169 and the NIMH NCS-A study page (www.nimh.nih.gov//archive/news/2010/national-survey-confirms-that-youth-are-disproportionately-affected-by-mental-disorders.shtml).

National Comorbidity Survey Replication (NCS-R)

Diagnostic Assessment and Population:

> The NCS-R is a nationally representative, face-to-face, household survey conducted between February 2001 and April 2003 with a response rate of 70.9%. DSM-IV mental disorders were assessed using a modified version of the fully structured World Health Organization Composite International Diagnostic Interview (WMH-CIDI), a fully structured lay-administered diagnostic interview that generates both International Classification of Diseases, 10th Revision, and DSM-IV diagnoses. The DSM-IV criteria were used here. Participants for the main interview totaled 9,282 English-speaking, non-institutionalized, civilian respondents. ADHD was assessed for a subsample of 3,199 respondents aged 18 to 44 years. The NCS-R was led by Harvard University.

Survey Non-response:

> In 2001-2002, non-response was 29.1% of primary respondents and 19.6% of secondary respondents. Reasons for non-response to interviewing include: refusal to participate (7.3% of primary, 6.3% of secondary); respondent was reluctant- too busy but did not refuse (17.7% of primary, 11.6% of secondary); circumstantial, such as intellectual developmental disability or overseas work assignment (2.0% of primary, 1.7% of secondary); and household units that were never contacted (2.0%).
> For more information, see PMID: 15297905 and the NIMH NCS-R study page (www.nimh.nih.gov//health/topics/ncsr-study/nimh-funded-national-comorbidity-survey-replication-ncs-r-study-mental-illness-exacts-heavy-toll-beginning-in-youth.shtml).

Last Updated: November 2017

STATISTICS HOME (www.nimh.nih.gov//health/statistics/index.shtml)

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EXHIBIT 73

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Attention-Deficit / Hyperactivity Disorder (ADHD)

Trends in the Parent-Report of Health Care Provider-Diagnosis and Medication Treatment for ADHD: United States, 2003—2011

Researchers from the Centers for Disease Control and Prevention (CDC) and the Health Resources and Services Administration have published a study: "Trends in the Parent-Report of Health Care Provider-Diagnosed and Medicated ADHD: United States, 2003—2011." Read the abstract [1]. See below for a summary of the findings from this article.

Health care providers who care for children with attention-deficit/hyperactivity disorder (ADHD) and public health practitioners should be aware that an estimated two million more US children were reported by their parents to be diagnosed by a health care provider with ADHD and a million more were reported to be taking medication for ADHD in 2011, compared to 2003. These health professionals should also be aware of the changing patterns of ADHD in the United States.

About attention-deficit/hyperactivity disorder and this study:

ADHD is a neurobehavioral disorder of childhood that often persists into adulthood. CDC uses national surveys that ask parents about their child's health to monitor the number of children with ADHD and the treatment patterns for these children. The largest of these surveys is the National Survey of Children's Health, which has been collected every four years since 2003. Previous results from the 2003 and 2007 surveys found that 7.8% and 9.5% of US children aged 4-17 years were reported by their parents to have ever been diagnosed with ADHD by a health care provider in 2003 and 2007, respectively. The current study looked at data from the third National Survey of Children's Health, conducted in 2011-2012. The findings tell us more about ADHD diagnosis and treatment patterns, and reflect the substantial impact that ADHD has on families.

Learn more about the data source: National Survey of Children's Health

Important findings from this study include:

More than 1 in 10 (11%) US school-aged children had received an ADHD diagnosis by a health care provider by 2011, as reported by parents.

- 6.4 million children reported by parents to have ever received a health care provider diagnosis of ADHD ,

including:

- 1 in 5 high school boys
- 1 in 11 high school girls

The percentage of US children 4-17 years of age with an ADHD diagnosis by a health care provider, as reported by parents, continues to increase.

- A history of ADHD diagnosis by a health care provider increased by 42% between 2003 and 2011:
  - 7.8% had ever had a diagnosis in 2003
  - 9.5% had ever had a diagnosis in 2007
  - 11.0% had ever had a diagnosis in 2011
- Average annual increase was approximately 5% per year

The percentage of children 4-17 years of age taking medication for ADHD, as reported by parents, increased by 28% between 2007 and 2011.

- Percentage of children taking medication for ADHD was:
  - 4.8% in 2007
  - 6.1% in 2011
- Average annual increase was approximately 7% per year

The average age of ADHD diagnosis was 7 years of age, but children reported by their parents as having more severe ADHD were diagnosed earlier.

- 8 years of age was the average age of diagnosis for children reported as having ***mild*** ADHD
- 7 years of age was the average age of diagnosis for children reported as having ***moderate*** ADHD
- 5 years of age was the average age of diagnosis for children reported as having ***severe*** ADHD

More US children were reported by their parents to be receiving ADHD treatment in 2011 compared to 2007, however treatment gaps may exist.

- In 2011, as many as 17.5% of children with current ADHD were reported by their parents as **not** receiving either medication for ADHD or mental health counseling
- More than one-third of children reported by their parents as **not** receiving treatment were also reported to have moderate or severe ADHD

The patterns in ADHD diagnosis and medication treatment showed increases in the percentages overall, however some new patterns emerged between 2007 and 2011.

- The percentage of children reported by their parents to have a history of health care provider diagnosed ADHD increased for most demographic groups (for example, across racial groups, boys and girls) from 2003 to 2011; however,
- Between 2007 and 2011, the percentage of children reported by their parents to have a history of a health care provider diagnosed ADHD:
  - Was similar among older teens
  - Decreased among multiracial children and children of other races when compared to black or white children

The number of US families impacted by ADHD continues to increase.

- An estimated 2 million more children were reported by their parents to be diagnosed by a health care professional with ADHD in 2011, compared to 2003
  - By 2011, 6.4 million children were reported by their parents to be diagnosed by a health professional with ADHD compared to 4.4 million in 2003
- An estimated 1 million more children were reported by their parents to be taking medication for ADHD in 2011, compared to 2003.
  - By 2011, 3.5 million children were reported by their parents to be taking medication for ADHD compared to 2.5 million in 2003

ADHD: CDC's Activities

CDC monitors the number of children who have been diagnosed with ADHD through the use of national survey data. Including questions about ADHD on national or regional surveys helps us learn more about the number of children with ADHD, their use of ADHD treatments, and the impact of ADHD on children and their families. CDC has previously used national survey data to document increasing estimates of the number of children with ADHD from 2003-2007.[2] CDC has also used these data to estimate the percentage of children taking medication for ADHD, nationally and by state.[3]

CDC also conducts community-based studies to better understand the impact of ADHD. The Project to Learn about ADHD in Youth (PLAY) study methods have been implemented in four community sites. Information from the PLAY study helps us better understand ADHD as well as the needs of children and families living with ADHD.

CDC supports the National Resource Center on ADHD, a program of Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD), which is a Public Health Practice and Resource Center. Their web site (http://www.help4adhd.org/NRC.aspx) has links to information based on the current best medical evidence about the care for people with ADHD and their families. The National Resource Center operates a call center with trained, bilingual staff to answer questions about ADHD. Their phone number is 1-800-233-4050.

More Information

To learn more about ADHD, please visit https://www.cdc.gov/adhd.

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Page last reviewed: August 29, 2019
Content source: National Center on Birth Defects and Developmental Disabilities

EXHIBIT 74

Trends in the Parent-Report of Health Care Provider-Diagnosed and Medicated Attention-Deficit/Hyperactivity Disorder: United States, 2003–2011

Susanna N. Visser, MS, Melissa L. Danielson, MSPH, Rebecca H. Bitsko, PhD, Joseph R. Holbrook, PhD, Michael D. Kogan, PhD, Reem M. Ghandour, DrPH, Ruth Perou, PhD, Stephen J. Blumberg, PhD

Objective: Data from the 2003 and 2007 National Survey of Children's Health (NSCH) reflect the increasing prevalence of parent-reported attention-deficit/hyperactivity disorder (ADHD) diagnosis and treatment by health care providers. This report updates these prevalence estimates for 2011 and describes temporal trends. **Method:** Weighted analyses were conducted with 2011 NSCH data to estimate prevalence of parent-reported ADHD diagnosis, current ADHD, current medication treatment, ADHD severity, and mean age of diagnosis for U.S. children/adolescents aged 4 to 17 years and among demographic subgroups. A history of ADHD diagnosis (2003–2011), as well as current ADHD and medication treatment prevalence (2007–2011), were compared using prevalence ratios and 95% confidence intervals. **Results:** In 2011, 11% of children/adolescents aged 4 to 17 years had ever received an ADHD diagnosis (6.4 million children). Among those with a history of ADHD diagnosis, 83% were reported as currently having ADHD (8.8%); 69% of children with current ADHD were taking medication for ADHD (6.1%, 3.5 million children). A parent-reported history of ADHD increased by 42% from 2003 to 2011. Prevalence of a history of ADHD, current ADHD, medicated ADHD, and moderate/severe ADHD increased significantly from 2007 estimates. Prevalence of medicated ADHD increased by 28% from 2007 to 2011. **Conclusions:** Approximately 2 million more U.S. children/adolescents aged 4 to 17 years had been diagnosed with ADHD in 2011, compared to 2003. More than two-thirds of those with current ADHD were taking medication for treatment in 2011. This suggests an increasing burden of ADHD on the U.S. health care system. Efforts to further understand ADHD diagnostic and treatment patterns are warranted. J. Am. Acad. Child Adolesc. Psychiatry, 2014;53(1):34–46. **Key Words:** attention-deficit/hyperactivity disorder (ADHD), epidemiology, medication, prevalence, stimulants

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with childhood onset.[1] Children with ADHD experience clinically significant functional impairment across settings (for example at home, in school, and with friends), resulting in higher rates of unintentional injury, emergency room visits, peer problems, and academic failure.[2-7] Approximately one-third of children diagnosed with ADHD retain the diagnosis into adulthood, supporting the recognition of ADHD as a chronic health condition.[8]

This article is discussed in an editorial by Dr. John T. Walkup on page 14.

Clinical guidance is available at the end of this article.

An interview with the authors is available by podcast at www.jaacap.org or by scanning the QR code to the right.

Supplemental material cited in this article is available online.

Best practices for diagnosing and treating ADHD exist and include conducting a clinical diagnostic evaluation, incorporating information from multiple respondents (e.g., parents, child,

teachers, child care staff) and across multiple settings (e.g., home, school, child care), and evaluating the child for co-occurring conditions.[9,10] ADHD medication has long been used to effectively treat ADHD symptoms of impulsivity, inattention, and hyperactivity and is the single-most effective treatment for reducing ADHD symptoms.[11,12] High-quality behavioral interventions can also improve functional outcomes of selected children with ADHD[13,14], but may not be as broadly available across the U.S.

Characterizing the evolving epidemiology of ADHD diagnosis and treatment informs the public health impact of diagnosis and treatment within communities, allows tracking changes over time, informs service use and needs, and provides a context for interpreting the impact of health alerts extending from adverse event reporting systems.[15-18] Population-based epidemiological estimates of ADHD can come from a variety of sources. Analyses of insurance claims data have documented steady increases in the prevalence of ambulatory visits for ADHD diagnoses between 2001 and 2010[19,20]; however, studies based on claims data are not necessarily representative of the uninsured or underinsured. A recent, large-scale community-based study from 4 school districts across 2 states suggests that the prevalence among elementary-aged children is 9% to 11%[21]; a large, national direct assessment of children 13 to 17 years of age suggested that the lifetime prevalence of ADHD among adolescents was 8.7%.[22] However, direct assessment of children in communities is resource intensive, and it is not an efficient method for monitoring prevalence over time. Large-scale surveys of parents that ask about clinician-diagnosed conditions provide an important cross-sectional picture of the impact of disorders, including ADHD, and can be repeated over time for surveillance purposes. Parent surveys can also be used to estimate both national and state-based prevalence of conditions.

Since 1996, parent reports of health care provider-diagnosed ADHD in childhood have been collected by nationally representative health surveys, beginning with the National Health Interview Survey (NHIS).[23] The reports of a diagnosis by a health care provider is a proxy for underlying ADHD, asking parents "Has a doctor or other health care provider ever told you that your child had attention deficit disorder (ADD) or attention-deficit/hyperactivity disorder (ADHD)?" This report of an ADHD diagnosis was included in the 2003, 2007, and 2011 National Survey of Children's Health (NSCH), which is a periodic parent survey of the physical and emotional health of US children, 0 to 17 years of age.[24,25,30] Increases in parent-reported ADHD diagnosis and medication treatment have been documented using data from NHIS and NSCH; average annual increases in parent-reported ADHD diagnosis ranged from 3% to 6% per year since the late 1990s.[26-28]

Based on data from the 2007 NSCH, an estimated 9.5% of children/adolescents 4 to 17 years of age had been diagnosed with ADHD; 78% of those children were characterized by their parents as having current ADHD, representing 7.2% (4.1 million) of school-aged children.[28] The estimated prevalence increased by 22% from 2003 to 2007, with an average annual increase of 5.5% per year from 2003 to 2007. Increases in prevalence were greatest among groups with historically lower rates of ADHD: older teens, Hispanics, and children who spoke a primary language other than English. Two-thirds of those with current ADHD were taking medication in 2007. ADHD medication treatment increased with ADHD severity. Nearly 1 in 20 (4.8%) of U.S. children/adolescents 4 to 17 years of age (2.7 million individuals) were taking ADHD medication in 2007, which is consistent with a 2008 Medical Expenditure Panel Survey estimate of 5.1% among children 6 to 12 years of age.[29]

Data from the most recent NSCH allow updated estimates of parent-reported ADHD diagnosis and treatment, as well as inspection of trends in these estimates over time. Based on previous reports, average annual growth rates of 3% to 6% for parent-reported ADHD diagnosis and a commensurate increase in parent-reported ADHD medication treatment were expected.

METHOD

The NSCH is a national cross-sectional, random-digit–dialed telephone survey conducted in 2003 to 2004 (designated as "2003"), 2007 to 2008 ("2007"), and 2011–2012 ("2011").[24,25,30] The NSCH uses the sampling frame of the National Immunization Survey[31]; because of the rise in the prevalence of cell-phone–only households, the 2011 NSCH added a sample of cell-phone numbers. Between February 2011 and June 2012, 95,677 interviews were completed, resulting in landline and cell-phone interview completion rates of 54.1% and 41.2%, respectively, and a 23.0% overall response rate.[30] Sample weights were used to adjust for unequal probability of selection of households

and children, nonresponse, and the underlying demographic distribution of U.S. noninstitutionalized children. The survey questions pertaining to ADHD diagnosis and treatment are included as a supplement to this article (Table S1, available online). A responding parent or guardian (referred to hereafter as "parent") was asked questions about 1 randomly selected child (aged 0–17 years) in the household. Analyses were conducted in SAS-callable SUDAAN version 11.0 (RTI International; Cary, NC) to account for the complex survey design and application of sample weights.

At all 3 time points, parents were asked if "a doctor or other health care provider ever told you that [child] had attention deficit disorder or attention-deficit/hyperactivity disorder, that is, ADD or ADHD." In 2007 and 2011, parents who reported a history of ADHD were asked whether the child currently had ADHD, and, in 2011, they were asked the age at which the diagnosis was made. Parents reporting current ADHD also described the severity of ADHD (mild, moderate, or severe). In each survey year, a question was included asking about current medication treatment for ADHD; however, a different subset of parents were asked this question in 2003 as compared to subsequent surveys. In 2003, parents who reported that their child had ever received a diagnosis were asked about current medication treatment, whereas in 2007 and 2011, only parents reporting current ADHD were asked about current medication treatment; this prohibited direct comparisons of medication for ADHD across the 3 surveys. Data allowed direct comparisons of ever-diagnosed ADHD (2003–2011), current ADHD (2007–2011), ADHD severity (2007–2011), and current medication for ADHD (2007–2011). Independent of ADHD diagnosis, all parents were asked if their child had received treatment or counseling from a mental health professional in the past 12 months.

Data Analysis

For the 2011 survey data, estimated prevalence of a history of parent-reported ADHD diagnosis (ever diagnosed), current ADHD, and current medication treatment were calculated for children/adolescents aged 4 to 17 years and compared across demographic subgroups using prevalence ratios (PRs). The mean age of diagnosis was calculated overall and contrasted with severity using a Wald F test.

The demographic groups and subgroups were comparable to those used in the previous reports describing the 2003 and 2007 data,[28,32] to allow direct comparison of the estimates over time. Estimated prevalence of ever-diagnosed ADHD in 2011 was compared to 2003 and 2007 NSCH estimates using PRs; differences in rate of change over time was tested with a Wald F test comparing the combination of yearly indicator regression coefficients. Estimates of current ADHD and current medication treatment from 2011 were compared to 2007 using PRs and 95% CI. Demographic subgroup differences for change over time were tested by a Wald F test on an interaction term. Parent-report of treatment or counseling by a mental health professional was combined with medication treatment to estimate ADHD treatment prevalence among children with current ADHD; the percentage of those with a current ADHD diagnosis reported to be in treatment was compared between 2007 and 2011.

RESULTS

All ADHD survey indicators extended from parent-reported data for children/adolescents aged 4 to 17 years; for brevity, the term "parent-reported" and age (4–17 years) is excluded as a qualifier of the relevant estimates that follow.

2011 Ever-Diagnosed and Current ADHD Prevalence Estimates and Demographic Patterns

In 2011, the estimated prevalence of ever-diagnosed ADHD among children was 11.0%, representing 6.4 million children nationwide (Table 1). Among children with ever-diagnosed ADHD, 82.3% had current ADHD resulting in an estimated national prevalence of 8.8% among children (5.1 million nationwide).

ADHD diagnosis (ever and current) was significantly associated ($p < .05$ based on χ^2 statistics) with every demographic indicator studied. Ever-diagnosed ADHD was higher among boys (15.1%) than girls (6.7%) and increased with age (Table 1). The highest point estimates were among boys (15.1%), children 11 and older (11–14 years: 14.3%, 15–17 years: 14.0%), and children with public health care coverage (14.4%). Prevalence was higher for black and white children compared to those of other races; the prevalence among Hispanics was half that of non-Hispanics. Those living in households where English was the primary language were more than 4 times as likely to have been diagnosed with ADHD as those living in households speaking another primary language. Prevalence was highest among children from households with 12 years (high school graduate) of education, compared to households with more or less education. Children living below 200% of the federal poverty level had a higher prevalence than children from higher-income families. Ever-diagnosed ADHD was more common among children with health care coverage than those without coverage, and among those with public coverage than with private coverage. Ever-diagnosed ADHD was lowest in the West, compared to other U.S. regions.

The demographic and state-based patterns for current ADHD were generally consistent with

TABLE 1 Weighted Prevalence Estimates of Parent-Reported Attention-Deficit/Hyperactivity Disorder (ADHD) Diagnosis by a Health Care Provider Among Children Aged 4–17 Years by Sociodemographic Characteristics (National Survey of Children's Health, United States, 2011)

		Ever Diagnosed with ADHD n = 76,015 respondents			Current ADHD n = 75,840 respondents			Current ADHD and Current Medication for ADHD n = 75,828 respondents		
Characteristic	**n**	**%**	**95% CI**	**PR**	**%**	**95% CI**	**PR**	**%**	**95% CI**	**PR**
Overall	76,015	11.0	10.5–11.5		8.8	8.4–9.3		6.1	5.7–6.5	
Sex										
Male	39,314	15.1	14.3–15.9	2.24	12.1	11.4–12.8	2.19	8.4	7.9–9.1	2.31
Female	36,701	6.7	6.2–7.3	1.00	5.5	5.0–6.0	1.00	3.7	3.3–4.1	1.00
Age										
4–10 years of age	36,219	7.7	7.2–8.3	1.00	6.8	6.2–7.4	1.00	4.9	4.5–5.4	1.00
11–14 years of age	21,409	14.3	13.3–15.4	1.85	11.4	10.5–12.4	1.69	8.0	7.2–8.8	1.63
15–17 years of age	18,387	14.0	12.9–15.2	1.81	10.2	9.2–11.3	1.51	6.5	5.7–7.3	1.32
Highest Educ. in Household										
<HS	4,453	8.5	7.2–9.9	0.78	6.9	5.7–8.2	0.79	4.2	3.4–5.2	0.70
12 years, HS graduate	11,569	13.3	12.1–14.6	1.23	11.0	9.9–12.2	1.27	7.7	6.8–8.8	1.29
>HS	58,550	10.8	10.3–11.4	1.00	8.6	8.1–9.2	1.00	6.0	5.6–6.4	1.00
Race										
White	54,927	12.2	11.5–12.8	1.00	9.8	9.2–10.4	1.00	7.1	6.6–7.6	1.00
Black	7,615	11.9	10.6–13.4	0.98[a]	9.5	8.3–10.9	0.98[a]	5.7	4.8–6.7	0.80
Other	11,450	7.2	6.3–8.1	0.59	5.8	5.1–6.7	0.60	3.5	2.9–4.3	0.50
Ethnicity										
Hispanic/Latino	9,676	6.9	5.9–8.1	0.56	5.5	4.6–6.6	0.56	3.1	2.5–3.9	0.44
Non-Hispanic/Latino	64,799	12.3	11.8–12.9	1.00	9.9	9.4–10.4	1.00	7.0	6.6–7.5	1.00
Primary Language in Home										
English	70,522	12.4	11.9–13.0	1.00	10.0	9.5–10.5	1.00	7.0	6.6–7.4	1.00
Any other language	5,455	2.7	1.9–3.7	0.21	2.0	1.3–3.0	0.20	1.0	0.6–1.6	0.14
Federal Poverty Level[b]										
≤100	10,974	12.9	11.7–14.2	1.30	10.9	9.8–12.1	1.38	6.9	6.0–7.8	1.22
>100 to ≤200	13,500	11.8	10.7–12.9	1.18	9.4	8.4–10.5	1.19	6.6	5.8–7.5	1.16[a]
>200	51,541	10.0	9.4–10.6	1.00	7.9	7.3–8.5	1.00	5.6	5.2–6.1	1.00
Any Health Care Coverage										
Yes[c]	72,525	11.3	10.8–11.8		9.2	8.7–9.6		6.3	6.0–6.7	
Medicaid/SCHIP (public)	20,313	14.4	13.5–15.4	1.53	11.9	11.0–12.9	1.58	8.1	7.4–8.9	1.52
Non-Medicaid (private)	51,440	9.4	8.9–10.0	1.00	7.5	7.0–8.1	1.00	5.3	4.9–5.8	1.00
No	3,380	6.4	5.0–8.2	0.68	4.1	3.0–5.5	0.54	2.3	1.4–3.7	0.42
Region										
Northeast	13,620	10.1	9.2–11.2	1.26	8.1	7.2–9.1	1.27	5.4	4.7–6.2	1.42
Midwest	17,870	12.1	11.3–13.0	1.50	10.0	9.3–10.8	1.57	7.1	6.5–7.8	1.88
South	25,327	12.6	11.8–13.4	1.56	10.1	9.3–10.9	1.58	7.3	6.7–8.0	1.94
West	19,198	8.1	7.0–9.3	1.00	6.4	5.4–7.5	1.00	3.8	3.1–4.6	1.00

Note: HS = high school; PR = prevalence ratio; SCHIP = State Children's Health Insurance Program.

[a] *PR not significant at the level of α = 0.05.*

[b] *Includes multiply imputed values for 9.4% of sample for which household income was missing.*

[c] *Prevalence ratio not shown because referent group is a subset of the population of children with any health insurance.*

those observed for ever-diagnosed ADHD, although current ADHD estimates were approximately 20% to 25% lower than ever-diagnosed estimates (Table 1). State-based estimates of current ADHD ranged from 4.2% in Nevada to 14.6% in Arkansas and 14.8% in Kentucky (Figure 1).

Among children with current ADHD, the median age of diagnosis was 6.2 years (95% CI = 6.0–6.4; mean = 7.0, 95% CI = 6.9–7.2). Age of diagnosis decreased with severity; children whose parents reported the child's ADHD as "mild" were diagnosed at a median age of 7.0

years (95% CI = 6.8–7.3; mean = 7.8, 95% CI = 7.5–8.1), compared to 6.1 (95% CI = 5.8–6.3; mean = 6.9, 95% CI = 6.7–7.1) and 4.4 (95% CI = 4.1–4.7; mean = 5.2, 95% CI = 4.9–5.5) years for those with "moderate" and "severe" ADHD, respectively.

2011 Medication Treatment for Current ADHD

Estimated prevalence of medication treatment for ADHD among US children was 6.1% (3.5 million nationwide). Of those with a current ADHD diagnosis, 69.0% were taking ADHD medication. ADHD medication treatment estimates were significantly associated with every demographic indicator studied ($p < 0.05$ by χ^2 statistics). The highest point estimates of parent-reported ADHD medication treatment were observed among boys (8.4%), whites (7.1%), non-Hispanics (7.0%), children living in households speaking English as the primary language (7.0%), children with public health care coverage (8.1%), and children living in the Midwest (7.1%) and South (7.3%) (Table 1). After increasing with age from 4 to 10 years to 11 to 14 years, current medication treatment prevalence decreased slightly among adolescents 15 to 17 years of age. Current medication treatment was lowest among children in households speaking a primary language other than English (1.0%). State-based estimates ranged from 2.0% in Nevada to 10.1% in Kentucky and 10.4% in Louisiana (Figure 2).

The proportion of children taking medication for ADHD increased with ADHD severity: 59.6% (95% CI = 55.6–63.5) for "mild" ADHD, 73.3% (95% CI = 69.2–77.0) for "moderate" ADHD, and 82.4% (95% CI = 76.0–87.3) for "severe" ADHD. The percentage of children with current ADHD who received any treatment or counseling from a mental health professional was 51.1% (95% CI = 48.4–53.7). The percentage of children receiving either medication for ADHD or mental health treatment was 82.5% (95% CI = 80.5–84.4).

Trends in Parent-Reported ADHD Indicators Over Time

Ever-Diagnosed and Current ADHD. Estimated prevalence of ever-diagnosed ADHD was 7.8%, 9.5%, and 11% in 2003, 2007, and 2011, respectively (Table 2). These estimates increased by 22% from 2003 to 2007 (average annual increase = 6%[28]) and 16% from 2007 to 2011 (average annual

FIGURE 1 Weighted prevalence estimates of parent-reported current attention-deficit/hyperactivity disorder (ADHD) among children/adolescents 4 to 17 years of age, by state (United States, 2011).

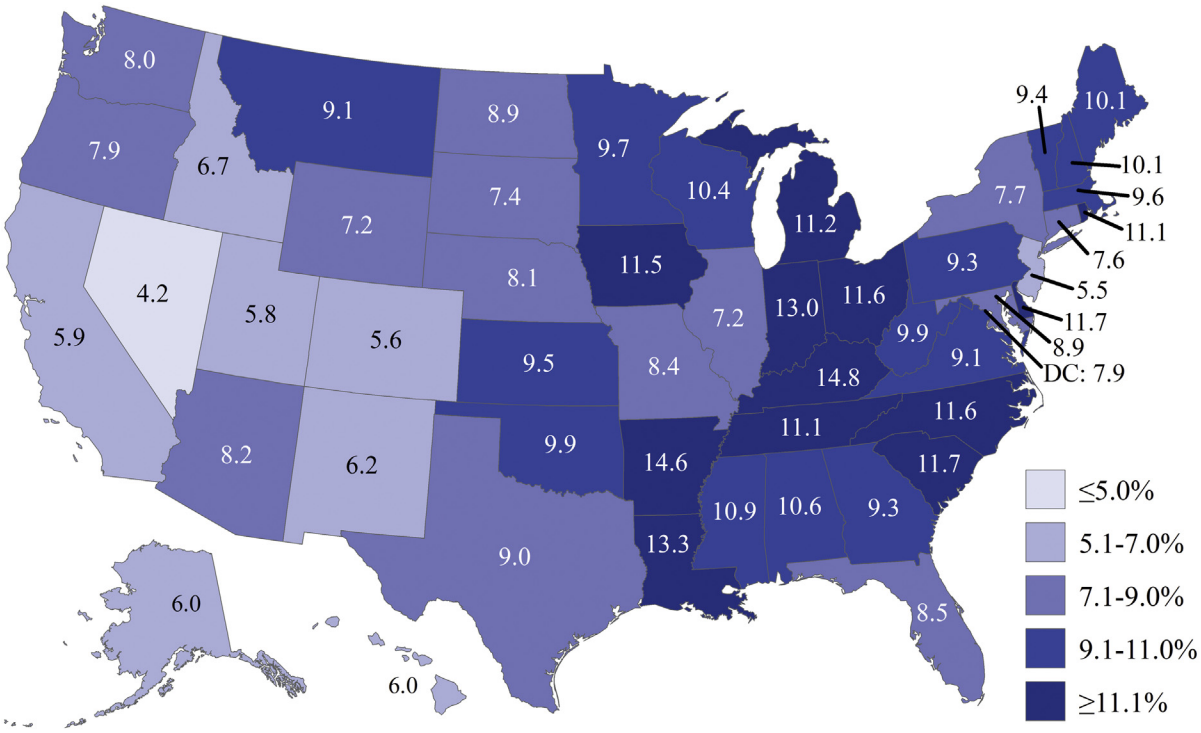
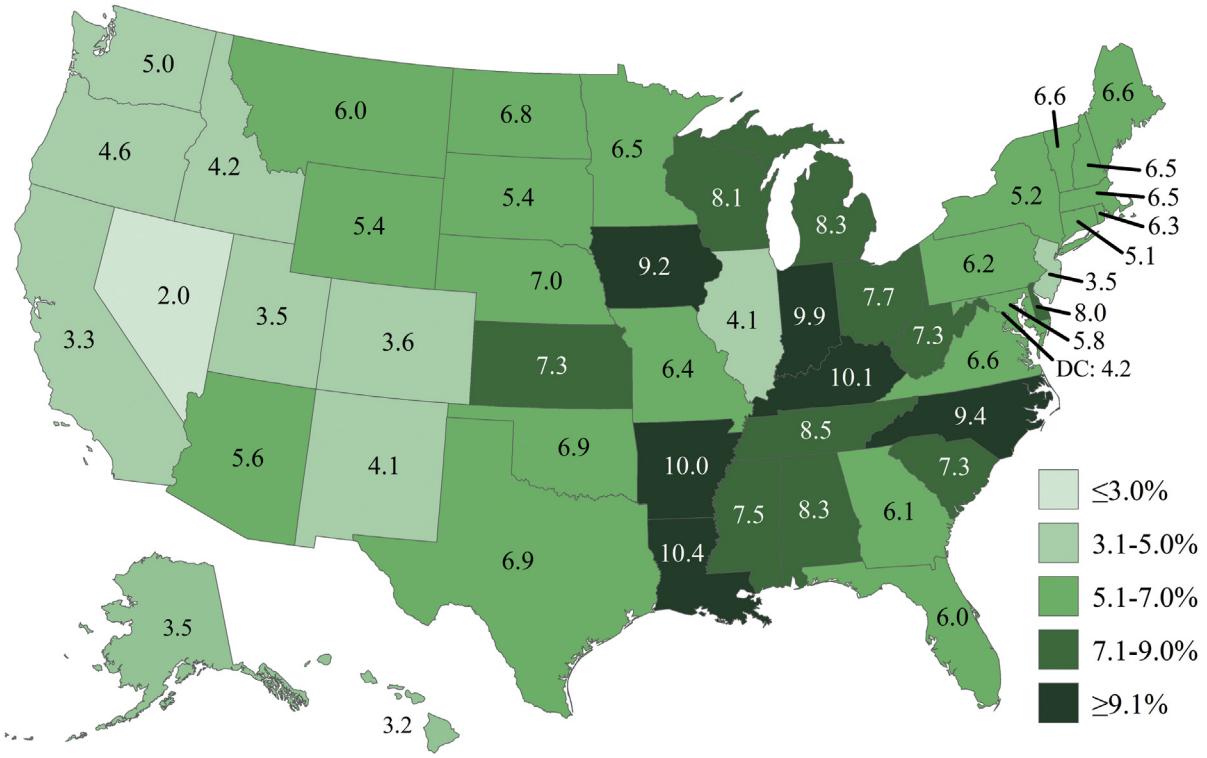


FIGURE 2 Weighted prevalence estimates of parent-reported current attention-deficit/hyperactivity disorder (ADHD) medication treatment among children/adolescents 4 to 17 years of age, by state (United States, 2011).



increase = 4%). The total increase from 2003–2011 was 42% (PR = 1.42, 95% CI = 1.33–1.50; average annual increase = 5%). The only 2 demographic subgroups for which there was not a significant change in ever-diagnosed ADHD from 2003 to 2011 were multiracial/other race children and children without health care coverage. The magnitudes of increase (slopes) from 2003 to 2007 and from 2007 to 2011 were equivalent for every subgroup studied, with the exception of the subgroup of 15- to 17-year-olds ($F_{1,57579} = 7.0$, $p < .01$), those living in households where the highest level of education was high school ($F_{1,39957} = 4.05$, $p < .05$) and children who were multiracial or of other races ($F_{1,24867} = 7.3$, $p < .01$), in which the magnitudes of increase were smaller for 2007 to 2011 than for 2003 to 2007. The greatest relative increases in ever-diagnosed ADHD from 2007 to 2011 were among children and adolescents aged 11 to 14 years, children living in a household with an adult with more than a high school education, whites, and children living in the Midwest. The pattern in the proportion of children with ever-diagnosed ADHD differed over time as a function of age ($F_{4,228249} = 2.57$, $p < .05$); ever-diagnosed ADHD increased from 2003 to 2011 for children 14 and under, but the growth leveled off for older children from 2007 to 2011 (Table 2).

Current ADHD increased by 23%, from 7.2% to 8.8% from 2007 to 2011 (Table 2). The increases were reflected in significantly higher 2011 prevalence among children less than 14 years of age, children from households with at least 12 years of education, whites, non-Hispanics, children living in households where English was a primary language, those living in households with incomes above 100% of poverty, children with health care coverage, and children living in the Midwest and South; the greatest relative increases were seen among girls, children and adolescents 11 to 14 years of age, whites, and children living in the Midwest. Prevalence was statistically similar between 2007 and 2011 among those with public health care coverage, but increased significantly among children with private health care coverage. The increase in prevalence of current ADHD among Hispanics did not reach statistical significance ($p = .06$). The proportion of children with current ADHD

TABLE 2 Weighted Prevalence Estimates of Parent-Reported Attention-Deficit/Hyperactivity Disorder (ADHD) Diagnosis by a Health Care Provider Among Children/Adolescents Aged 4 to 17 Years[a] by Sociodemographic Characteristics (National Survey of Children's Health, United States, 2003, 2007, and 2011)

	Ever Diagnosed with ADHD							Current ADHD				Current ADHD and Current Medication for ADHD			
	2003	2007	2011	2003–2011		2007–2011		2007	2011	2007–2011		2007	2011	2007–2011	
	%	%	%	PR	95% CI	PR	95% CI	%	%	PR	95% CI	%	%	PR	95% CI
Overall	7.8	9.5	11.0	1.42	1.33–1.50	1.16	1.08–1.24	7.2	8.8	1.23	1.13–1.33	4.8	6.1	1.28	1.16–1.41
Sex															
Male	11.0	13.2	15.1	1.37	1.28–1.48	1.15	1.06–1.24	10.3	12.1	1.17	1.07–1.29	6.9	8.4	1.22	1.09–1.36
Female	4.4	5.6	6.7	1.52	1.36–1.71	1.19	1.04–1.37	4.0	5.5	1.38	1.19–1.59	2.5	3.7	1.46	1.24–1.72
Age															
4–10 y	5.7	6.6	7.7	1.35	1.22–1.50	1.17	1.03–1.31	5.5	6.8	1.24	1.09–1.41	3.7	4.9	1.33	1.15–1.55
11–14 y	9.8	11.2	14.3	1.46	1.32–1.61	1.28	1.14–1.43	8.6	11.4	1.33	1.17–1.51	6.3	8.0	1.26	1.08–1.47
15–17 y	9.6	13.6	14.0	1.46	1.31–1.63	1.03	0.91–1.17	9.3	10.2	1.10	0.94–1.29	5.2	6.5	1.24	1.02–1.50
Highest Education in Household															
<HS	6.5	8.4	8.5	1.31	1.02–1.69	1.01	0.80–1.29	6.5	6.9	1.06	0.80–1.40	4.0	4.2	1.06	0.74–1.50
12 Years, HS Graduate	8.6	12.2	13.3	1.55	1.37–1.75	1.09	0.94–1.26	9.0	11.0	1.22	1.03–1.43	5.9	7.7	1.30	1.07–1.57
>HS	7.6	8.7	10.8	1.43	1.33–1.54	1.24	1.14–1.35	6.7	8.6	1.29	1.17–1.42	4.5	6.0	1.32	1.18–1.48
Race															
White	8.6	9.9	12.2	1.42	1.32–1.52	1.23	1.14–1.34	7.5	9.8	1.31	1.19–1.43	5.2	7.1	1.37	1.23–1.52
Black	7.7	10.1	11.9	1.54	1.30–1.83	1.18	0.99–1.40	7.8	9.5	1.22	0.99–1.50	5.1	5.7	1.12	0.86–1.45
Other	6.6	9.2	7.2	1.09	0.86–1.37	0.78	0.63–0.97	7.2	5.8	0.81	0.64–1.04	4.4	3.5	0.81	0.59–1.11
Ethnicity															
Hispanic/Latino	3.7	5.6	6.9	1.88	1.48–2.38	1.22	0.94–1.60	4.1	5.5	1.33	0.99–1.81	2.4	3.1	1.32	0.90–1.93
Non-Hispanic/Latino	8.6	10.5	12.3	1.43	1.35–1.52	1.18	1.10–1.26	8.0	9.9	1.24	1.15–1.35	5.4	7.0	1.30	1.18–1.43
Primary Language in Home															
English	8.6	10.5	12.4	1.44	1.35–1.53	1.18	1.10–1.27	8.0	10.0	1.26	1.16–1.36	5.3	7.0	1.31	1.19–1.44
Any other language	1.3	2.3	2.7	2.10	1.33–3.33	1.15	0.72–1.85	1.8	2.0	1.10	0.61–1.97	0.9	1.0	1.08	0.49–2.38
Federal Poverty Level[b]															
≤100	9.3	11.6	12.9	1.39	1.21–1.61	1.11	0.96–1.29	9.2	10.9	1.18	1.00–1.39	6.3	6.9	1.09	0.88–1.34
>100 to ≤200	7.9	10.3	11.8	1.49	1.31–1.70	1.14	0.97–1.33	7.7	9.4	1.22	1.03–1.46	4.7	6.6	1.40	1.14–1.71
>200	7.3	8.6	10.0	1.37	1.27–1.48	1.16	1.06–1.28	6.5	7.9	1.22	1.09–1.36	4.4	5.6	1.29	1.14–1.47
Any Health Care Coverage															
Yes	8.1	9.8	11.3	1.40	1.32–1.49	1.15	1.07–1.24	7.6	9.2	1.21	1.11–1.31	5.1	6.3	1.25	1.13–1.37
Medicaid/SCHIP (public)	10.8	13.6	14.4	1.33	1.21–1.47	1.06	0.95–1.18	10.9	11.9	1.10	0.97–1.24	7.5	8.1	1.08	0.93–1.25
Non-Medicaid (private)	6.9	8.1	9.4	1.36	1.25–1.47	1.17	1.06–1.28	6.1	7.5	1.23	1.10–1.37	4.1	5.3	1.31	1.15–1.48
No	4.9	6.7	6.4	1.32	0.96–1.81	0.96	0.67–1.37	3.7	4.1	1.11	0.74–1.65	1.7	2.3	1.32	0.72–2.43

TABLE 2 Continued

	Ever Diagnosed with ADHD								Current ADHD								Current ADHD and Current Medication for ADHD							
	2003		2007		2011		2003–2011			2007–2011		2007		2011		2007–2011		2007		2011		2007–2011	
	%		%		%		PR	95% CI		PR	95% CI	%		%		PR	95% CI	%		%		PR	95% CI
Region																								
Northeast	7.4		9.4		10.1		1.38	1.20–1.58		1.08	0.92–1.27	7.4		8.1		1.09	0.91–1.30	4.6		5.4		1.18	0.94–1.48
Midwest	7.9		9.9		12.1		1.53	1.38–1.68		1.22	1.10–1.35	7.6		10.0		1.32	1.17–1.49	5.3		7.1		1.35	1.18–1.55
South	9.1		10.9		12.6		1.38	1.26–1.51		1.15	1.04–1.27	8.3		10.1		1.22	1.09–1.37	5.8		7.3		1.25	1.09–1.45
West	5.8		7.0		8.1		1.40	1.15–1.69		1.16	0.91–1.47	5.1		6.4		1.24	0.95–1.63	2.9		3.8		1.32	0.95–1.84

Note: [a]*Analytic sample included 79,264 children in 2003, 73,123 children in 2007, and 76,015 children in 2011. HS = high school; PR = prevalence ratio; SCHIP = State Children's Health Insurance Program.*
[b]*Federal poverty level; multiple imputations were used for 10.0% of 2003, 8.9% of 2007, and 9.4% of 2011 for which household income was missing.*

among those with ever diagnosed ADHD increased from 2007 to 2011, from 78.1% to 82.3% (χ^2_1=7.93, $p < .01$). The distribution of ADHD severity shifted from 2007–2011 (mild: 46.7% vs. 41.4%, moderate: 39.5% vs. 43.1%, severe: 13.8% vs. 15.5%; χ^2_2=3.09, $p < .05$). The pattern in the proportion of children reported to have current ADHD over time varied as a function of child race ($F_{2,\ 142348} = 6.40$, $p < .005$). Specifically, the proportion of children with current ADHD decreased among children who were multiracial or of other races, whereas it increased among children of white or black races (Table 2).

Current Medication Treatment for ADHD and Treatment by a Mental Health Professional. ADHD medication treatment increased 28% from 2007 to 2011 from 4.8% to 6.1% (Table 2), an average annual increase of 7%. The proportion of children taking medication within strata of parent-reported severity was statistically similar in 2007 and 2011. Descriptively, the demographic groups with the greatest relative increases in current medication prevalence were females, 4- to 10-year-olds, whites, children living above 100% of the Federal poverty level, and children living in the Midwest. The pattern of the proportion of children taking medication for ADHD varied as a function of child race ($F_{2,142334} = 5.55$, $p < .005$); the proportion of children taking medication for ADHD decreased among children of multiracial/other races whereas it increased among children of white or black races (Table 2).

Although the prevalence of current mental health treatment or counseling among those with current ADHD remained similar from 2007 to 2011, the percentage of children who either received that treatment or were taking ADHD medication increased (from 78.9% to 82.5%; $\chi^2_1 = 3.90$, $p < .05$), due to increases in ADHD medication treatment. Among those not receiving either of the 2 forms of treatment, 63.6% were reported as having mild ADHD (95% CI = 57.8–69.1), 29.5% as moderate (95% CI = 24.5–35.1), and 6.9% as severe (95% CI = 4.4–10.5).

ADHD Prevalence and Medicated Prevalence Stratified by Age and Sex. Prevalence of ADHD diagnosis and current medication treatment for ADHD are presented by sex-stratified age groups across the 3 survey periods in Figure 3. Increasing prevalence over time can be seen from the growing size of the inverted pyramid, with a relatively consistent sex ratio for each indicator. Among boys, the 2003 prevalence of ever-diagnosed ADHD (outer bars) was less than

15%, regardless of age; in 2007, the estimates exceeded 15% for individuals 9 to 17 years of age, with the exception of those 12 years of age (13.6%); in 2011 the estimates exceeded 15% for those 10 to 17 years, and exceeded 20% for those 11 years and 14 years. Among girls, the 2003 prevalence of ever-diagnosed ADHD (outer bars) increased from ages 4 to 8 years, then stabilized at 5% to 6% for those 9 to 17; in 2007, the prevalence increased with estimates ranging from 5.7% among 10-year-olds to 11.5% among 16-year-olds; in 2011 the prevalence ranged from slightly more than 5% to slightly more than 10% for all but 14-year-olds, for whom the estimated prevalence of ever-diagnosed ADHD was 11.6%.

The medication treatment question was asked of parents reporting ever-diagnosed ADHD in 2003 and parents reporting current ADHD in 2007 and 2011. In 2003, medicated ADHD prevalence increased from ages 4 to 9, stabilized, and then decreased in the teen years for both sexes. Estimates of medicated ADHD increased in 2011, as compared to 2007, particularly among teen boys. In 2011, the highest medicated ADHD prevalence was among 11-year-old boys (13.3%). Among girls, medicated ADHD remained at less than 5% until 2011, when the estimates met or exceeded 5% for girls 9 to 10 and 14 to 15 years of age.

DISCUSSION

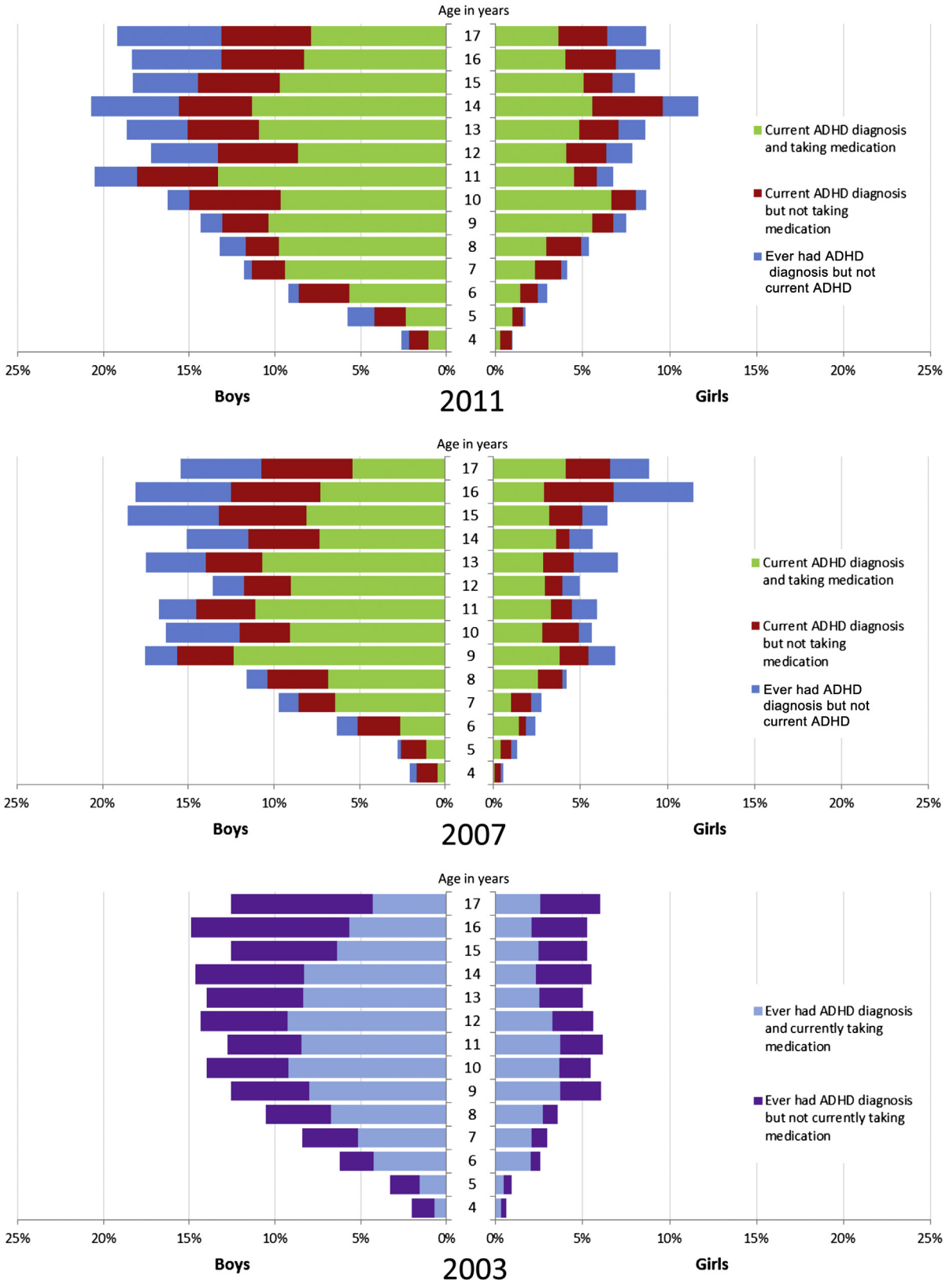
The epidemiological profile for ADHD diagnosis and treatment continues to evolve. Based on parent-reported indicators of health care provider–diagnosed ADHD diagnosis and treatment, more than 1 in 10 school-aged children (11%) had received an ADHD diagnosis by a health care provider by 2011, representing more than 6.4 million children nationally. Nearly 1 in 5 high school boys and 1 in 11 high school girls had been diagnosed with ADHD. Of those with a history of ADHD, 83% had current ADHD in 2011 (8.8% nationwide), and 69% of these children and adolescents (6.1% nationwide) were taking medication for ADHD. These estimates are all significantly higher than comparable 2007 estimates.[28] Specifically, after a 22% increase in parent-reported history of ADHD diagnosis from 2003 to 2007, the prevalence increased another 16% from 2007 to 2011, a total increase of 42% from 2003 to 2011. Medicated ADHD among children living in the United States increased by 27% from 2007 to 2011. Among children with a history of ADHD, proportionately more had current ADHD in 2011, as compared to 2007. Taken together, an estimated 2 million more American children were diagnosed with ADHD, and 1 million more were taking ADHD medication in 2011 compared to 2003.

This study reveals a number of important and consistent demographic patterns for ADHD diagnosed by health care providers. Parent-report of ADHD diagnosis increased for most demographic subgroups; however, after increasing significantly from 2003 to 2007, the prevalence of a history of ADHD diagnosis was statistically similar between 2007 and 2011 among older teens and decreased among children who were multi-racial or of other races.

Direct comparisons of the 2003 to the other medication indicators were not appropriate. From 2007 to 2011, medicated ADHD prevalence increased overall but remained statistically similar among children who were multi-racial or of other races. Medicated ADHD estimates within each ADHD severity strata were statistically similar during this time period. The estimated treated prevalence of ADHD (mental health treatment plus medication) increased from 2007 to 2011, due to increases in medicated ADHD; however, as many as 17.5% of children with current ADHD were not receiving 1 of the forms of treatment for ADHD in 2011, more than one-third of whom had moderate or severe cases.

The findings in this report are subject to several limitations. First, as noted earlier, the ADHD indicators used here did not assess ADHD symptoms but, rather, relied on parent-report of diagnosis by a health care provider, which may introduce recall bias. The parent-reported indicators have not been clinically validated; however, a recent analysis indicated that parent-reported survey data produced similar estimates as those from insurance claims data, providing evidence of convergent validity for parent-reported ADHD diagnosis by a health care provider.[33] Second, the cell phone sample inclusion could have affected the 2011 estimates; analyses of restricted-use data suggest that children living in cell phone–only households in 2011 were more likely to have current ADHD than children living in landline phone households (10.0% vs. 8.4%); therefore, non-coverage of cell phone–only households in 2007 may have underestimated prevalence. Third, survey responses were limited to those who agreed to participate, and response rates in 2011 were

FIGURE 3 Weighted prevalence estimates (%) of parent-reported attention-deficit/hyperactivity disorder (ADHD) diagnosis by a health care provider among children, by age and medication status (United States, 2003, 2007, and 2011).



lower than those in 2003 and 2007; however, nonresponse bias is attenuated by the inclusion of demographic factors in the sample weight calculations, although nonresponse bias cannot be ruled out. Fourth, although medication treatment and mental health treatment indicators were included in this study, other forms of treatment for ADHD were not collected, and estimates of ADHD treatment may therefore underestimate treated prevalence. Finally, the cross-sectional data in this report cannot be used to determine the cause of increased prevalence or the appropriateness of diagnosis or medication treatment. However, these data do allow for ecological analyses of changes in policies and demographic characteristics, as conducted by Fulton *et al.*[34]

The increasing prevalence estimates of parent-reported ADHD diagnosis are generally consistent with previous rates of increase. These increases could indicate that the actual prevalence of underlying ADHD has increased consistently over time; however, the proxy data used in this report prohibits drawing firm conclusions about changes in the underlying prevalence of ADHD. The increases could also reflect better detection of underlying ADHD, due to increased health education and awareness efforts. A number of contextual factors are known to influence the frequency with which childhood ADHD is diagnosed, including increased awareness efforts, educational policies, physician characteristics, cultural factors, and changes in public perception.[34-37] Other factors, such as increased confidence to treat ADHD among clinicians and increased exposure to etiologic factors (e.g., environmental contaminants) may also play a role. The magnitude of increases documented with these cross-sectional data warrant future efforts to more fully understand the factors affecting ADHD diagnosis.

The increases in parent-reported medication for ADHD are consistent with previous research[29,38] and should be considered within a broad context. Medication treatment is the single most effective ADHD treatment, resulting in immediate and meaningful improvements in ADHD symptoms that surpass the efficacy of behavioral therapy alone.[11,12] The effectiveness of ADHD medication on ADHD symptoms has likely contributed to the ADHD medication initiation and continuance. However, we do not fully understand the long-term impact of taking ADHD medication over time. Long-term functional outcomes are consistently and heavily influenced by symptom trajectory, sociodemographic factors, and treatment history.[39] However, there is also some evidence that long-term use of ADHD medication normalizes right dorsolateral prefrontal cortex activation.[40] There has been concern and conflicting evidence about the risk of ADHD medication use and later substance use disorders among adolescents and young adults[41-43]; however, a recent meta-analysis of this research suggests that ADHD medication neither protects against nor increases the risk of substance use disorders.[44] Given the increasing medication treatment patterns and the developing literature about the risks of both intervening and failing to intervene, continued research on the long-term benefits of ADHD treatment, both pharmacological and behavioral, is needed.

Nationally, the increases in parent-reported ADHD diagnosis and associated medication treatment occurred during a period in which the Food and Drug Administration (FDA) issued 3 Public Health Alerts and a series of communications regarding cardiac and psychiatric risks of ADHD medications.[45,46] Others have documented upward trends in ADHD medication treatment despite these safety alerts, which contrast with the downward trends seen in pediatric antidepressant use after alerts regarding suicidality.[45,47,48] Prevalence of ADHD medication use also increased despite an overall downward trend in pediatric medication prescriptions.[49] Notably, there has been an increase in antipsychotic medication use among children, including concomitant use of multiple psychotropic medications, with the most common combination being ADHD medication and an antidepressant.[50,51] Finally, the 2011 medication treatment estimates may have been somewhat constrained by the ADHD medication shortages experienced throughout the United States from 2009 to 2011.[52,53]

The findings of this report have several important clinical and public health implications. Parent-reported prevalence estimates provide insight into the demand that this population has on the systems supporting them, and these data suggest that the impact of ADHD may be increasing. ADHD is commonly diagnosed before age 5 years in children with severe ADHD; children diagnosed with ADHD in early childhood may benefit from targeted interventions. Attention to the transitional needs of the large population of high school students taking medication for ADHD (6.4%) may be

warranted, particularly given increasing concerns about abuse, misuse, and diversion of medication to others.[54-56] Based on this report's estimates, the cross-sector costs associated with ADHD likely exceed the previously estimated upper bound of $78 billion.[57] Future cross–public health system efforts should continue to describe and monitor ADHD diagnostic and treatment patterns, assess the alignment of these patterns to best practices, and seek to understand the factors influencing the evolving prevalence of ADHD diagnosis and treatment. &

CG Clinical Guidance

- The parent-reported prevalence of a history of an attention-deficit/hyperactivity disorder (ADHD) diagnosis by a health care provider among U.S. school-aged children increased from 7.8% in 2003 to 11% in 2011, an increase of 42% in less than a decade.
- In 2011, the median age of ADHD diagnosis was approximately 6 years of age, but children reported by their parents as having more severe ADHD were diagnosed earlier.
- The percentage of US school-aged children with a parent-report of current medication treatment for ADHD increased from 4.8% in 2007 to 6.1% in 2011, an increase of 27% in approximately 4 years.
- More U.S. school-aged children were receiving ADHD treatment in 2011 than in 2007, but nearly 1 in 5 with current ADHD were not receiving either medication for ADHD or mental health counseling in 2011.

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TABLE S1 National Survey of Children's Health 2011–2012: Attention-Deficit/Hyperactivity Disorder (ADHD)–Related Survey Questions

K2Q31A	Has a doctor or other health care provider *ever* told you that [S.C.] had... Attention Deficit Disorder or Attention Deficit Hyperactivity Disorder, that is, ADD or ADHD? **HELP SCREEN** (K2Q31A): A child with Attention Deficit Disorder or Attention Deficit Hyperactivity Disorder has problems paying attention or sitting still. It may cause the child to be easily distracted. (1) YES (2) NO (77) DON'T KNOW (99) REFUSED
K2Q31B	Does [S.C.] *currently* have ADD or ADHD? (1) YES (2) NO (77) DON'T KNOW (99) REFUSED
K2Q31C	Would you describe [his/her] ADD or ADHD as mild, moderate, or severe? (1) MILD (2) MODERATE (3) SEVERE (77) DON'T KNOW (99) REFUSED
K2Q31D	Is [S.C.] currently taking medication for ADD or ADHD? (1) YES (2) NO (77) DON'T KNOW (99) REFUSE
K2Q31A_1	Earlier you told me that [S.C.] currently has ADD or ADHD. How old was [S.C.] when you were first told by a doctor or other health care provider that [he/she] had ADD or ADHD? RECORD AGE IN YEARS OR MONTHS (77) DON'T KNOW (99) REFUSED

FIGURE S1 Percentage distribution of age at attention-deficit/hyperactivity disorder (ADHD) diagnosis by a health care provider based on retrospective parent report, by parent-reported current ADHD severity (United States, 2011–2012).

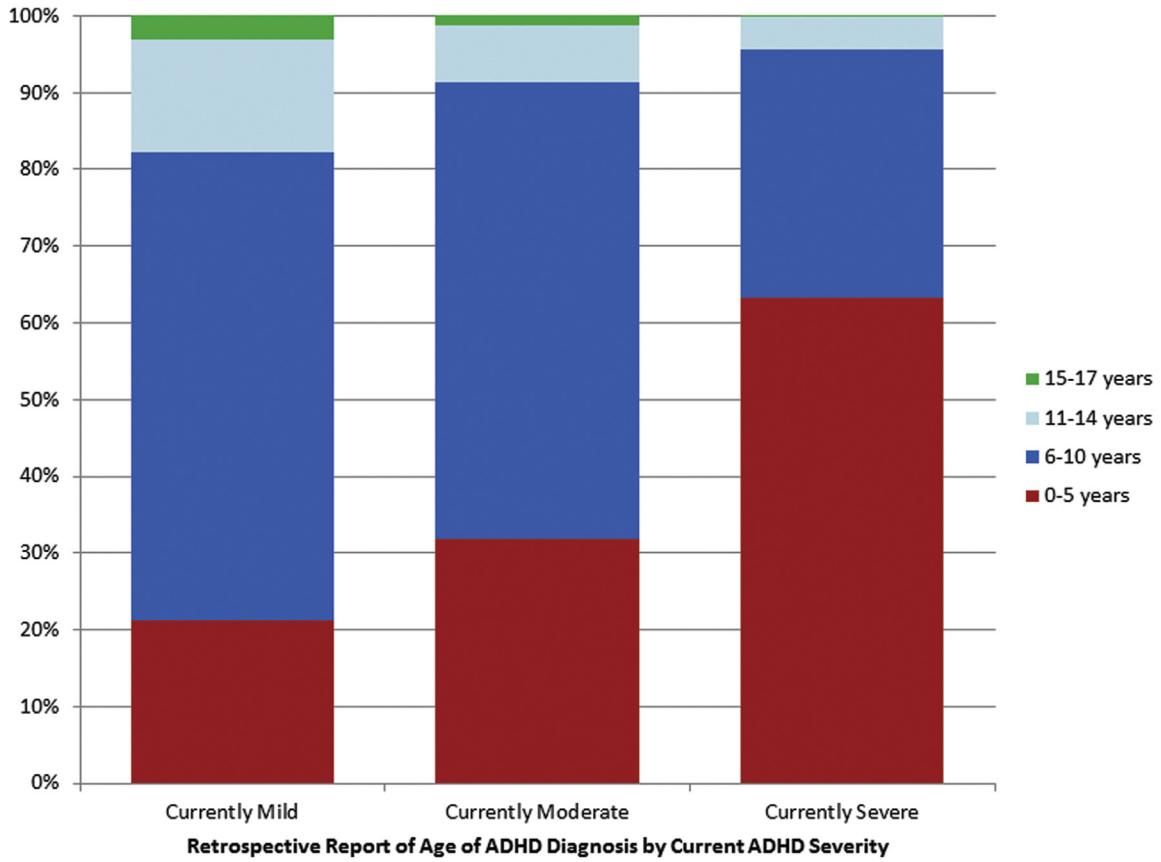

EXHIBIT 76

Attention Deficit Hyperactivity Disorder: Causes of ADHD

No one knows exactly what causes ADHD, but certain things are known to play a role.

IN THIS ARTICLE

The Family Connection

ADHD runs in families. Anywhere from one-third to one-half of parents with ADHD will have a child with the disorder. There are genetic characteristics that seem to be passed down.

If a parent has ADHD, a child has more than a 50% chance of having it. If an older sibling has it, a child has more than a 30% chance.

Pregnancy Problems

Children born with a low birth weight, born premature, or whose mothers had difficult pregnancies have a higher risk of having ADHD. The same is true for children with head injuries to the frontal lobe of the brain, the area that controls impulses and emotions.

Studies show that pregnant women who smoke or drink alcohol may have a higher risk of having a child with ADHD. Exposure to lead, PCBs, or pesticides may also have a role.

Researchers believe that some toxins may interfere with brain development. That, they say, could lead to hyperactivity, impulsive behavior, and trouble paying attention.

What Doesn't Cause ADHD

Although it's been debated, research does not show that ADHD is linked to eating too much sugar or watching a lot of TV.

What Goes On in the Brain

Studies show that brain chemicals, called neurotransmitters, don't work the same in children and adults with ADHD. There also tend to be differences in the way nerve pathways work.

Certain parts of the brain may be less active or smaller in children with ADHD than those without the disorder.

The brain chemical dopamine may also play a role. It carries signals between nerves in the brain and is linked to movement, sleep, mood, attention, and learning.

WebMD Medical Reference | Reviewed by Smitha Bhandari, MD on June 07, 2019

Sources

ADHD Medica
Myths and facts

RECOMMENDED FOR YOU

SLIDESHOW
ADHD in Children

ARTICLE
Is It ADHD or Autism?

SLIDESHOW
Helping Your Child With ADHD to Go to Sleep

ARTICLE

EXHIBIT 77

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The Delinquency Outcomes of Boys with ADHD with and without Comorbidity

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Abstract

This study examined the association between childhood ADHD and juvenile delinquency by examining data from the Pittsburgh ADHD Longitudinal Study (PALS), a follow-up study of individuals diagnosed with ADHD in childhood (ages 5–12) and recontacted in adolescence and young adulthood for yearly follow-up (age at first follow-up interview *M*= 17.26, *SD*=3.17). Participants were 288 males with childhood ADHD and 209 demographically similar males without ADHD who were recruited into the follow-up study. Delinquency information gathered yearly during the second through eighth follow-up provided a comprehensive history of juvenile delinquency for all participants. Four childhood diagnostic groups [ADHD-only (*N*=47), ADHD +ODD (*N*=135), ADHD+CD (*N*=106), and comparison (*N*=209)] were used to examine group differences on delinquency outcomes. Analyses were conducted across three dimensions of delinquency (i.e., severity, age of initiation, and variety). Individuals with childhood ADHD+CD displayed significantly worse delinquency outcomes than the other three groups, across almost all indices of offending. When compared to comparison participants, boys with ADHD-only and ADHD+ODD in childhood displayed earlier ages of delinquency initiation, a greater variety of offending, and higher prevalence of severe delinquency. These findings suggest that although childhood ADHD+CD creates the greatest risk for delinquency, boys with ADHD-only and ADHD+ODD also appear at a higher risk for later offending. The patterns of offending that emerged from the PALS are discussed in the context of the relationship between ADHD, comorbidity, and delinquency.

Keywords

ADHD; Delinquency; Conduct Disorder

Every year thousands of individuals fall victim to criminal acts committed by juveniles in the United States. In 2006, 19.1% of property crimes and 12.1% of violent crimes involved only juveniles (U.S. Department of Justice, 2007). The young individuals who commit these crimes are at a high risk of continuing this criminality into adulthood (Loeber, 1982; Moffitt, Caspi, Harrington, & Milne, 2002), which also incurs a high economic cost to society. By one estimate, a lifetime criminal costs the public between $1.3 million and $1.5 million

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(Cohen, 1998). In addition to the increased risk of adult criminality, delinquent adolescents are also more likely to experience multiple negative personal outcomes in adulthood, ranging from substance abuse to work-related problems (Loeber, Stouthamer-Loeber, & White, 1999; Moffitt et al., 2002).

Given the gravity of juvenile offending, much attention has been directed toward identifying developmental pathways to serious delinquency in order to identify children who are most at risk for this costly outcome. Although minor delinquency appears to be somewhat normative and transient in adolescence, a subset of offenders display a pattern of severe and persistent offending that begins in childhood (Loeber, 1988; Moffitt 1993; 2003). These individuals are most troublesome as they are more likely to continue their criminal behavior into adulthood, commit more severe and violent crimes, and experience a variety of poor personal outcomes (Moffit & Caspi, 2001; Stouthamer-Loeber & Loeber, 2002). There is currently consensus that the progression to serious delinquency begins early, with problems at school, at home, and with peers. Most agree with the hypothesis that this troubling path begins with impulsivity, ADHD, undercontrolled temperament, or some variant thereof (Loeber, 1988; McMahon & Kotler, 2006; Moffitt, 1993; Patterson, DeGarmo, & Knutson, 2000). Negative environmental factors (e.g., poor parenting, life stressors) are thought to lead to an escalation of antisocial behavior that qualifies many for a comorbid diagnosis of Oppositional Defiant Disorder (ODD) and, eventually, Conduct Disorder (CD; Burke, Loeber, Lahey, & Rathouz, 2005; Lahey & Loeber, 1994; Patterson et al., 2000). By one estimate, the progression to comorbid ODD develops in 59% of school-aged children with ADHD (Barkley, 2006). In about two-thirds of these children diagnosed with ADHD+ODD, CD later develops (Greene, 2005). In these children, antisocial behavior often becomes chronic and evolves into a pattern of problematic delinquency.

Data from many longitudinal samples of children with ADHD support the hypothesis that these children are at an increased risk of qualifying for CD in adolescence (Gittelman, Mannuzza, Shenker, & Bonagura, 1985; Lambert, 1988; Mannuzza, Klein, Abikoff, & Moulton, 2004). However, few studies examine the relation between childhood ADHD and subsequent delinquent offending (Lee & Hinshaw, 2004; Loeber, Brinthaupt, & Green, 1990; Molina et al., 2007a; Satterfield, Hoppe, & Schell, 1982; Satterfield, Swanson, Schell, & Lee, 1994). The distinction between these outcomes is important as the overlap between CD and delinquency is only partial. The CD criteria include non-criminal acts such as lying, staying out past curfew, and bullying (APA, 2000), and they do not provide a comprehensive list of delinquent behaviors. As such, delinquency is present in a minority of children with CD (Burke, Loeber, Mutchka, & Lahey, 2002), and many children who commit delinquent acts fail to qualify for a diagnosis of CD (Molina et al., 2007a). The studies cited above provide evidence that children with ADHD are more likely than those without ADHD to offend in adolescence; however, most data suggest that this relationship is influenced by the development of childhood conduct problems subsequent to the onset of ADHD (Biederman, Mick, Faraone, & Burback, 2001; Lee et al., 2004; Lilienfeld & Waldman, 1990; Loeber, Burke, Lahey, Winters, & Zera, 2000). This repeated finding is consistent with the hypothesis that many children with ADHD follow a maladaptive pathway to serious delinquency, but that only those who develop childhood CD become severe and persistent offenders.

Some evidence also suggests that children with ADHD who do not have serious conduct problems in childhood are also at a higher risk for later delinquent offending. Several studies have found elevated rates of later delinquency in children with ADHD who were not diagnosed with comorbid ODD or CD (Loeber et al., 1990; Farrington, Loeber, & Van Kammen, 1990; Satterfield et al., 1994; Molina et al., 2007a). There are also established links between the core symptoms of ADHD and delinquent offending (Carroll et al., 2006;

Kagan & Zentner, 1996; Klinteberg, 1997; Loeber, Pardini, Stouthamer-Loeber, & Raine, 2007; White et al., 1994), even after controlling for conduct problems (Babinski et al., 1999; Pardini, Obradovic, & Loeber, 2006), although exceptions to these findings exist (Lahey et al., 2000; Satterfield & Schell, 1997) Mixed findings on the relationship between ADHD and delinquency highlight the need for further studies with more exhaustive techniques for examining this association.

Notably, a number of questions remain about the relationship between childhood ADHD and delinquency. For example, although studies have examined the presence of offending within the ADHD population (Biederman et al., 2001; Satterfield, 1982; 1994), there has been less emphasis on delinquency severity (Lee et al., 2004; Molina et al., 2009a) and variety (Loeber et al., 1990). Delinquency severity is an important characteristic of the persistent offender (Loeber, 1988) and delinquency variety shows associations with lower self-control and a greater propensity to offend repeatedly (Mazerolle, Brame, Paternoster, Piquero, & Dean, 2000). Furthermore, examinations of severity and variety outcomes in ADHD samples have involved very young adolescents who have not likely reached their offending peak (Lee et al., 2004; Loeber et al., 1990; Molina et al., 2007a). Variety of offending (i.e., the number of different delinquent acts that a participant endorses in the lifetime) is also likely to increase with age simply due to the passage of time and increased opportunity. Consequently, follow-up studies that span adolescence are needed to investigate the timing of delinquency initiation in ADHD samples. In addition, almost no research examines risk for delinquency among children with ADHD and comorbid ODD (Satterfield et al., 1994). Given the important role of ODD in the progression from ADHD to CD (Burke et al., 2005), better understanding of this association may elucidate the relative contributions of ADHD, ODD, and CD toward the later development of delinquency.

The current study seeks to address the questions raised above by examining the delinquent behavior of the males in the Pittsburgh ADHD Longitudinal Study (PALS; Molina et al., 2007b). The PALS is a study of individuals diagnosed with and treated for ADHD in childhood (baseline) and recontacted in adolescence and young adulthood for yearly follow-up visits. In the current study, we examined the contribution of childhood diagnosis (ADHD-only, ADHD+ODD, ADHD+CD, and no diagnosis) to the prediction of later lifetime delinquency severity and variety as well as to the age of initiation at each delinquency severity level (i.e., mild, moderate, severe). We hypothesized the following: 1) that overall prevalence of severe offending would increase incrementally with the severity of childhood diagnostic group, but mild and moderate offending would not due to the more normative nature of these lesser offense categories (Junger-Tas, Terlouw, & Klein, 1994), 2) that across delinquency severity levels, earlier ages of initiation would correspond with the severity of childhood diagnosis, and (3) that variety of offending would also increase in a stepwise fashion along with the severity of childhood diagnosis.

Method

Participants

Probands—At the start of the follow-up study, probands were recruited from a pool of 466 study-eligible adolescent and young adult males who were previously diagnosed with DSM-III-R or DSM-IV ADHD and treated at the ADD clinic at the Western Psychiatric Institute and Clinic in Pittsburgh, PA in childhood (baseline). In the current study, probands were 288 males in the PALS who were age 12 or younger at baseline. Of the 466 study eligible adolescent and young adult males, 23 could not be located at follow-up, 129 refused or failed to participate, and 26 were older than 12 at initial referral to the clinic (baseline). Age at baseline evaluation ranged from 5.0 to 12.83 years (M= 8.92, SD=1.79).

In childhood (baseline), all probands participated in the Summer Treatment Program (STP) for children with ADHD, an 8-week intervention that included behavioral modification, parent training, and psychoactive medication trials where indicated (Pelham & Hoza, 1996). Children were referred to the STP from across Allegheny County, PA by several large public sources, such as Pittsburgh Public Schools. Diagnostic information for probands was collected at baseline using parent and teacher DSM-III-R and DSM-IV symptom ratings scales (DBD; Pelham, Evans, Gnagy, & Greenslade, 1992) and a semi-structured diagnostic interview administered to parents by a Ph.D. level clinician. The interview consisted of the DSM-III-R or DSM-IV descriptors for ADHD, ODD, and CD with supplemental probe questions regarding situationality and severity. It also included queries about other comorbidities to determine whether additional assessment was needed (instrument available at http://ccf.fiu.edu). Following DSM guidelines, diagnoses of ADHD, ODD, and CD were made if a sufficient number of symptoms were endorsed (considering information from both parents and teachers) to result in diagnosis. Two Ph.D. level clinicians independently reviewed ratings and interviews to confirm diagnoses and when disagreement occurred, a third clinician reviewed the file and the majority decision was used. Exclusion criteria for probands were assessed at this baseline assessment and included a full-scale IQ < 80, a history of seizures or neurological problems, and/or a history of pervasive developmental disorder, schizophrenia, or other psychotic or organic mental disorders.

Probands began participation in the follow-up study an average of 8.35 (*SD*=2.79) years after baseline assessment and treatment at the ADD clinic. They were recontacted and admitted to the study on a rolling basis as adolescents and young adults (11 to 28 years of age; all but three <25) and completed their first follow-up interview upon enrollment. Participants in the follow-up study were compared with the eligible individuals who did not enroll on demographic (i.e., age at first treatment, race, parental education level, and marital status) and diagnostic (i.e., parent and teacher ratings of ADHD and related symptomatology) variables collected at baseline. Only one of 14 comparisons was statistically significant at the $p<.05$ significance level. Participants had a slightly lower average CD symptom rating on a four point scale as indicated by a composite of parent and teacher ratings (participants $M = .43$, non-participants $M = .53$).

Comparison Group—Comparison participants were 209 males without ADHD. Comparison participants were recruited for the PALS from the greater Pittsburgh community at the same time as probands were recontacted to enroll in the follow-up study. These individuals were recruited from several sources including pediatric practices in Allegheny County (40.8%), advertisements in local newspapers (27.5%), local universities and colleges (20.8%), and other methods (10.9%) such as Pittsburgh Public Schools and word of mouth. Like probands, comparison participants were recruited on a rolling basis. Comparison recruitment lagged three months behind proband enrollment in order to facilitate efforts to obtain demographic similarity (discussed below). A telephone screening interview was administered to parents of potential comparison participants to gather basic demographic characteristics, history of diagnosis or treatment for ADHD and other behavior problems, presence of exclusionary criteria as previously listed for probands, and a full checklist of ADHD symptoms. Older individuals (age 18+) also provided self-report. ADHD symptoms were counted as present if reported by either the parent or the young adult. Individuals who met DSM-III-R criteria for ADHD, either currently or historically, were immediately excluded from study consideration. Although a history of ODD and CD were not exclusion criteria for comparison participants, parent and self-report indicated that only one comparison participant had a history of ODD-like behaviors in childhood and no comparison participants displayed a history of CD-like behaviors. At recruitment, average ADHD symptom severity for the comparison group was .65 (0–3 scale).

If a potential comparison participant passed the initial phone screen, senior research staff members met to determine whether he was demographically appropriate for the study. Four demographic characteristics were examined for each potential comparison participant: 1) age, 2) gender, 3) race, and 4) parent education level. A comparison participant was deemed study-eligible if his enrollment increased the comparison group's demographic similarity to the probands. At the end of the recruitment process, the proband and comparison groups were equivalent on the four demographic variables noted above. An unsuccessful attempt was made to obtain equivalence on the proportion of parents who were married (see Table 1).

Procedure

As noted, baseline diagnoses were gathered for probands at initial referral to the clinic during childhood. Follow-up interviews in adolescence and young adulthood were conducted by post-baccalaureate research staff. All questionnaires (paper and pencil or web-based) in the current study were completed privately. During informed consent, participants were assured of the confidentiality of disclosed materials. In cases where distance prevented participant travel to WPIC, information was collected through mail, telephone correspondence, and home visits. PALS follow-up interviews were conducted yearly beginning in the year of enrollment. As a result, the year (e.g., 2000) in which a participant completed a given interview (e.g., follow-up interview 1) varied across individuals. The collection of lifetime delinquency data began at the second annual interview. Data for the current study were from the second through the eighth annual interviews. By the 8th interview, all participants had turned 18 years old which provided a cumulative record of delinquency through age 18 for all participants.

Measures of Delinquency

Delinquency ratings were calculated from data collected by the Self-Reported Delinquency questionnaire (SRD; Elliott, Huizinga, & Ageton, 1985). During the second (age *M* = 18.11, *SD*= 3.18), third (age *M* = 19.15, *SD*= 3.16), and fourth (age *M* = 20.22, *SD*= 3.23) annual interviews, all participants and parents were asked to provide information about lifetime engagement in 37 delinquent acts (e.g., Have you ever snatched someone's purse or wallet?), including initiation age (e.g., How old were you when you first snatched someone's purse or wallet?), setting (e.g., Did any of these occur at school?), and the value of damages (e.g., What was the dollar value?). At least three lifetime reports were available for most participants (88.7%). A minority provided lifetime delinquency information at only two interviews (6.5%) or at one interview (4.8%). At the fifth follow-up interview, only participants who were still under 18 at the previous interview (18%) were administered the SRD. These individuals were asked to report on delinquency during the past year until the follow-up interview at which they reached the age of 18. Past-year reporting continued for 12.3% of the sample at the sixth follow-up interview, 7.8% at the seventh follow-up interview, and 3.2% at the eighth follow-up interview.

At each follow-up interview, parent report was compared to self-report and an act was counted if endorsed by either reporter. In a few cases (*N*=12), follow-up interviews were not conducted with parents and youth report alone was used. Because the current study concerns itself only with juvenile delinquency, acts reported as being committed after the age of 18 (according to SRD follow-up questions) were not included in analyses. All available reports were integrated to provide a comprehensive lifetime history of juvenile offending for all participants.

Severity—Lifetime severity ratings were coded according to the scheme developed by Wolfgang, Figlio, Tracey, and Singer (1985) and used extensively in the Pittsburgh Youth

Study (Loeber et al., 1991). Three levels of delinquency severity were coded at each follow-up interview based on whether or not a participant or his parent reported an act at a given level: mild = minor delinquency outside of the home (e.g., vandalism with damages less than $100, avoiding payment, theft of less than $5); moderate = moderately serious delinquency (e.g., credit card fraud, theft of $5 or more, arson with damages over $100, joyriding); severe = serious delinquency (e.g., breaking and entering, vehicle theft, attacking someone with a weapon with the intent to seriously hurt or kill, rape). For each participant, codes from each available follow-up interview were integrated to indicate the presence of offending (yes/no) and age of initiation (up to age 18) for each severity level of delinquency (based on the SRD follow-up questions).

Variety—A lifetime estimate of delinquency variety was obtained by summing the total number of types of acts (out of 34) that a participant or his parent endorsed as occurring before age 18 (Loeber et al., 1990; Mazerolle et al., 2000). Three acts are routinely omitted from coding due to deviation from the delinquency construct (i.e., arrest, carrying a concealed weapon, drug selling). The variety categorization did not account for the number of times each act was committed, rather served as a measure of variety across category. A participant's variety score consisted of the total number of acts a participant endorsed across all follow-up interviews.

Analytic Plan

Prior to the analyses all demographic characteristics were examined by the four childhood diagnostic subgroups [ADHD-only (N=47), ADHD+ODD (N=135), ADHD+CD (N=106), no diagnosis (N=209)]. Single parent household and parental education tended toward group differences but were not statistically significant (p<.25). Nevertheless, these variables were included as covariates in all models to ensure that they were not contributing to subgroup differences in delinquency outcomes. The three proband diagnostic groups did not significantly differ in their average age at baseline [$F(2,285)$= .60, p=.55]; however, given the wide age range (11–28) at enrollment into the follow-up study, age at the first follow-up interview was also entered into all models to control for any differential recall that may have occurred as a result of the participant's age at follow-up.

Severity—Three survival analyses were conducted to examine potential childhood diagnostic group differences (ADHD-only, ADHD+ODD, ADHD+CD, no diagnosis) in the prevalence of offending at each severity level (mild, moderate, severe). Survival rates were expressed as percentages of youth who had offended at a given severity level through age 18 calculated using the Cox regression method. Cox regression curves and log-likelihood tests were used to test the difference between the groups' offending curves. For severe delinquency, additional planned comparisons (ADHD-only vs. ADHD+ODD; ADHD-only vs. ADHD+CD; ADHD+ODD vs. ADHD+CD) were conducted in order to further examine the relative risk of childhood diagnosis in predicting this most clinically significant variable. A Bonferroni correction for three planned comparisons set a pre-established alpha-level of . 02 for this analysis.

Age of Initiation—A Generalized Linear Model using a normal distribution and an identity link function was employed to compare the four childhood diagnostic groups on age of initiation for mild, moderate, and severe delinquency. Comparison participants were used as a reference group and childhood diagnosis dummy codes (ADHD-only: yes vs. no; ADHD + ODD: yes vs. no; ADHD + CD: yes vs. no) as the independent variable. Additional planned comparisons (ADHD-only vs. ADHD+ODD; ADHD-only vs. ADHD +CD; ADHD+ODD vs. ADHD+CD) were conducted to examine the relative risk of comorbid ODD and CD diagnosis. A Bonferroni correction for three planned comparisons

set a pre-established alpha-level of .02 for this analysis. Generalized Linear Modeling has been shown to be a powerful method of detecting relationships involving normally and non-normally distributed variables (McCullagh & Nelder, 1989).

Variety—A Generalized Linear Model using a normal distribution and an identity link function was employed to compare the four childhood diagnostic groups on delinquency variety. Comparison participants were used as a reference group and childhood diagnosis dummy codes (ADHD-only: yes vs. no; ADHD + ODD: yes vs. no; ADHD + CD: yes vs. no) as the independent variable. Additional planned comparisons (ADHD-only vs. ADHD +ODD; ADHD-only vs. ADHD+CD; ADHD+ODD vs. ADHD+CD) were conducted in order to further examine the relative risk of comorbid ODD and CD diagnosis. A Bonferroni correction for three planned comparisons set a pre-established alpha-level of .02 for this analysis.

Results

Severity

Figures 1a–1c display prevalence of offending for the childhood diagnostic groups across mild, moderate, and severe delinquency. Only 23.9% of comparison participants, 29.8% of ADHD-only, 25.9% of ADHD+ODD, and 17.8% of ADHD+CD completely abstained from delinquent offending at any severity level. For mild delinquency, the overall test of the model was non-significant [$X^2(8)=6.55$, $p=.59$], indicating that all four groups showed a similar prevalence of mild offendng (see Table 2). For moderate delinquency, the overall test of the model was significant [$X^2(58)=46.99$, $p<.01$], and after controlling for the covariates, only probands with a childhood diagnosis of ADHD+CD displayed a pattern of moderate offending that was significantly different from that of comparison participants (see Table 2). For severe delinquency, the overall test of the model was also significant [$X^2(5)=37.35$, $p<.01$], and after controlling for the covariates, probands with childhood ADHD+CD and ADHD+ODD displayed a prevalence of severe offending that was significantly higher than comparison participants. ADHD-only probands did not significantly differ from comparison participants ($p=.12$), despite displaying a nearly identical pattern of severe offending to the ADHD+ODD group (see Table 2 & Figure 1c). Planned comparisons revealed that risk for severe offending did not differ significantly between the ADHD-only and the ADHD+ODD groups (*OR*=1.63, $p=.36$) or between the ADHD+ODD and the ADHD+CD groups (*OR*=1.58, $p=.22$); however, individuals with a childhood diagnosis of ADHD+CD (*OR*= 2.57, $p=.07$) were more likely than individuals with a childhood diagnosis of ADHD-only to engage in severe delinquency.

Age of Initiation

For mild delinquency, the overall test of the model was significant [$X^2(8)=388.42$, $p<.01$]. Results revealed that after controlling for the covariates, the ADHD-only (*Estimated M*=11.42, *SE*=.21, *b*=−1.04, *SE*=.22, *Wald*= 22.38, $p<.01$), ADHD+ODD (*Estimated M*=10.96, *SE*=.12, *b*=−1.50, *SE*=.15, *Wald*=105.76, $p<.01$), and ADHD+CD (*Estimated M*=10.36, *SE*=.14, *b*=−2.10, *SE*=.16, *Wald*=175.53, $p<.01$) groups initiated mild delinquency at significantly earlier ages than the comparison group (*Estimated M*=12.46, *SE*=.10). Additional planned comparisons revealed that after controlling for the covariates, the ADHD+CD group also initiated mild delinquency at significantly earlier ages than the ADHD+ODD and ADHD-only groups.

For moderate delinquency, the overall test of the model was significant [$X^2(8)=258.27$, $p<.01$] and after controlling for the covariates, the ADHD-only (*Estimated M*=13.36, *SE*=.24, *b*=−1.14, *SE*=.26, *Wald*= 19.03, $p<.01$), ADHD+ODD (*Estimated M*=13.43, *SE*=.14, *b*=

−1.08, *SE*=.18, *Wald*=35.37, *p*<.01), and ADHD+CD (*Estimated M*=11.99, *SE*=.14, *b*= −2.52, *SE*=.17, *Wald*=218.82, *p*<.01) groups initiated moderate delinquency at significantly earlier ages than comparisons (*Estimated M*=14.50, *SE*=.12). Additional planned comparisons revealed that after controlling for the covariates, the ADHD+CD group initiated moderate delinquency at significantly earlier ages than the ADHD+ODD and ADHD-only groups.

For severe delinquency, the overall test of the model was significant [$X^2(8)=88.99$, $p<.01$] and the analysis revealed that after controlling for the covariates, the ADHD+CD group (*Estimated M*=12.87, *SE*=.18, *b*=−.89, *SE*=.27, *Wald*= 10.75, *p*<.01) initiated severe delinquency at significantly earlier ages than the comparison group (*Estimated M*=13.76, *SE*=.22). The ADHD+ODD (*Estimated M*=14.59, *SE*=.19, *b*=.83, *SE*=.29, *Wald*=8.13, *p*<. 01) group initiated severe delinquency at significantly later ages than the comparison group. The ADHD-only group (*Estimated M*=13.99, *SE*=.34, *b*=−.23, *SE*=.40, *Wald*=.33, *p*=.57) was not significantly different from the comparison group on age of severe delinquency initiation. Additional planned comparisons revealed that after controlling for the covariates, the ADHD+CD group initiated severe delinquency at significantly earlier ages than the ADHD+ODD and ADHD-only groups.

Variety

The overall model was significant [$X^2(5)=644.32$, $p<.01$] and the analysis revealed that after controlling for the covariates, the ADHD-only (*Estimated M*=6.19, *SE*=.16, *b*=.82, *SE*=.17, *Wald*= 22.33, *p*<.01), ADHD+ODD (*Estimated M*=6.72, *SE*=.10, *b*=1.35, *SE*=.12, *Wald*=129.58, *p*<.01), and ADHD+CD (*Estimated M*=8.69, *SE*=.12, *b*=3.32, *SE*=.13, *Wald*=630.30, *p*<.01) groups committed a significantly higher variety of delinquent acts than the comparison group (*Estimated M*=5.37, *SE*=.08). In addition, all planned comparisons were significant indicating that the three proband groups also significantly differed from each other.

Discussion

The findings of this study suggest that regardless of comorbidity, all children with ADHD are at some type of increased risk for delinquency. Specific findings were that: (a) compared to the other three childhood diagnostic subgroups (no diagnosis, ADHD-only, ADHD +ODD), children with ADHD+CD were at a higher risk for all but one index of delinquency examined in this study (prevalence of mild delinquency); b) children with ADHD-only and ADHD+ODD displayed a slightly elevated prevalence of severe offending, were at risk for earlier initiation of mild and moderate delinquency, and committed a greater variety of acts than the comparison group; and (c) the risks exhibited by the ADHD-only and ADHD+ODD groups were very similar, only differing on variety of offending. We shall discuss each of these findings in turn.

The clearest finding that emerged from this study was that children diagnosed with ADHD +CD were at the highest risk for delinquent offending across measures of severity, variety, and age of initiation. This finding is consistent with most if not all studies that examine the relationship between childhood ADHD, childhood conduct problems, and adolescent delinquency (Loeber et al., 1990; 2000). The pervasiveness of this finding highlights the grave trajectory shared by these individuals. Most of these boys (≈70%) initiated mild and moderate delinquency, doing so early (mild *Estimated M*=10.36, moderate *Estimated M*=11.99). A subset of the boys with ADHD+CD (45.3%) also initiated severe delinquency, again doing so at earlier ages than offenders in the other groups (*Estimated M*=12.87). These boys also committed a greater variety of acts than the other subgroups. Although these results implicate childhood CD as a precursor to severe delinquent offending, at least when

it co-occurrs with ADHD, only half (51.6%) of severe offenders with childhood ADHD were diagnosed with CD at baseline, despite the high rate of CD in our sample. Thus, something other than CD appears to account for the development of severe delinquency in about half of the PALS severe offenders. Of course, it is possible that some of these boys developed CD after baseline assessment (Lahey et al., 1995).

The only exception to the elevated risk displayed by ADHD+CD probands was prevalence of mild delinquency. Our data show a high prevalence of mild delinquency in all four childhood diagnostic groups, which suggests that mild offending may be normative in adolescence. In fact, a high proportion of participants in all four childhood diagnostic groups committed at least one delinquent act (Range= 70.2%–82.2%). This finding is consistent with cross-national prevalence rates that suggest that most adolescents will self-report at least one criminal act during their youth (Junger-Tas et al., 1994). Thus, group differences did not emerge on mild delinquency because of prevalent normative offending in the comparison group.

Our data also revealed that boys with childhood ADHD-only and childhood ADHD+ODD showed elevated risks for delinquent offending by age 18. Specifically, these two groups were more likely to offend earlier, commit a greater variety of crimes, and initiate severe delinquency than comparison participants (see Table 2). These findings suggest that boys with ADHD who are low on antisocial behaviors in elementary school are still at risk for later delinquent offending. This risk is concerning given that early offending and varied offending are both associated with non-normative offending trajectories (Mazerolle et al., 2000;Moffitt, 2003). This claim is also consistent with other studies showing that adolescents with ADHD begin offending earlier than those without this disorder (Forehand, Wierson, Frame, Kempton, & Armistead, 1991;Moffitt, 1990). With respect to severe delinquency, boys with ADHD-only (23.4%, *OR*=1.84) and with ADHD+ODD (25.4%, *OR*=2.01) were at a similar risk (see Figure 1c); however, this risk was non-significant in the ADHD-only group (p=.12). Despite this non-significance– perhaps because the sample size was about 1/3 of that for the ADHD+ODD group - both groups were about twice as likely as comparison participants to engage in severe delinquency, such as forcible theft, breaking and entering, vehicle theft, rape, or murder.

Only delinquency variety displayed the stepwise risk that we predicted would occur in correspondence with childhood diagnostic severity. This finding was consistent with the only other study of ADHD and delinquency variety (Loeber et al., 1990), which reported that variety scores in youth with ADHD+CD were higher than those possessed by youth with ADHD-only, which in turn were higher than the comparison group. Studies of delinquency volume draw a similar conclusion. These findings suggest that ADHD is related to overall volume of crime, but not any particular type of crime, with high rates of offending across a wide variety of crimes (Barkley et al., 2007; Dalteg & Levander, 1998; Torgersen et al., 2006). It is not surprising that the variety variable displayed our hypothesized incremental risk, as delinquency variety is an index that is conceptualized by some to reflect low self-control (Hirschi & Gottfredson, 1993), which is also a hallmark feature of ADHD (Barkley, 2006). Indeed, one characteristic of the PALS sample was that baseline ADHD severity increased with the severity of one's childhood diagnosis (see Table 1), which may account for some of the relative increased delinquency variety.

While it came as no surprise that boys with ADHD+CD offended at the highest rates, the similar pattern of offending displayed by boys with ADHD-only and ADHD+ODD was somewhat unexpected (see Table 2 & Figure 1a–c). A full understanding of this finding requires careful consideration of the composition of these groups. Although as discussed above, the ADHD+ODD group showed somewhat elevated levels of baseline ADHD

symptomatology, compared to the ADHD-only group, they differed vastly on ODD symptomatology (see Table 1). Furthermore, the ADHD+ODD and ADHD+CD shared very similar levels of baseline ODD symptoms, but displayed disparate risks for later offending (see Tables 1 & 2 & Figures 1b–c). Consequently, these data seem to suggest that elevations in ODD symptomatology do not increase the risk for most of the delinquency indices examined in this study. Although theory heavily implicates coercive family processes and subsequent ODD in the development of conduct problems and later delinquency (Moffitt, 1990;Patterson et al., 2000;Snyder, Cramer, Afrank, & Patterson, 2005), our data suggest that oppositional behavior may carry a limited risk for non-normative delinquency if this disorder does not evolve into symptoms of CD. However, given the finding that about two-thirds of children with ADHD+ODD develop CD (Greene, 2005), it may be particularly effective to intervene with boys with ADHD+ODD in order to prevent the especially severe offending trajectory demonstrated by boys with ADHD+CD.

These trends suggest that while individuals without ADHD are mostly at risk for committing delinquent acts of mild to moderate severity during adolescence, individuals with childhood ADHD are at an earlier and unremitting risk for offending at all delinquency severity levels and across a wider variety of crimes (see Table 2). Unfortunately, earlier and more severe offending would seem to suggest that children with ADHD, and especially with comorbid CD, are also at risk for offending that persists into adulthood (Moffitt, 1993;2003). Our data also indicate that clinically significant levels of childhood conduct problems propel the risk for earlier, more severe, and more varied delinquency. However, given the incremental gains in ADHD symptomatology as one moves to a more severe childhood diagnosis (see Table 1;Waschbusch, 2002), it is also possible that some of the risk accrued by comorbidity may be attributable to more severe ADHD symptoms. Unfortunately, without childhood measures on the comparison group, we were unable to fully investigate the contribution of childhood symptom severity to the development of later delinquency. This is an important limitation to our study.

There are other limitations as well. As a clinic-referred sample, the outcomes found in the PALS may not generalize to epidemiological samples of children with ADHD. Thus, there is a need to replicate these results using a community sample. Another limitation to our study is that our baseline data represents a diagnostic snapshot of each proband in childhood. Therefore, it is also possible that some of the probands without a baseline diagnosis of comorbid CD (age range: 5–12 years; M = 8.92, SD= 1.79) might have developed CD between baseline and follow-up. It is also possible that some participants who met criteria for ODD or CD during baseline may have experienced a remission of these symptoms after the baseline assessment. In addition, eligible participants who did not enroll in the study possessed slightly higher baseline CD severity scores than enrollees. It is possible that had these eligible participants enrolled, delinquency estimates in the proband groups could have been different. For probands with a comorbid diagnosis of CD, delinquent acts committed prior to initial assessment may have actually been the cause of a CD diagnosis. Although we attempted to reduce this possibility by excluding participants who were over age 12 at baseline, we were regrettably unable to completely remove these acts from our analyses due to the nature of the SRD questionnaire (Elliot et al., 1985). It is also the case that some of the delinquency history collected from our sample was based on retrospective report. We attempted to safeguard against the complications associated with retrospective report of delinquency (Kazemian & Farrington, 2005) by asking participants and parents to report lifetime delinquency three times and using age at follow-up as a covariate. However, it is possible that we were unable to identify all acts ever committed by the participants. Given that our delinquency measure did not assess for the number of times each act was committed, we were also unable to examine differential patterns in delinquency volume.

Given the small number of boys in our sample who qualified for diagnosis of ADHD-Predominantly Inattentive Subtype, we were also unable to examine whether offending patterns differed amongst the subtypes of ADHD. In addition, while our sample was demographically representative of the county in which the study occurred, it is important to note that many of our participants came from middle-class families. As a result, our findings may be most generalizable to middle-class, racial-majority males with parents who are high school graduates. For example, evidence suggests that females display different normative and non-normative patterns of offending than males (Silverthorn & Frick, 1999).

Future Directions

An important future line of research is the investigation of symptom clusters and child characteristics that give rise to non-normative delinquency. For example, Callous-Unemotional (CU) traits show evidence of a unique pathway to severe offending (Frick, 2004); however, no study has examined the role of these traits in predicting delinquency outcomes in a childhood ADHD sample. Future research must also address influences, such as parenting, that occur between childhood and adolescence and likely influence whether or not a child with ADHD initiates or maintains an antisocial pathway. Additionally, future work should address the adulthood persistence of criminal offending within the ADHD population, thereby extending the patterns examined in the current study and addressing whether the early-onset offending found in the ADHD group represents life-course persistent criminality.

Clinical Implications

For children with ADHD, an elevated risk for non-normative delinquency is just one of a slew of probable negative life outcomes, including school drop-out, interpersonal difficulties, substance use, and unemployment (Barkley et al., 2007; Mannuzza, Gittelman-Klein, Bessler, Malloy & LaPadula, 1993; Molina et al., 2007b; Weiss & Hechtman, 1993). These outcomes highlight the intense need for treatment in individuals diagnosed with ADHD. All PALS probands participated in an 8-week intensive Summer Treatment Program and their parents received a standard course of behavioral parent training (Pelham & Hoza, 1996). They also received an average of 6 years of pharmacological intervention. However, the findings of this study and others from this same sample (Molina et al., 2007b; Kent et al., under review) suggest that these interventions were not sufficient to prevent the negative outcomes that are common for children with ADHD. This is especially true for children with comorbid CD. Our findings suggest that in individuals with ADHD, there is a need for chronic treatment that begins early in childhood and persists into adolescence (Eyberg, Nelson, & Boggs, 2008; Pelham & Fabiano, 2008). For many children with ADHD, antisocial behavior begins in childhood but peaks in adolescence. However, treatment for adolescents with ADHD (Smith, Waschbusch, Willoughby, & Evans, 2000) is not well-researched and scarcely offered in most communities. Further work is sorely needed to develop prevention and intervention efforts in childhood and effective interventions for adolescents with ADHD.

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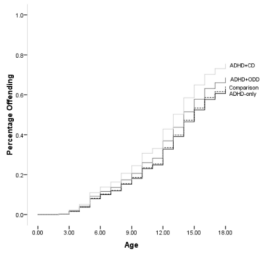

Figure 1a. Mild Delinquency

Note. Y-axis represents % initiating mild delinquency at the mean of the covariates (single parent status, parental education, and age at follow-up).

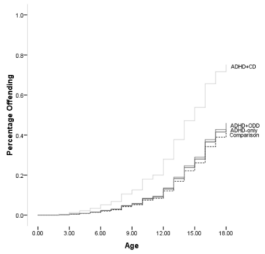

Figure 1b. Moderate Delinquency Pattern

Note. Y-axis represents % initiating moderate delinquency at the mean of the covariates (single parent status, parental education, and age at follow-up).

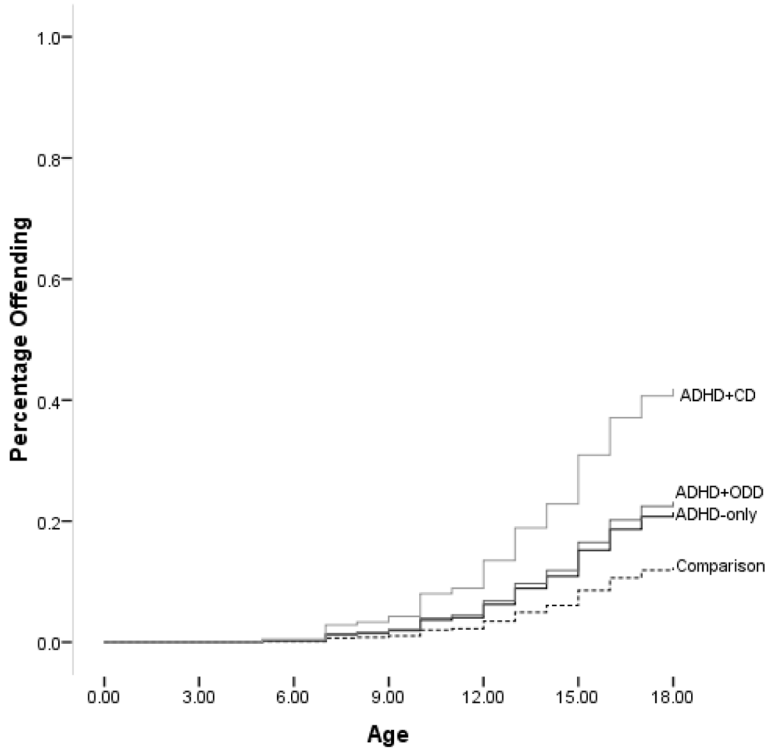

Figure 1c. Severe Delinquency Pattern

Note. Y-axis represents % initiating severe delinquency at the mean of the covariates (single parent status, parental education, and age at follow-up).

Table 1

Characteristics of the Sample at Baseline and First Follow-up Visit

	Comparison (*N*=209)	ADHD-only (*N*=47)	ADHD+ODD (*N*=135)	ADHD+CD (*N*= 106)
Diagnostic Variables at Baseline				
ADHD				
Symptoms Endorsed	----------	11.23(1.90)	12.88(1.60)	13.09(1.34)
Severity Score	----------	2.05 (.44)	2.28(.41)	2.40(.36)
ODD				
Symptoms Endorsed	----------	2.57 (1.17)	7.08(1.35)	7.82(1.20)
Severity Score	----------	.83 (.32)	1.93(.51)	2.23(.44)
CD				
Symptoms Endorsed	----------	.38 (.61)	1.13(.76)	4.14(1.39)
Severity Score	----------	.15 (.11)	.32(.18)	.72(.27)
Demographics at First Follow-up				
Age (M, SD)	17.00 (3.15)	17.68 (3.02)	16.84(3.04)	17.59(3.38)
Racial Minority (%)	14.4	15.6	21.2	15.5
African-American (%)	8.1	11.1	14.4	5.8
Other (%)	6.3	4.5	6.8	9.7
Highest Parent Education†				
High School Grad or GED (%)	9.1	4.9	8.3	9.1
Partial College (%)	29.9	46.3	31.7	47.7
College or University Grad (%)	26.4	19.5	31.7	25.0
Graduate Training (%)	34.5	29.3	28.3	18.2
% Single Parent Household†	24.7	31.7	36.3	32.6

Note. Symptom endorsed is total number of symptoms reported by either parent or teacher on the DBD rating scale or DBD interview. Severity score is the higher score reported by either parent or teacher on the DBD rating scale, calculated by taking the average symptom level on a scale from 0 “not at all present” to 3 “very much present

† $p<.25$.

Table 2

Group Differences in the Initiation of Mild, Moderate, and Severe Delinquency

	Age of Initiation[a]	Rate	b	SE	Wald	Sig.	OR
Mild Acts							
Comparison	12.46	67.9%	--	--	--	--	--
ADHD-only	11.42	59.6%	−.03	.22	.01	.91	.98
ADHD+ODD	10.96	67.4%	.12	.15	.72	.40	1.13
ADHD+CD	10.36	70.8%	.32	.16	3.97	.05	1.37
Moderate Acts							
Comparison	14.50	43.1%	--	--	--	--	--
ADHD-only	13.36	46.8%	.08	.26	.10	.75	1.09
ADHD+ODD	13.43	45.9%	.12	.18	.48	.49	1.13
ADHD+CD	11.99	67.9%	.94	.17	29.11	<.01	2.55
Severe Acts							
Comparison	13.76	13.4%	--	--	--	--	--
ADHD-only	13.99	23.4%	.61	.39	2.39	.12	1.84
ADHD+ODD	14.59	25.2%	.70	.28	6.23	.01	2.01
ADHD+CD	12.87	45.3%	1.42	.27	27.33	<.01	4.13

Note: Mild offenses include: property damage<$100, minor fire-setting, theft<$5, avoiding payment, cheating others. Moderate offenses include: gang fighting, property damage>$100, fire-setting with major damage, theft>$5, purse snatching, picking pocket, stealing from a car, dealing stolen goods, joyriding, check fraud, credit card fraud, counterfeiting. Severe offenses include: forcible theft, breaking and entering, vehicle theft, rape, attacking someone with the intent to seriously injure or kill, attack with a weapon.

[a] Represents the estimated marginal mean age of initiation after controlling for demographic covariates.

EXHIBIT 78

The effect of ADHD on the life of an individual, their family, and community from preschool to adult life

V A Harpin

Arch Dis Child 2005;**90**(Suppl I):i2–i7. doi: 10.1136/adc.2004.059006

Attention deficit/hyperactivity disorder (ADHD) may affect all aspects of a child's life. Indeed, it impacts not only on the child, but also on parents and siblings, causing disturbances to family and marital functioning. The adverse effects of ADHD upon children and their families changes from the preschool years to primary school and adolescence, with varying aspects of the disorder being more prominent at different stages. ADHD may persist into adulthood causing disruptions to both professional and personal life. In addition, ADHD has been associated with increased healthcare costs for patients and their family members.

Attention deficit/hyperactivity disorder (ADHD) is a chronic, debilitating disorder which may impact upon many aspects of an individual's life, including academic difficulties,[1] social skills problems,[2] and strained parent-child relationships.[3] Whereas it was previously thought that children eventually outgrow ADHD, recent studies suggest that 30–60% of affected individuals continue to show significant symptoms of the disorder into adulthood.[4] Children with the disorder are at greater risk for longer term negative outcomes, such as lower educational and employment attainment.[5] A vital consideration in the effective treatment of ADHD is how the disorder affects the daily lives of children, young people, and their families. Indeed, it is not sufficient to merely consider ADHD symptoms during school hours—a thorough examination of the disorder should take into account the functioning and wellbeing of the entire family.

As children with ADHD get older, the way the disorder impacts upon them and their families changes (fig 1). The core difficulties in executive function seen in ADHD[7] result in a different picture in later life, depending upon the demands made on the individual by their environment. This varies with family and school resources, as well as with age, cognitive ability, and insight of the child or young person. An environment that is sensitive to the needs of an individual with ADHD and aware of the implications of the disorder is vital. Optimal medical and behavioural management is aimed at supporting the individual with ADHD and allowing them to achieve their full potential while minimising adverse effects on themselves and society as a whole.

The aim of this paper is to follow the natural history of this complex disorder through preschool years, school life, and adulthood and to consider its effect on the family, the community, and society as a whole. In addition, comorbidities and healthcare costs are examined.

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THE PRESCHOOL CHILD

Poor concentration, high levels of activity, and impulsiveness are frequent characteristics of normal preschool children. Consequently, a high level of supervision is the norm. Even so, children with ADHD may still stand out. In this age group there is often unusually poor intensity of play and excessive motor restlessness.[8 9] Associated difficulties, such as delayed development, oppositional behaviour, and poor social skills, may also be present. If ADHD is a possibility, it is vital to offer targeted parenting advice and support. Even at this early stage parental stress may be huge when a child does not respond to ordinary parental requests and behavioural advice.[9] Targeted work with preschool children and their carers has been shown to be effective in improving parent child interaction and reducing parental stress.[10 11] A useful review of the available evidence and methods is provided by Barkley.[12]

PRIMARY SCHOOL YEARS

The primary school child with ADHD frequently begins to be seen as being different as classmates start to develop the skills and maturity that enable them to learn successfully in school. Although a sensitive teacher may be able to adapt the classroom to allow an able child with ADHD to succeed, more frequently the child experiences academic failure, rejection by peers, and low self esteem (fig 2). Comorbid problems, such as specific learning difficulties, may also start to impact on the child, further complicating diagnosis and management. Assessment by an educational psychologist may help to unravel learning strengths and difficulties, and advise on necessary support in the classroom.

Frequently, difficulties at home or on outings with carers (for example, when shopping, out in the park, or visiting other family members) also become more apparent at this age. Parents may find that family members refuse to care for the child, and that other children do not invite them to parties or out to play. Many children with ADHD have very poor sleep patterns, and although they appear not to need much sleep, daytime behaviour is often worse when sleep is badly affected. As a result, parents have little time to themselves; whenever the child is awake they have to be watching them. Not surprisingly,

Abbreviations: CHQ, Child Health Questionnaire; ODD, oppositional defiant disorder.

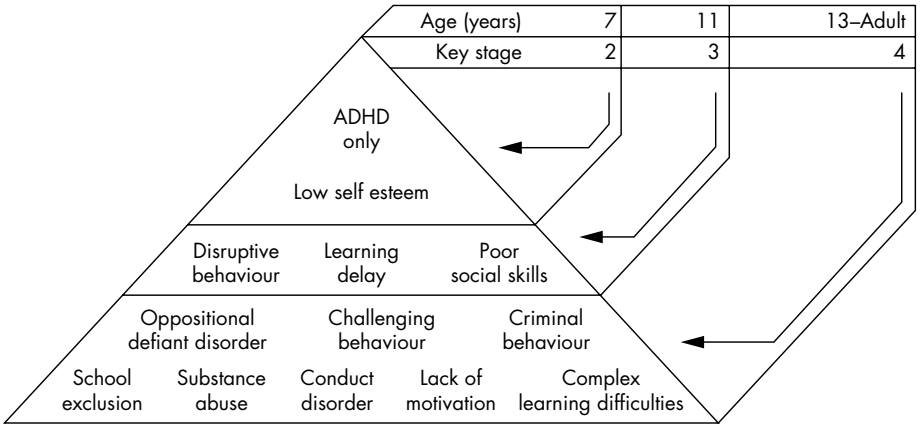

Figure 1 Stages of ADHD. Adapted from Kewley G (1999).[6]

family relationships may be severely strained, and in some cases break down, bringing additional social and financial difficulties.[14] This may cause children to feel sad or even show oppositional or aggressive behaviour.

Assessing the quality of life of the child suffering from ADHD is difficult. Behavioural assessments are usually carried out by parents, teachers, or healthcare professionals, and it can usually only be inferred how the child must feel. However, data from self evaluations indicate that children with ADHD view their most problematic behaviour as less within their control and more prevalent than children without ADHD.[15] Participation in a school based, nurse led support group was associated with an increase in self worth in pre-adolescents with ADHD.[16]

Johnston and Mash reviewed the evidence of the effect of having a child with ADHD on family functioning.[14] They concluded that the presence of a child with ADHD results in increased likelihood of disturbances to family and marital functioning, disrupted parent-child relationships, reduced parenting efficacy, and increased levels of parent stress, particularly when ADHD is comorbid with conduct problems.

In a survey of the mothers and fathers of 66 children, parents of children with ADHD combined and inattentive subtypes expressed more role dissatisfaction than parents of control children.[17] Furthermore, ADHD in children was reported to predict depression in mothers.[18] Pelham *et al* reported that the deviant child behaviours that represent major chronic interpersonal stressors for parents of ADHD children are associated with increased parental alcohol consumption.[19]

Limited attention has been given to sibling relationships in families with ADHD children. While it has been reported that siblings of children with ADHD are at increased risk for conduct and emotional disorders,[20] a more recent study presenting sibling accounts of ADHD identified disruption caused by symptoms and behavioural manifestations of ADHD as the most significant problem.[21] This disruption was experienced by siblings in three primary ways: victimisation, caretaking, and sorrow and loss. Siblings reported feeling victimised by aggressive acts from their ADHD brothers through overt acts of physical violence, verbal aggression, and manipulation and control. In addition, siblings reported that parents expected them to care for and protect their ADHD brothers because of the social and emotional immaturity associated with ADHD. Furthermore, as a result of the ADHD symptoms and consequent disruption, many siblings described feeling anxious, worried, and sad.[21]

Broader social and family functioning has been assessed using the Child Health Questionnaire (CHQ), a parent rated health outcome scale that measures physical and psychosocial wellbeing.[22–24] The studies demonstrated that treatment of ADHD with atomoxetine, a new non-stimulant medication for ADHD, resulted in improved perception of quality of life, with improvements being apparent in social and family functioning, and self esteem. Further research assessing the ongoing quality of life for the child and their family following multimodal input is urgently needed.

ADHD IN YOUNG PEOPLE

Adolescence may bring about a reduction in the overactivity that is often so striking in younger children, but inattention, impulsiveness, and inner restlessness remain major difficulties. A distorted sense of self and a disruption of the normal development of self has been reported by adolescents with ADHD.[25] Furthermore, excessively aggressive and antisocial behaviour may develop, adding further problems (fig 3). A study by Edwards *et al*[27] examined teenagers with ADHD and

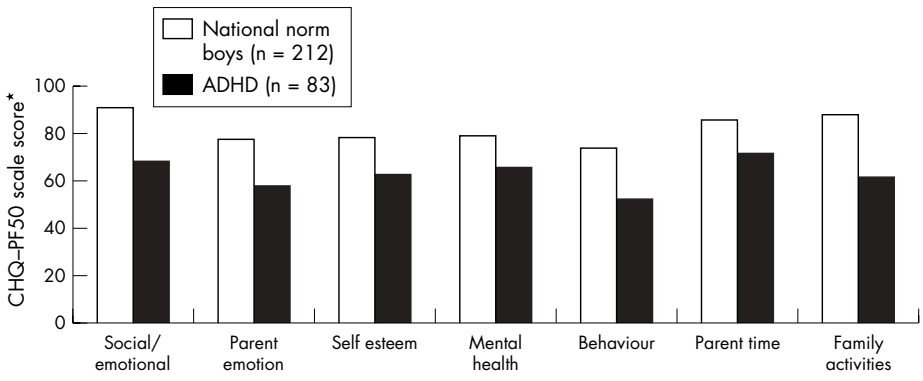

Figure 2 Emotional and family functioning in children with ADHD compared with controls.[13] *Higher scores indicative of greater functioning. CHQ, Child Health Questionnaire.[13]

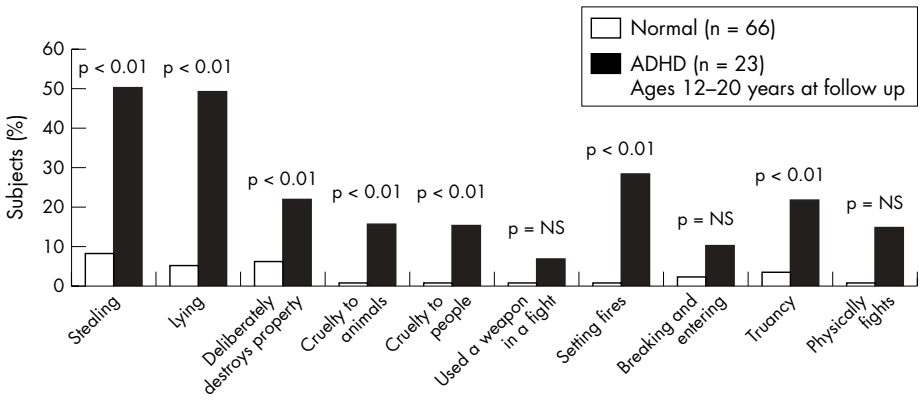

Figure 3 Antisocial behaviour in adolescents with ADHD.[26] Data primarily represents outcomes in those with conduct disorder as teenagers.

oppositional defiant disorder (ODD), which is defined by the *presence* of markedly defiant, disobedient, provocative behaviour and by the *absence* of more severe dissocial or aggressive acts that violate the law or the rights of others. These teenagers rated themselves as having more parent-teen conflict than did community controls. Increased parent-teen conflict was also reported when parents of teenagers with ADHD carried out the rating exercise. In addition, a survey of 11–15 year olds showed that those with hyperkinesis were twice as likely as the overall population to have "a severe lack of friendship".[28]

Young people with ADHD are at increased risk of academic failure, dropping out of school or college, teenage pregnancy, and criminal behaviour (fig 4A and B). Driving poses an additional risk. Individuals with ADHD are easily distracted from concentrating on driving when going slowly, but while driving fast may also be dangerous. It has been shown that, compared with age matched controls, drivers with ADHD are at increased risk of traffic violations, especially speeding, and are considered to be at fault in more traffic accidents, including fatal ones (fig 5).[30] The risk of such events was increased further by the presence of concomitant ODD.[29] However, it has been suggested that treatment may have a positive effect on driving skills.[31]

ADULT LIFE

As many as 60% of individuals with ADHD symptoms in childhood continue to have difficulties in adult life.[32 33] Adults with ADHD are more likely to be dismissed from employment and have often tried a number of jobs before being able to find one at which they can succeed.[5] They may need to choose specific types of work and are frequently self employed. In the workplace, adults with ADHD experience more interpersonal difficulties with employers and colleagues. Further problems are caused by lateness, absenteeism, excessive errors, and an inability to accomplish expected workloads. At home, relationship difficulties and break-ups are more common. The risk of drug and substance abuse is significantly increased in adults with persisting ADHD symptoms who have not been receiving medication.[34] The genetic aspects of ADHD mean that adults with ADHD are more likely to have children with ADHD. This in turn causes further problems, especially as the success of parenting programmes for parents of children with ADHD is highly influenced by the presence of parental ADHD.[35] Thus, ADHD in parents and children can lead to a cycle of difficulties.

COMORBIDITIES

Comorbid disorders may impact on individuals with ADHD throughout their lives. It is estimated that at least 65% of children with ADHD have one or more comorbid conditions.[36] The reported incidence of some of the most frequent comorbidities is shown in figure 6, with neurodevelopmental problems, such as dyslexia and developmental coordination disorder, being particularly common. Many children with ADHD also suffer from tic disorders (not related to stimulant

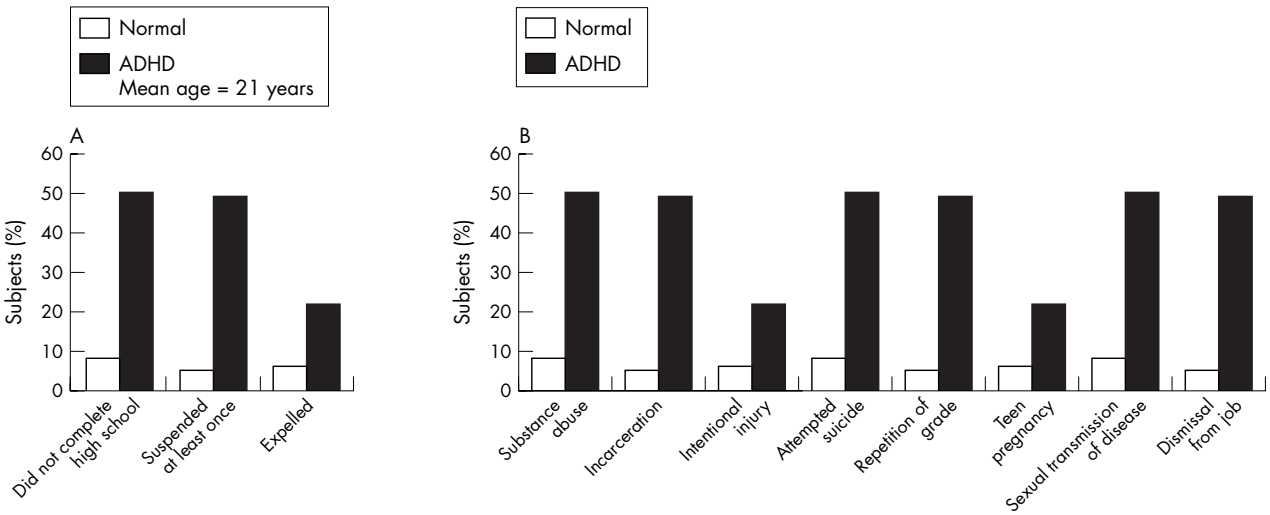

Figure 4 Impact of ADHD in adolescence. Data from Barkley RA;[26] (A) Impact at school; (B) impact on health, social, and psychiatric wellbeing.

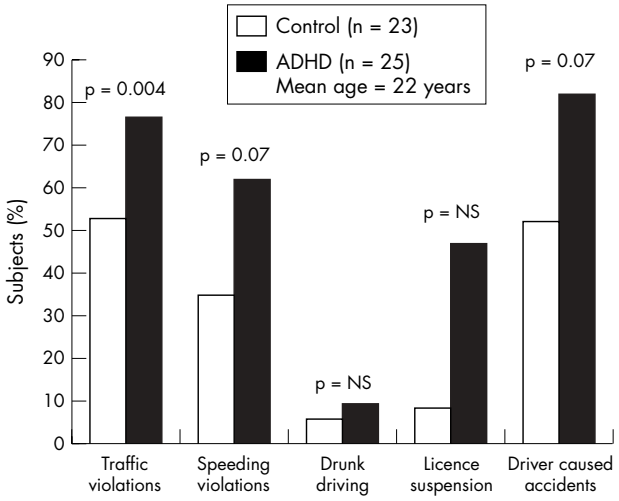

Figure 5 Driving-related offences in young adults with ADHD and controls. NS, not significant. Data from Barkley RA *et al*.[29]

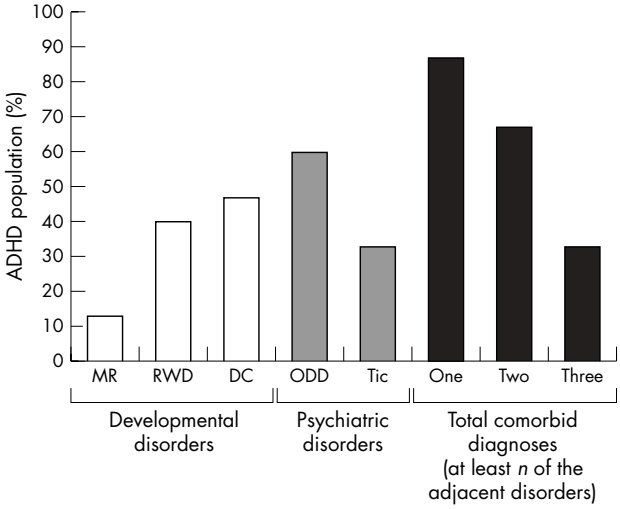

Figure 6 ADHD and comorbidity in Swedish school age children.[37] MR, mental retardation; RWD, reading/writing disorder; DC, developmental coordination; ODD, oppositional defiant disorder.

medication). In addition, around 60% of children with Tourette's Syndrome fulfil criteria for ADHD,[38 39] and autistic spectrum disorder is increasingly recognised with comorbid ADHD.[39] Initially, excessive hyperactivity may mask the features of autistic spectrum disorder until the child receives medication. Conduct disorder and ODD coexist with ADHD in at least 30%, and in some reports up to 90%, of cases.[36] These most frequently occurring comorbidities can, however, be considered more as complications of ADHD, with adversity in their psychological environment possibly determining whether children at risk make the transition to antisocial conduct.[40]

PROBLEMS ASSOCIATED WITH TREATMENT

Growth deficits in children receiving stimulant treatment for ADHD have long been the subject of scientific discussion. Conflicting results have been reported with some authors indicating that stimulants do indeed affect growth in children,[41–43] but that this only occurs during active treatment phase and does not compromise final height.[44] Other studies, however, have not found any evidence to suggest that stimulants influence growth.[45 46] Taken together, the results suggest that clinicians should monitor the growth of hyperactive children receiving stimulants, and consider dose reduction in individual cases should evidence of growth suppression occur.

Another frequently quoted concern about treatment of ADHD with stimulant medications is that it could lead to drug addiction in later life. Young people with ADHD are by nature impulsive risk takers, and there is clear evidence that untreated ADHD—especially with concomitant conduct disorder—is associated with a three- to fourfold increase in the risk of substance misuse.[47 48] In contrast, patients medicated with stimulants have a similar risk of substance misuse to controls.[49] These data therefore provide strong evidence in favour of careful treatment and support for young people with ADHD.

HEALTHCARE COSTS

Healthcare costs for individuals with ADHD in the UK have not been fully estimated, but evidence from the USA suggests that they are increased compared with age matched controls. A population based, historical cohort study followed 4880 individuals from 1987 to 1995 and compared the nine year median medical cost per person: ADHD medical costs were US$4306, whereas non-ADHD medical costs were US$1944 ($p<0.01$).[50] These findings are likely to reflect increased injury following accidents and a rise in use of substance abuse services and other outpatient facilities, although poor ability to comply with advice on medication (for example, asthma management) may also be implicated. A study of the injuries to children with ADHD established that children with ADHD were more likely to be injured as pedestrians or bicyclists than children not suffering from ADHD. They were more likely to sustain injuries to multiple body regions, head injuries, and to be severely injured.[51] ADHD has been found to represent a risk factor for substance abuse,[47 52] and an investigation of prevalence of ADHD among substance abusers has established that ADHD was significantly over-represented among inpatients with psychoactive substance use disorder.[53] Increased use of health services is also seen in the relatives of individuals with ADHD. A study has shown that direct and indirect medical costs were twice as high as those of family members of a control group.[54] The difference in these costs was primarily due to a higher incidence of mental health problems in the family members of ADHD patients, which reflects the increased stresses and demands of living with an adult or child with ADHD. Indeed, ADHD related family stress has been linked to increased risk of parental depression and alcohol related disorders.[55–57]

It is vital to consider the role of treatment of ADHD in decreasing the individual's risk of adverse outcomes. A number of studies on the effect of treatment of ADHD on the risk of substance abuse encouragingly demonstrate a fall in risk to that of the normal population.[58–60]

CONCLUSION

Mannuzza's review of the long term prognosis in ADHD concludes that childhood ADHD does not preclude high educational and vocational achievements (for example, Master's degree or medical qualification).[61] However, ADHD is a disorder that may affect all aspects of a child's life. Careful assessment is paramount, and if this demonstrates significant impairment as a result of ADHD, there is clear evidence that treatment of ADHD should be instituted.[62 63] Current treatment focuses mainly on the short term relief of core symptoms, mainly during the school day. This means that important times of the day, such as early mornings before school and evening to bedtime, are frequently unaffected by current treatment regimes. This can negatively

impact on child and family functioning and fail to optimise self esteem and long term mental health development.

In 2003, the American Academy of Pediatrics recommended that clinicians should work with children and their families to monitor the success (or failure) of treatment, using certain criteria to assess specific areas of difficulty and quality of life as a whole.[64] There has been a reluctance in the UK to treat ADHD with medication, fuelled by concerns about possible over-prescription in the USA. In addition, newspaper and media coverage of ADHD is often negative and stigmatising. The evidence of potentially severe difficulties for the child, the family, and, in some cases, for society as a whole, means that coordinated multi-agency effort to support the child and family is essential. Moreover, healthcare professionals have an important role in providing balanced and supportive information about ADHD and meeting the needs of affected individuals and their families.

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Social and emotional difficulties in children with ADHD and the impact on school attendance and healthcare utilization

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Abstract

Background: The objective of this study was to examine the impact of co-occurring social and emotional difficulties on missed school days and healthcare utilization among children with attention deficit/hyperactivity disorder (ADHD).

Methods: Data were from the 2007 U.S. National Health Interview Survey (NHIS) and were based on parental proxy responses to questions in the Sample Child Core, which includes questions on demographics, health, healthcare treatment, and social and emotional status as measured by questions about depression, anxiety, and phobias, as well as items from the brief version of the Strength and Difficulties Questionnaire (SDQ). Logistic regression was used to assess the association between co-occurring social and emotional difficulties with missed school days and healthcare utilization, adjusting for demographics.

Results: Of the 5896 children aged 6–17 years in the 2007 NHIS, 432 (7.3%) had ADHD, based on parental report. Children with ADHD and comorbid depression, anxiety, or phobias had significantly greater odds of experiencing > 2 weeks of missed school days, ≥ 6 visits to a healthcare provider (HCP), and ≥ 2 visits to the ER, compared with ADHD children without those comorbidities (OR range: 2.1 to 10.4). Significantly greater odds of missed school days, HCP visits, and ER visits were also experienced by children with ADHD who were worried, unhappy/depressed, or having emotional difficulties as assessed by the SDQ, compared with ADHD children without those difficulties (OR range: 2.2 to 4.4).

Conclusions: In children with ADHD, the presence of social and emotional problems resulted in greater odds of missed school days and healthcare utilization. These findings should be viewed in light of the limited nature of the parent-report measures used to assess social and emotional problems.

Keywords: Comorbidities, Attention deficit hyperactivity disorder, Resource use, Outcomes

Background

Attention-deficit/hyperactivity disorder (ADHD) is a common neuropsychiatric condition in children [1-5] with an estimated prevalence of 3 to 7% [1]. Attention-deficit/hyperactivity disorder is characterized by symptoms of inattention and/or hyperactivity-impulsivity that are more frequently displayed and more severe than typically observed in individuals at a comparable level of development [1], are usually evident in more than one setting (e.g., home and school), and result in impairment in multiple domains of functioning [3,6,7]. A rich literature speaks to the burden that ADHD imposes on patients, families, and society as a whole, including negative effects on individual educational [8,9] and social outcomes [3,6], negative effects on patient and parent quality of life [7], and increased utilization of and spending on healthcare services [10-17].

Social and emotional difficulties are particularly common and problematic in children with ADHD. Social difficulties present in a variety of forms and can lead to conflicts with family and problems with peers [18-21]. Emotional difficulties often include poor emotional self-

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regulation, aggression, and reduced empathy [22,23]. It should be noted that these challenges exist on a continuum. Relatively mild difficulties may fail to come to clinical attention, while in other cases such difficulties can contribute to overt, physician-diagnosed, comorbid mental health disorders, including anxiety, depression, and conduct disorder [22-24]. Major depressive disorder has been reported to occur in 12-50% of children with ADHD in community samples [25-27], and anxiety disorder, established by formal diagnostic interview, was comorbid in one third of ADHD patients enrolled in the commonly cited Multimodal Treatment Study of Children With ADHD [28]. Comorbid mental health conditions, including anxiety and depression, are extremely typical among children with ADHD and have been shown to be associated with greater functional impairment and worse educational outcomes [29-33].

Given the above data, it is important to understand the ways in which co-occurring conditions, including those characterized as social and emotional difficulties, can lead to various types of poor outcomes and functional impairment in children with ADHD, so that caregivers and providers can target interventions appropriately. In this study, we used data from the United States (U.S.) National Health Interview Survey (NHIS) to explore the association between social and emotional difficulties in children with ADHD and select outcomes. Available measures included both parent report of social and emotional difficulties (the brief version of the Strength and Difficulties Questionnaire [SDQ]) and parent report of physician-diagnosed depression, anxiety, and phobias. Unfortunately, teacher ratings and physician diagnoses were not available, and thus independent validation of parent reports was not possible. Available outcomes of interest included school days missed and emergency room (ER) and healthcare provider (HCP) visits over the past 12 months. We hypothesized that the presence of social and emotional difficulties in children with ADHD would be associated with increased school absenteeism and increased healthcare utilization, compared to ADHD children without these difficulties.

Methods

Data

The data were from a subset of the publicly available 2007 NHIS [4,34]. The NHIS is an annual cross-sectional survey designed to capture health-related trends in a sample representative of the civilian, non-institutionalized population of the U.S.; these data can be weighted to represent the U.S. population [35,36]. The sampling plan for the NHIS followed a multistage area probability design and oversampled African Americans, Hispanics, and Asians. Data were collected by trained interviewers from the U.S. Census Bureau who visited each selected household and administered the NHIS in person. Interviewers collected basic health and socio-demographic information on all household members, and gathered more extensive information on one sample adult and one sample child per family. An adult from the household, typically the child's parent, served as the proxy respondent for each child. Of the 10,658 children under 18 years of age eligible for the Sample Child Core questionnaire, the NHIS 2007 survey obtained data from 9417 sample children with a conditional response rate of 88.4%.

Measures

Data analyzed in the current study are from the Sample Child Core of the 2007 NHIS [37], which includes questions on demographics, health, healthcare treatment, healthcare access, healthcare utilization, and social and emotional status. All information was obtained based on parental/adult proxy reports. Demographic information was collected on gender, age, race, family income, and health insurance status.

ADHD status was ascertained based on the parent reporting whether they had ever been told by a doctor or healthcare professional that their "child had Attention Deficit Hyperactivity Disorder (ADHD) or Attention Deficit Disorder (ADD)." The presence of depression, phobias, and anxiety, respectively, were defined based on the parent's responses to the following 3 questions: "During the past 12 months, has a doctor or other health professional told you that your child had: (1) depression, (2) phobias or fears, (3) anxiety or stress?" For each child, an incremental internalizing burden index was computed by adding the number of internalizing problems (i.e., depression, anxiety, phobias) they experienced.

Parental reports of their child's social and emotional difficulties were also defined using items from the brief version SDQ [38,39]. The SDQ is a 25-item behavioral screening questionnaire for 4–17 year olds and includes five scales, each with five-items that assess the following domains: Emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and prosocial behavior. The SDQ has demonstrated evidence of validity and reliability [40]. The 2007 NHIS included 6 questions from the SDQ, which asked parents to report whether, over the preceding 6-month period, their child: 1) was well behaved, usually did what adults requested; 2) had many worries, or often seemed worried; 3) was often unhappy, depressed or tearful; 4) got along better with adults than with other children; 5) had good attention span, sees chores or homework through to the end; and 6) had difficulties in any of the following areas: emotions, concentration, behavior, or being able to get along with other people. Responses were dichotomized based on positive ("somewhat true" and "certainly true") versus negative ("not true") responses.

Two questions were used to define HCP and ER visits in the preceding 12 months. Parents reported on the number of times the child had "seen a doctor or other healthcare professional about his/her health at a doctor's office, a clinic, or some other place." The responses were dichotomized into < 6 versus ≥ 6 visits (i.e., on average, ≥ 1 HCP visit every other month). Parents also reported on the number of times the child had "visited a hospital emergency room (ER) about his/her health." The responses were dichotomized into < 2 versus ≥ 2 visits to the ER (i.e., on average, ≥ 1 ER visit every 6 months). School attendance was based on parental reports on the number of days their child "missed from school because of illness or injury in the past 12 months." The responses were dichotomized as having missed < 2 or ≥ 2 weeks (i.e., 10 days) of school.

Sample construction

The analyses for the current study included children aged 6–17 years whose adult proxy answered the ADHD diagnosis question in the NHIS 2007 survey. Children and adolescents less than 6 years of age (n=3284); those with mental retardation, developmental delay, or autism (n=230); and those who were missing the ADHD status variable (n=7) were excluded. The final sample included 5896 children and adolescents, including 432 with ADHD. The 5464 children and adolescents without ADHD were included in some of the secondary analyses.

Analyses

The primary analysis for this study was focused on the association between co-occurring social and emotional difficulties with missed school days and healthcare utilization among children with ADHD. To assess this association, logistic regression models with dichotomized outcomes (i.e., missed school days, HCP visits, ER visits) as dependent measures and comorbid condition (e.g., depression, incremental internalizing burden index, SDQ items) as independent measures adjusting for gender, age category (6–11 years [children], 12–17 years [adolescents]), race, income, insurance status, and ADHD medication-use were employed.

To give context to the primary analysis and determine if there was a differential association between comorbid conditions on missed school days and healthcare utilization by ADHD status, logistic regression models with outcome as the dependent measure and ADHD status, comorbid condition, and ADHD status-by-comorbid condition interaction as independent measures adjusting for gender, age category, race, income, and insurance status were utilized. Finally, descriptive statistics were used to characterize the ADHD and non-ADHD subsamples.

All analyses were conducted in SAS version 9.1 (SAS Institute Inc., NC), using procedures specifically designed to properly analyze complex survey data which employ sample weight, stratification, and cluster information. All percentages, means, and estimates were adjusted to account for the NHIS survey design. All statistical tests of differences in independent measures, including interactions, were conducted using a 2-sided significance level of 0.05.

Results

Of the 5896 children aged 6–17 years in the 2007 NHIS, 432 (7.3%) had ADHD based on parental reports. The majority of children with ADHD were male (69.7%), adolescent (65.9%), white (75.5%), insured (91.3%), and with a family income less than $75,000 per year (68.8%). Sixty-eight percent of these children with ADHD had been and/or were currently being treated with a prescription medication to treat difficulties with concentration, hyperactivity, or impulsivity. Approximately one-third of these ADHD children had comorbid anxiety, while comorbid depression (16.5%) and phobias (7.2%) were less common. Compared with a reported formal diagnosis, a higher percentage of parents reported that their ADHD child was unhappy or depressed (27.4%) or often seemed worried (47.3%). Similarly, about 40% reported their ADHD child got along better with adults than with children and did not have good attention, while about one-third reported their child had difficulties in emotions, concentration, behavior, or being able to get along with other people. Despite this data, over 90% of parents of ADHD children reported that their child was generally well behaved (Table 1). Descriptive statistics are also provided in Table 1 for the non-ADHD sample.

Table 2 presents the percentages of missed school days, ER visits, and HCP visits overall and by reported presence of social and emotional difficulties for children with ADHD. In addition, Table 2 presents odds ratios (OR [95% confidence interval (CI)]) that represent the association between co-occurring social and emotional difficulties and missed school days, ER visits, and HCP visits.

Overall, more ADHD children experienced at least 6 HCP visits (31%), compared with experiencing at least 2 ER visits (11%) and missing more than 2 weeks of school (8%). When assessing the impact of co-occurring social and emotional difficulties on school attendance and healthcare utilization, ADHD children with anxiety had significantly greater odds of missing more than 2 weeks of school (3.4 [2.2, 5.1]), having at least 2 ER visits (2.1 [1.2, 3.6]), and having at least 6 HCP visits (2.9 [2.0, 4.4]), compared with those without anxiety. For ADHD children with depression, those with the comorbid condition were 10 times as likely as those without the comorbid condition to miss more than 2 weeks of school

Table 1 Descriptive statistics

Characteristics	ADHD (n=432)	non-ADHD (n=5464)
Gender, n (%)		
Male	309 (69.7)	2717 (48.8)
Age, n (%)		
6-11 years	153 (34.1)	2531 (49.5)
12-17 years	279 (65.9)	2933 (50.5)
Race, n (%)		
White	317 (75.5)	3956 (76.1)
Black	79 (16.2)	966 (15.5)
Asian	6 (1.0)	292 (4.0)
Other	30 (7.3)	242 (4.4)
Family Income, n (%)		
$0 - $34,999	140 (33.1)	1637 (29.5)
$35,000 - $74,999	132 (35.7)	1641 (33.4)
$75,000 - $99,999	52 (13.5)	647 (14.5)
$100,000 and over	73 (17.7)	1006 (22.6)
Medical Insurance, n (% yes)	391 (91.3)	4801 (89.8)
Medication Ever Prescribed for Difficulties with Concentration, Hyperactivity, or Impulsivity, n (% yes)	278 (67.6)	39 (0.8)
Outcome Measures, n (% yes)		
≥ 2 ER visits past 12 months	40 (11.1)	286 (5.6)
≥ 6 Doctor or HCP visits past 12 months	122 (30.9)	481 (9.4)
≥ 2 weeks of school missed in past 12 months	41 (8.4)	204 (3.6)
Social and Emotional Difficulties, n (% yes)		
Anxiety/stress in past 12 months	117 (32.2)	330 (6.3)
Depression in past 12 months	58 (16.5)	106 (2.0)
Phobias/fears in past 12 months	35 (7.2)	111 (1.9)
Strength and Difficulties Questionnaire*, n (%)		
SDQ 1 - Not well behaved	35 (7.0)	133 (2.3)
SDQ 2 - Often seems worried	194 (47.3)	1115 (21.3)
SDQ 3 - Unhappy/depressed	106 (27.4)	533 (9.8)
SDQ 4 - Gets along better with adults than children	196 (42.7)	1706 (31.0)
SDQ 5 - Doesn't have good attention	186 (44.7)	414 (7.9)
SDQ 6 - Difficulties w/emot/conc/beh/getting along	126 (32.8)	101 (2.0)

Note: Percents reported are based on weighted frequencies and thus may vary slightly from the expected values based on the reported n's.
* SDQ1: He/she is generally well behaved, usually does what adults request; SDQ2: He/she has many worries, or often seems worried; SDQ3: He/she is often unhappy, depressed, or tearful; SDQ4: He/she gets along better with adults that with other children/youth; SDQ5: He/she has good attention span, sees chores or homework through to the end; SDQ6: Overall, do you think that [name] has difficulties in any of the following areas: emotions, concentration, behavior, or being able to get along with other people?

(10.1 [5.7, 17.8]); 7 times as likely to have at least 6 HCP visits (7.4 [4.3, 12.7]); and 3.5 times as likely to have at least 2 ER visits (3.5 [2.0, 6.4)]. Similarly, ADHD children with comorbid phobias were 10 times as likely to miss more than 2 weeks of school (10.4 [4.2, 26.2]) as those without phobias, while being 3 times as likely to have at least 6 HCP visits (3.0 [1.3, 7.2]) and 2 times as likely to have at least 2 ER visits (2.4 [1.0, 5.4]). In addition, with each incremental increase in internalizing burden, ADHD children had significantly greater odds of missing at least 2 weeks of school (3.1 [2.4, 4.0]), having at least 6 HCP visits (2.2 [1.7, 2.8]), and having at least 2 ER visits (1.7 [1.3, 2.2]).

For the single, general SDQ item assessing difficulties in emotions, concentration, behavior, or being able to get along with other people (item 6), ADHD children with at least one of these complications experienced significantly greater odds of missing more than 2 weeks of school (4.4 [2.8, 6.9]), experiencing at least 2 ER visits (3.0 [1.8, 5.0]), and having at least 6 HCP visits (3.8 [2.6, 5.4]), compared with those who did not have these difficulties.

For the SDQ items associated with emotional difficulties (items 2 and 3), ADHD children who were worried had significantly higher odds of missing more than 2 weeks of school (3.2 [2.1, 4.8]), experiencing at least 2 ER visits (2.6 (1.4, 4.7]), and having at least 6 HCP visits (2.2 [1.5, 3.1]), compared with those who were not worried. Likewise, ADHD children who were unhappy/depressed experienced significantly greater odds of missing more than 2 weeks of school (3.9 [2.3, 6.4]), experiencing at least 2 ER visits (2.2 (1.3, 3.8]), and having at least 6 HCP visits (2.6 [1.7, 3.8]), compared with those who were not unhappy/depressed.

For the SDQ items associated with social or behavioral symptoms of ADHD (items 1, 4, and 5), children who did not have good attention were about 3 times as likely as children who did have good attention to miss more than 2 weeks of school (2.9 [1.8, 4.6]) and 2.5 times as likely to have at least 2 ER visits (2.5 [1.6, 4.1]), while experiencing at least 6 HCP visits was similar for those with and without good attention (1.5 [1.0, 2.4]). As observed with good attention, ADHD children who were not well behaved had significantly higher odds of missing more than 2 weeks of school (5.5 [2.2, 13.8]) and experiencing at least 2 ER visits (5.2 (2.0, 13.5]), compared with those who were well behaved, while the odds for having at least 6 HCP visits were similar between those who were well behaved and who were not well behaved (1.4 [0.7, 2.9]). ADHD children who got along better with adults experienced similar odds of missing more than 2 weeks of school (0.7 [0.4, 1.3]), having at least 2 ER visits (0.9 (0.5, 1.6]), and having at least 6 HCP visits (1.0 [0.6, 1.5]),

Table 2 Social and emotional difficulties and SDQ items for subjects with ADHD

	Missed School Days (>2 weeks)			ER Visits (≥2 visits)			HCP Visits (≥6 visits)		
All ADHD Subjects	**8.4%**			**11.1%**			**30.9%**		
Social and Emotional Difficulties	**Yes (%)**	**No (%)**	**OR [95% CI]**	**Yes (%)**	**No (%)**	**OR [95% CI]**	**Yes (%)**	**No (%)**	**OR [95% CI]**
Anxiety/stress in past 12 months	14.2	5.7	3.4 [2.2, 5.1]	17.4	8.2	2.1 [1.2, 3.6]	51.9	21.4	2.9 [2.0, 4.4]
Depression in past 12 months	25.7	4.8	10.1 [5.7, 17.8]	26.5	7.8	3.5 [2.0, 6.4]	72.3	22.5	7.4 [4.3, 12.7]
Phobias/fears in past 12 months	33.0	6.5	10.4 [4.2, 26.2]	22.6	10.2	2.4 [1.0, 5.4]	53.2	29.2	3.0 [1.3, 7.2]
Strength and Difficulties Questionnaire*	**Yes (%)**	**No (%)**	**OR [95% CI]**	**Yes (%)**	**No (%)**	**OR [95% CI]**	**Yes (%)**	**No (%)**	**OR [95% CI]**
SDQ 1 - Not well behaved	22.4	7.5	5.5 [2.2, 13.8]	30.3	9.5	5.2 [2.0, 13.5]	37.4	30.6	1.4 [0.7, 2.9]
SDQ 2 - Often seems worried	13.4	4.1	3.2 [2.1, 4.8]	16.7	5.7	2.6 [1.4, 4.7]	42.0	21.3	2.2 [1.5, 3.1]
SDQ 3 - Unhappy/depressed	17.0	5.3	3.9 [2.3, 6.4]	19.9	7.6	2.2 [1.3, 3.8]	52.5	23.3	2.6 [1.7, 3.8]
SDQ 4 - Gets along better with adults than children	7.6	9.2	0.7 [0.4, 1.3]	9.9	11.7	0.9 [0.5, 1.6]	29.4	32.1	1.0 [0.6, 1.5]
SDQ 5 - Doesn't have good attention	12.1	5.7	2.9 [1.8, 4.6]	15.4	7.4	2.5 [1.6, 4.1]	37.9	25.5	1.5 [1.0, 2.4]
SDQ 6 - Difficulties w/emot/conc/beh/ getting along	16.2	4.8	4.4 [2.8, 6.9]	20.2	6.5	3.0 [1.8, 5.0]	54.6	19.4	3.8 [2.6, 5.4]

Note: Interaction effects were significant for ADHD status and SDQ item 4 for missed school days (P=0.0490), ADHD status and SDQ item 1 for ER visits (P=0.0060), and ADHD status and SDQ item 2 for ER visits (P=0.0420).

* SDQ 1: He/she is generally well behaved, usually does what adults request; SDQ 2: He/she has many worries, or often seems worried; SDQ 3: He/she is often unhappy, depressed, or tearful; SDQ 4: He/she gets along better with adults that with other children/youth; SDQ 5: He/she has good attention span, sees chores or homework through to the end; SDQ 6: Overall, do you think that [name] has difficulties in any of the following areas: emotions, concentration, behavior, or being able to get along with other people?

compared with those who did not get along better with adults.

When assessing if there was a differential effect of comorbid condition on missed school days and health-care utilization by ADHD status, three interactions were significant. As stated above, children with ADHD who got along better with adults had lower odds, although not significant, of missing more than 2 weeks of school compared with ADHD children who did not get along better with adults (0.7 [0.4, 1.3]). Conversely, non-ADHD children who got along better with adults experienced significantly higher odds of missing more than 2 weeks of school (1.8 [1.2, 2.7]), compared with those who did not get along better with adults. This diametric relationship resulted in a significant interaction effect (P=0.0490). Significant interactions were also observed for ADHD status and being well behaved (P=0.0060), as well as being worried (P=0.0420), for children experiencing at least 2 ER visits. ADHD children who were not well behaved had significantly greater odds of having at least 2 ER visits, compared with those who were well behaved (5.2 [2.0, 3.5]), while non-ADHD children who were not well behaved had lower odds of having at least 2 visits to the ER, compared with non-ADHD children who were well behaved (0.5 [0.2, 1.2]). On the other hand, both ADHD and non-ADHD children who worried experienced increased odds of having at least 2 ER visits; however, the comparison was significant for the ADHD cohort (2.6 (1.4, 4.7]) and was not significant for the non-ADHD group (1.2 [0.9, 1.7]).

Discussion

This study adds to the literature which demonstrates that social and emotional difficulties in children with ADHD can contribute to higher rates of unfavorable outcomes. In particular, these data suggest that both parent-observed child social difficulties (e.g., not being "well behaved") and emotional difficulties (e.g., worry) and parent report of physician diagnosed affective disorders (e.g., depression) can be used to identify children with significantly elevated rates of school absenteeism and ER and HCP utilization. Strikingly, a positive response on a single general item from the SDQ (i.e., item 6, "had difficulties in any of the following areas: emotions, concentration, behavior, or being able to get along with other people") identifies a subset of children 3 to 4 times as likely as peers answering negatively, to exhibit all three of the examined adverse outcomes. While this general association is compelling, consideration of the other independent measures provides additional insights. The remaining eight items examined can be organized according to the clinical/psychological domain to which they speak: Three to anxious symptoms (i.e., the SDQ "worry" item and the physician-diagnosed "anxiety or stress" and "phobias or fears" items); two to mood (i.e., the SDQ "unhappy/depressed" item and physician-diagnosed "depression"); and three to core ADHD symptoms or social behavior (i.e., the "well behaved," "good attention span," and "got along better with adults" SDQ items).

In general, the presence of anxious symptoms had a more pronounced impact on school absenteeism than

on ER or HCP utilization. While no further detail as to the nature of the anxiety was available, anxiety-related school avoidance is a well described phenomenon, and, in this regard, it is notable that of the three items, the strongest relationship with school absenteeism was observed for physician-diagnosed phobias (OR 10.4). It is also interesting that parent observation of "worry" (SDQ item 2) was as strongly predictive of increased absenteeism as was report of physician-diagnosed anxiety (OR 3.2 vs. 3.4, respectively).

Consistent with what has been observed in other studies, parent report of physician-diagnosed depression was associated with worse outcomes [7,41], and it predicted the largest increase in odds of more HCP visits, across all items examined. This result may be due, in part, to the fact that depression is more likely to lead to closer physician follow-up, greater use of pharmacotherapy, and higher rates of specialist referral relative to children with anxiety disorders or phobias, which are generally managed through behavioral therapies. In contrast to the pattern seen with the anxiety items, physician-diagnosed depression was associated with substantially greater odds of both increased school absenteeism (OR 10.1 vs. 3.9) and HCP visits (OR 7.4 vs. 2.6) than was the parental report of a child being "often unhappy, depressed or tearful" (SDQ item 3). These findings suggest that the 16.5% of ADHD children with physician-diagnosed depression are likely a more severely affected subgroup of the 27.4% of children rated positive on SDQ item 3.

The impact of the remaining SDQ items on the outcomes of interest was mixed. A negative response on SDQ item 1 (i.e., "was well behaved, usually did what adults requested") was actually the strongest predictor of multiple ER visits across all items, and the strongest among SDQ items of school absenteeism; in contrast, poor attention span (SDQ item 5) was more weakly associated with these outcomes. This result is consistent with the fact that children with predominantly inattentive forms of ADHD are more likely to exhibit more subtle problems (e.g., school failure) than their more declarative peers with hyperactivity. Finally, a child's getting along "better with adults than with other children" (SDQ item 4) did not appear to be associated with any of the outcomes examined, perhaps because of the ambiguous nature of the question (i.e., could be interpreted as a positive or negative attribute). This outcome is further reinforced by the significant interaction between ADHD status and this item in the models that predict school absenteeism (P=0.049). For non-ADHD children, those who got along better with adults tended to miss more school than those who did not; while amongst children with ADHD, those who got along better with adults tended to miss less school. One possible explanation for this finding is that, among children with ADHD, peer rejection is the norm [42]; thus, the ability to "get along better with adults than peers" may indicate positive relationships with teachers in a formalized setting. In contrast, this trait may reflect interpersonal or social deficits in children without ADHD that are associated with increased problems at school.

The use of nationally representative survey data from NHIS represents a particular study strength, permitting generalization of findings to the entire U.S. population of children with ADHD. The sampling design enhances validity by ensuring that participants are selected for inclusion in the study independent of their status for the predictor and outcome variables of interest. Another study strength is the use of the brief SDQ, which has been shown to be a reliable and valid screening instrument for child psychiatric disorders [43,44].

Our findings should be interpreted in light of several important considerations regarding the measures available within the NHIS survey. First, relatively few items were available to assess emotional and social difficulties, and indeed no information was available regarding the duration or severity of these problems. Furthermore, measures of both emotional and social difficulties and of the outcomes of interest were based on parent report. The use of direct parent report measures of both independent and dependent measures is both a strength and weakness. On the positive side, it permits the collection of data elements that are not available in secondary sources, such as administrative claims. On the negative side, parent report data are subject to recall bias and are necessarily inferior to school attendance and healthcare claims records for the outcomes of interest. In other studies using the SDQ, investigators have reported greater validity and reliability of estimates of emotional and behavioral problems based on reports from multiple informants including parents, teachers, and, for some age groups, children [44,45]. As parallel assessments from these sources were not available, we were unable to independently verify parents' assessments. Finally, it should be noted that the thresholds chosen when dichotomizing outcome measures were somewhat arbitrary; these choices are in no way intended to imply that school absences or healthcare utilization above these thresholds were unnecessary or inappropriate in any way.

Several additional study limitations deserve mention. The definition of ADHD status was based on the parent response to a single item. While the validity of this approach is suspect, it should be noted that the prevalence of ADHD in this sample is very close to what would be expected based on estimates from other studies [2,3] and the prevalence reported in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [1]. Information about the presence of ADHD

and mood disorders in parents was also unavailable. Thus, while these factors could clearly serve as an important source of bias, we were unable to examine their impact on the outcomes assessed. Also, a substantial proportion of the sample (9.6%) was missing data on the income variable and, therefore, those subjects were not included in the analysis. A sensitivity analysis was performed using multiple imputations, and the results were consistent with those presented for the non-imputed samples. It is important to note that the sample size was considerably smaller for ADHD children with a reported diagnosis of depression and phobias, as well as for ADHD children who were not well behaved compared to ADHD children without these social and emotional difficulties. Given this information, the comparisons for these particular difficulties should be interpreted with caution. The NHIS also has very limited information regarding the medications the children were taking at the time of the study and, thus, the analyses did not control for medication status, types of medications, or medication adherence. Finally, the current study reports on the results of a large number of statistical tests in which the *P*-values were not adjusted for multiple comparisons to control the type I error rate. This study was intended to generate hypotheses rather than confirm specific hypotheses. Based on all of the aforementioned limitations, these results would need to be replicated in future studies.

Conclusions

Our findings provide further evidence that the presence of social and emotional difficulties in children with ADHD contributes to the functional impairment observed in this population. In particular, children manifesting these problems are more likely to experience greater school absenteeism and to incur more ER and HCP visits than their unaffected peers. Greater awareness of these associations, together with focused efforts to identify and manage these children appropriately, could lead to improved patient outcomes (e.g., improved school attendance) and to decreased healthcare utilization.

Abbreviations

ADD: Attention Deficit Disorder; ADHD: Attention-Deficit/Hyperactivity Disorder; CI: confidence interval; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; ER: Emergency room; HCP: Healthcare provider; NHIS: National Health Interview Survey; OR: Odds ratio; SDQ: Strength and Difficulties Questionnaire; U.S.: United States.

Competing interests

PC, DM, SW, KS, and JJ are employees and shareholders of Eli Lilly and Company.

Authors' contributions

PC was the principle scientist for this study. PC, DM, and JJ collaboratively wrote the first draft of the manuscript. All authors reviewed and edited subsequent drafts, and read and approved the final manuscript.

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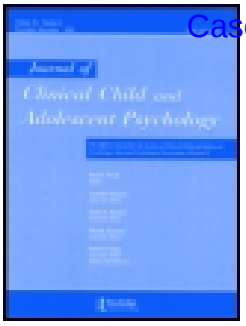
EXHIBIT 80



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Adults with childhood attention-deficit hyperactivity disorder (ADHD) experience impairment in core functional domains (e.g., educational attainment, occupational status, social relationships, substance abuse, and criminal behavior), but it is currently unclear which impairments co-occur and whether subgroups experience differentiable patterns, none, or all aforementioned functional domains. Latent profile analysis (LPA) was used to characterize patterns of impairment. Data from the Pittsburgh ADHD Longitudinal Study were used. The 317 participants were 25 years old and had childhood ADHD. LPA characterized the variability across substance use (alcohol consumption, cigarette smoking, marijuana use), criminal behavior, peer impairment, educational attainment, maternal relationship, financial dependence, and sexual activity among young adults with childhood ADHD. Childhood predictors of profiles were examined, and ADHD profiles were compared to a matched comparison group without ADHD also followed longitudinally (n = 217). Five profiles were found: prototypic impairment group (54%), high binge-drinking group (17%), high marijuana use group (10%), high criminal activity group (3%), and high cross-domain impairment group (17%). All profiles were impaired compared to non-ADHD young adults. Childhood variables rarely significantly predicted profiles. Young adults with childhood ADHD have differentiable impairment patterns that vary based on substance use, criminal behavior, and number of clinically impaired domains. Nearly all young adult ADHD profiles were impaired in peer, educational, and financial domains, and there was not a nonimpaired ADHD profile. Use of specific substances was elevated among subgroups of, but not all, young adults with ADHD histories. Finally, the high cross-domain impairment profile was impaired in all domains.

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by primary symptoms of inattention and hyperactivity/impulsivity (*Diagnostic and Statistical Manual of Mental Disorders*, 5th ed.; *DSM-5*; American Psychiatric Association, 2013; Nigg & Barkley, 2014). Impairments in childhood include academic underperformance, deficits in peer relationships, and problems interacting with adults (Nigg & Barkley, 2014). ADHD persists into adolescence and adulthood in most cases and is associated with continued impairment and large societal, familial, and individual costs, although severity of dysfunction varies across individuals (Hechtman et al., 2016; Pelham, Foster, & Robb, 2007; Robb et al., 2011; Sibley et al., 2012, 2012).

Available prospective, longitudinal research has used variable and group-centered approaches to investigate differences between adults with and without childhood ADHD across domains of functioning (e.g., Milwaukee Longitudinal Study of Hyperactive children: Barkley, Murphy, & Fischer, 2008; McGill prospective studies: Weiss & Hechtman, 1993; Multimodal Treatment of ADHD Study: Hechtman et al., 2016; New York Study: Klein et al., 2012; Pittsburgh ADHD Longitudinal Study: Molina, Sibley, Pedersen, & Pelham, 2016). Studies consistently indicate higher risk for negative

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outcomes among ADHD probands versus non-ADHD comparison groups across core impairment domains including educational attainment, financial outcomes, social functioning, criminal behavior, and substance use, and such findings have been critical to our understanding of the life course of ADHD. At the same time, prospective longitudinal studies indicate marked variability in adult outcome among those diagnosed with ADHD in childhood (detailed next).

This variability in adult outcome mirrors the well-known heterogeneity of childhood ADHD symptomatology and associated impairments (Barkley, 2015; Pelham, Fabiano, & Massetti, 2005). ADHD comprises three major symptoms—hyperactivity, impulsivity, and inattention—and, consistent with all mental health problems, impairment is necessary for diagnosis, and comorbidity is common. Important to note, the impairment that characterizes children with ADHD varies considerably across children. For example, it has long been known that many children with ADHD have serious problems with peer relationships (Hoza et al., 2005; Pelham & Bender, 1982). Some are aggressive toward peers, whereas others have an interrupting/intrusive style that, although not aggressive, interferes with peers' activities. Inappropriate classroom behavior (e.g., disruptive behavior) and poor academic achievement characterize many, but not all, children with ADHD. Finally, children with ADHD experience heightened conflict with parents, teachers, and other adults, and many parents of children with ADHD demonstrate inappropriate parenting practices (e.g., authoritarian and inconsistent; Johnston & Chronis-Tuscano, 2015; Musser, Karalunas, Dieckmann, Peris, & Nigg, 2016).

When taken together, it is clear that the variability in core symptom presentation and concurrent problems in daily life functioning likely give rise to a number of different types of children with ADHD that may vary in longitudinal outcome. It is important to investigate the diversity of adult outcomes among children with ADHD (i.e., multifinality; Cicchetti & Rogosch, 1996), which may be as heterogeneous as childhood ADHD and able to be best described in terms of cross-domain functioning among individuals. When investigating the variability in long-term outcome of childhood ADHD, the focus is often on comorbidity and symptom persistence (e.g., Agnew-Blais et al., 2016; Hechtman et al., 2016; Yoshimasu et al., 2018). However, using a framework that focuses instead on variability or patterns of cross-domain impairments in daily life functioning in adulthood, aligning with the focus on impairment in childhood, may be beneficial to our understanding of the outcomes of childhood ADHD. This approach is distinct from but not unlike the approach taken by Krueger and others who apply a similarly non-*DSM*-based framework to adult psychopathology (Kotov et al., 2017; Krueger, Markon, Patrick, Benning, & Kramer, 2007), though we focus solely on functional impairment herein.

The literature focused on impairment among adults with childhood ADHD has exclusively applied group-centered analyses and generally taken the approach of independently examining functional outcome domains (e.g., Barkley, Fischer, Smallish, & Fletcher, 2006, Sibley et al., 2011, Weiss & Hechtman, 1993) cumulatively indicating marked impairment among those with ADHD histories across a variety of core functional domains. Yet, prior studies have failed to characterize *patterns* of ADHD-related impairment across functional domains in adulthood. Specific profiles of various impairments may suggest functional relationships that could pinpoint mechanisms for research and targets for treatment. Person-centered analysis (e.g., latent profile analyses [LPAs]), in contrast to group- and variable-centered approaches used previously, has the potential to improve understanding of longitudinal outcomes among adults with ADHD histories by deriving subgroups of individuals who have differentiable patterns of scores on a set of variables. Despite its utility in characterizing cross-domain functioning, LPA has not yet been employed to characterize the diverse set of negative outcomes that likely characterize young adults with ADHD. LPA can potentially facilitate exploration of the functional relationships between the domains previously identified as impaired among adults with ADHD histories—that is, educational attainment, financial/vocational outcomes, interpersonal functioning (e.g., relationships with parents, peers, and significant others), substance use (e.g., alcohol, marijuana, and cigarettes), and antisocial behavior/criminal activity (Barkley et al., 2008; Hechtman et al., 2016; Molina et al., 2014; Weiss & Hechtman, 1993).

To investigate *patterns* of co-occurring ADHD-related functional impairment in adulthood, we first review the literature on these core domains and highlight findings that suggest which impairments may co-occur among young adults with ADHD histories. First, the majority of adults with ADHD histories evidence continued achievement deficits and limited educational attainment. Overall, prospective longitudinal studies indicate that adults with childhood ADHD are less likely to graduate from high school and less likely to enroll in and complete higher education (Barkley et al., 2006; Kent et al., 2011; Klein et al., 2012; Kuriyan et al., 2013; Mannuzza, Klein, Bessler, Malloy, & Lapadula, 1993; Mannuzza, Klein, Bessler, Malloy, & Hynes, 1997). About one fourth of ADHD probands enroll in 4-year institutions (compared to 77% of controls; Barkley et al., 2006; Kuriyan et al., 2013), and only 11% to 15% earn bachelor's degrees by their mid-20s compared to about half of demographically similar peers (Hechtman et al., 2016; Kuriyan et al., 2013; Mannuzza et al., 1997, 1993).

Analogous and related to their educational impairment, adults with childhood ADHD, on average, achieve lower occupational statuses and are more likely to be unemployed (Barkley et al., 2008; Hechtman et al., 2016; Klein et al., 2012; Kuriyan et al., 2013; Mannuzza et al., 1997, 1993) despite having comparable IQs and family socioeconomic status as controls. In terms of financial outcomes and

independence, at age 25, individuals with ADHD have lower annual income, have more credit card debt, and are more likely to be living with and otherwise financially dependent on their parents and public subsidies compared to typically developing peers (Altszuler et al, 2016). In the Altszuler and colleagues (2016) study, there was variability in the ADHD sample with lower education and higher delinquency predicting poorer financial outcomes. Therefore, those with higher educational attainment are likely to have higher financial success.

Childhood ADHD also predicts social impairment into young adulthood (Biederman et al., 1995; Molina et al., 2014; Weiss & Hechtman, 1993) and continued difficulty getting along with others, including peers and family members (Barkley et al., 2006). Although young adults with and without childhood ADHD report similar rates of dyadic relationships (Barkley et al., 2006), those with ADHD histories report increased risky sexual behaviors such as a higher number of sexual partners, more partner violence, and lower consistency of birth control use (Barkley et al., 2006; Flory, Molina, Pelham, Gnagy, & Smith, 2006; Wymbs et al., 2012). Based on their childhood characteristics, some adults with childhood ADHD would be expected to have a range of intrusive social styles that would cause problems with coworkers and may contribute to their vocational difficulties (e.g., frequent job changes). Further, childhood peer problems predict a host of problems in adulthood (e.g., criminal activity and substance use) both within (Lee & Hinshaw, 2004; Satterfield et al., 2007) and outside of (Dishion, 2014; Hawkins, Catalano, & Miller, 1992; Huesmann, Eron, Lefkowitz, & Walder, 1984) the ADHD literature that may then co-occur with adult social impairment.

Another domain of dysfunction among adults with childhood ADHD is substance use, including alcohol, marijuana, and tobacco. Molina and Pelham (2014) reviewed numerous papers that examine substance use outcomes in ADHD, and elevations in alcohol, marijuana, and tobacco use were evident at the group level across samples (Barkley et al., 2008; Lambert & Hartsough, 1998; Molina & Pelham, 2003; Pedersen et al., 2016; Rhodes et al., 2016; Sibley et al., 2014). The rate of current substance use disorders is elevated, ranging from 12% to 16% throughout adulthood for those with ADHD histories compared to about 4% in control adults (Derefinko & Pelham, 2016; Hechtman et al., 2016; Klein et al., 2012; Mannuzza et al., 1993; Mannuzza, Klein, Bessler, Malloy, & Lapadula, 1998). Further, young adults with childhood ADHD are more likely to be daily smokers and report heightened withdrawal and craving during cigarette abstinence (Fuemmeler, Kollins, & Mcclernon, 2007; Lambert & Hartsough, 1998; Rhodes et al., 2016). Notably, there is variability in these outcomes—that can be explored with LPA—with regard to the number of individuals who exhibit problems in substance use, severity of use, and substance being used such that it is currently unclear if some ADHD individuals are using a variety of substances and what proportion are not using any substances. Similarly, LPA may elucidate whether heightened substance use co-occurs with social problems or other functional impairments among young adults with ADHD histories.

Antisocial behavior and aggression are also more severe among young adults with childhood ADHD compared to peers (Weiss & Hechtman, 1993). Young adults with ADHD histories are more likely than peers to have committed a variety of crimes such as disorderly conduct, assault with fists and with a weapon, setting serious fires, and stealing property (Barkley et al., 2006; Hechtman et al., 2016; Molina et al., 2009; Sibley et al., 2011), and longitudinal research shows that criminal outcomes are predicted by impaired social relationships in childhood (Loeber, Farrington, Stouthamer-Loeber, & Van Kammen, 1998). However, group- and variable-centered analytic approaches have not provided information about whether individuals in ADHD samples who are engaging in criminal behavior are also presenting with impairment in other core domains of functioning such as substance use and social problems.

Altogether, the literature using group-centered analyses to investigate adult outcomes of childhood ADHD indicates poor functioning at the group level in academic, vocational/financial, social/interpersonal, substance use, and criminal domains, though only a portion of adults with ADHD histories experience each negative outcome. However, no study has empirically examined whether negative outcomes occur within the same individuals across some or all of these core impairment domains. It is likely that co-occurring problems in adulthood are common, as most adolescents with childhood ADHD experience difficulties in multiple domains across symptoms, academic functioning, and social functioning (Lee, Lahey, Owens, & Hinshaw, 2008), though which impairments or symptoms were most likely to co-occur among adolescents was not examined. Based on a recent study that categorized adults with childhood ADHD as symptom persistent or symptom desistent, it appears that educational and vocational impairments co-occur and are ubiquitous among those with ADHD histories whereas substance use problems are less common (Hechtman et al., 2016). As the ADHD sample in that study was categorized based on symptoms, not impairment, however, co-occurrence of functional impairment was not empirically evaluated as is possible with person-centered analyses. Studies investigating co-occurring problems in non-ADHD populations indicate that vocational and educational outcomes are often related (Dubow, Huesmann, Boxer, Pulkkinen, & Kokko, 2006) and that criminal behavior co-occurs with polysubstance use (Moss, Chen, & Yi, 2007; Windle & Scheidt, 2004). Indeed, one would expect externalizing problems in general (e.g., aggression and substance use) to be functionally related (Kotov et al., 2017; Krueger et al., 2007).

Investigating multifinality across the diverse set of dysfunctional outcomes of childhood ADHD is an important extension of the available literature, and a person-centered statistical approach (i.e., LPA) would appear to be a useful next step in characterizing relationships among these negative outcomes. Using person-centered analyses would allow individuals with ADHD histories to be separated into subgroups that have similar patterns of impairments across the variables examined. Such analyses provide information beyond what is available from group-centered approaches such as whether a subgroup of ADHD probands is unimpaired across domains or, alternatively, impaired across many domains and which impairments are most likely to co-occur among adults with ADHD histories. Despite these advantages, person-centered analyses have not been used in prospective, longitudinal ADHD research.

The current study aimed to use a person-centered approach to investigate the co-occurrence of functional impairment among young adults with ADHD histories and to characterize multifinality in impairment. First, we estimated latent profiles among young adults with childhood ADHD using data from the Pittsburgh ADHD Longitudinal Study (PALS) to determine patterns of functioning that best capture variability in the core impairment domains just discussed. After deriving profiles for the ADHD probands, we compared ADHD profiles to controls. We hypothesized that individuals with ADHD would cluster into groups that present with distinct patterns of impairment that may shed light on differences in long-term outcome in this population. Given the lack of available literature about the co-occurrence of functional impairments in this population, we present exploratory hypotheses as opposed to traditional hypotheses herein. We expected that poor vocational and educational outcomes would co-occur (Altszuler et al., 2016; Dubow et al., 2006). Further, we hypothesized that a subset of adults with childhood ADHD would exhibit consistently severe problems across multiple domains (Lee et al., 2008). Conversely, the fact that a portion of adults with childhood ADHD do not have problems in a given domain raises the possibility that a subgroup may be relatively unimpaired across domains in adulthood. Despite this possibility of a low-impairment group of ADHD probands, we hypothesized that all or almost all ADHD profiles would be impaired compared to control young adults based on the large body of longitudinal research just reviewed. Finally, as an exploratory addition to the LPA, we examined childhood and familial predictors (e.g., demographics, child functioning, familial risk) of profile membership, and no a priori hypotheses regarding predictors were made.

METHOD

Participants

Pittsburgh ADHD Longitudinal Study

The ADHD group was recruited from a pool of clinically referred children who had attended the Summer Treatment Program at Western Psychiatric Institute and Clinic between the years of 1987 and 1996. The first wave of longitudinal follow-up spanned 1999–2003, and 364 of the original 516 study-eligible children were enrolled in PALS (493 of the original 516 were recontacted during PALS enrollment). ADHD probands were diagnosed in childhood based on parent and teacher ratings on standard *DSM-III-R* and *DSM-IV* symptoms scales (Disruptive Behavior Disorder rating scale; Pelham, Evans, Gnagy, & Greenslade, 1992) and semistructured clinical and diagnostic interviews with parents administered by a Ph.D.-level clinician. By comparison, typically developing participants (original $n = 240$) were recruited from the same geographical area at the first wave of follow-up, and recruitment lagged 3 months behind ADHD group enrollment to facilitate efforts to obtain demographic similarity. All families consented, and the PALS has had consistent Institutional Ethics Board approval (IRB No. REN16110041/IRB970723).

Current subsample

Data from the age 25 wave of data collection were used for the current study. Table 1 contains demographic information. At the time of analysis, 317 participants with ADHD had at least one data point available among the functional outcome variables analyzed from the age 25 wave of data collection. No significant differences between the ADHD probands used in the current analyses and those not included ($n = 47$) were found on 10 of the 11 baseline demographic and symptom variables examined ($ps > .05$). Significantly more male ADHD probands were missing data ($p = .046$), with one female and 46 male participants missing age 25 data.

Controls were *not* included in the LPA but were included as a reference. At the time of analysis, 217 control participants had at least one data point available from the age 25 variables used in the profile analyses, and those included in analyses were not significantly different than those not included ($n = 23$) on demographic variables (see Table 1, $ps > .05$).

Measures

LPA variables

From the Substance Use Questionnaire (a self-report, paper-and-pencil questionnaire developed for PALS; Molina & Pelham, 2003), individual items of self-reported frequencies of alcohol consumption, binge drinking (defined as five or more drinks in a single drinking event), cigarette smoking, and marijuana use over the last 12 months were used. The Self-Reported Delinquency scale (Loeber et al., 1998) was used to indicate the number of distinct criminal acts (including violent crimes, drug related offenses, and theft) that the individual engaged in during the past year.

The peer item on the parent-report Impairment Rating Scale (Fabiano et al., 2006), a 0-to-6 Likert-type scale, indicated how

TABLE 1
Demographic Characteristics of Study Participants

	ADHD %[a]	*Controls %*[b]
Gender (% Male)**	88.3	87.6
Race		
White/Caucasian	84.9	84.8
African American	12.0	9.7
Other	3.2	5.5
Highest Parent Education*		
Partial High School	0.3	0.0
High School Grad or GED	9.4	7.4
Technical/Specialized Training	7.5	9.8
Partial College	17.6	12.6
Associate's/2-Year Degree	15.0	8.4
College or University Grad	25.4	26.5
Graduate Training	24.8	35.3
Age 25 Education Level*		
No High School	7.0	0.5
High School Grad or GED	18.0	1.8
Vocational/Technical Training	24.9	10.1
Partial College	32.8	25.3
Associate's/2-Year Degree	1.8	1.4
Bachelor's Degree	13.2	44.2
Graduate Training	2.5	16.6
Age 25 Employment Status*		
Unemployed	28.8	17.5
Part-Time Employed	22.7	10.4
Full-Time Employed	45.6	70.3
Military	2.9	1.9
Estimated Full-Scale IQ[c] (*M, SD*)*	100.11 (15.57)	111.34 (14.42)

[a]n = 317.

[b]n = 217.

[c]At the first wave of follow-up, the Block Design and Vocabulary subtests from the Wechsler Intelligence Scale for Children–III (Wechsler, 1991) or the Wechsler Adult Intelligence Scale–Revised (Wechsler, 1981), depending on participant age, were administered to estimate Full-Scale IQ.

*Attention-deficit hyperactivity disorder (ADHD) and comparison samples significantly different, $p < .05$. **Participants significantly differed from nonparticipants, $p < .05$.

severe impairment and need for treatment were in the peer domain. The number of sexual partners in the past 12 months was collected via self-report on the Health and Sex Behavior Questionnaire, developed for the PALS (Flory et al., 2006). The Conflict Behavior Questionnaire–Adolescent Report (this study, α = 0.95; Prinz, Foster, Kent, & O'Leary, 1979) was used as a measure of the young adult's relationship with his or her mother and is scored such that a higher number indicates more dysfunctional interactions or negative attributions.

For educational level, self-report of the last grade completed was collected and reverse-coded such that a higher score indicates worse outcome as is consistent with all profile indicators. Financial dependence was used as the financial outcome due to the high relation and redundancy between educational attainment and occupational status. Parents rated how financially dependent the young adult was compared to peers of the same age on the General Life Functioning in Adulthood scale (Altszuler et al., 2016) on a scale from 1 (*a good deal further ahead of peers*) to 5 (*a good bit behind peers*).

Baseline and Wave 1 predictors (ADHD group only)

Baseline refers to variables collected in childhood, and Wave 1 refers to variables collected when participants were first interviewed for the PALS follow-up study (average of 8 years later). Twenty-one predictor variables were examined. Child gender and race and parent marital status, highest education, and household income were evaluated as predictors. Participants' estimated full-scale IQs were assessed using the Wechsler Intelligence Scale for Children–Revised (Wechsler, 1991) or the Wechsler Preschool and Primary Scale of Intelligence (Wechsler, 1989) depending on the participant's age. The Woodcock–Johnson Revised (Woodcock & Johnson, 1989) was used to assess academic achievement in reading, written language, and math (after 1994, the Wechsler Individual Achievement Test [Wechsler, 1992] screener was used instead of the Woodcock–Johnson Revised).

Teacher ratings on the IOWA Conners Rating Scale (Atkins, Pelham, & Licht, 1989; Milich, Loney, Landau, & Kramer, 1982) Inattention/Overactivity (α = .75) and Oppositional/Defiant (α = .92) subscales completed at baseline indicated symptom presence and severity. Using the Swanson, Nolan, and Pelham Questionnaire, or SNAP (Pelham & Bender, 1982), teacher ratings, a variable indicating peer problems was created by summing the seven peer interaction items (e.g., acts bossy, teases, annoys peers; α = .89). Items on the IOWA and SNAP were ordered from 0 (*not at all*) to 3 (*very much*). Combined parent and teacher ratings on the Disruptive Behavior Disorder rating scale were used to indicate inattention (α = .97) and hyperactive/impulsive (α = .96) symptom severity at baseline (Pelham et al., 1992). Raw scores on the Anxious/Depressed and Withdrawn/Depressed composite scales were from the Child Behavior Checklist (Achenbach, 1991).

At the first wave of the PALS follow-up, a combination of the Michigan Alcohol Screening Test (Selzer, Vinokur, & Van Rooijen, 1975; Sher & Descutner, 1986) and the Structured Clinical Interview for *DSM-IV*, Nonpatient Edition, was used to derive an index of paternal alcohol problems (see Molina, Gnagy, Joseph, & Pelham, 2016). The Mann Family Tree (Mann, Sobell, Sobell, & Pavan, 1985) was used to determine alcohol problems among male participants by dividing the number of male relatives endorsed to have problems by the number of male relatives. The Alcohol/Substance Use During Pregnancy scale was developed for the PALS, administered at Wave 1, and individual, self-report items assessing the use of cigarettes and alcohol by the biological mother while pregnant were

used. Maternal depression was evaluated using the Beck Depression Inventory (Beck, Epstein, Brown, & Steer, 1988; α = .89) at Wave 1, with higher scores indicating more severe depressive symptoms.

Analyses

LPA was completed in Mplus Version 7.3 (Muthén & Muthén, 1998–2017) using a maximum likelihood framework robust to non-normality. LPA is not affected by slight differences in scaling in the profile indicator variables (Vermunt & Magidson, 2002). Multiple indices of model fit (Bayesian Information Criteria [BIC], where a lower value indicates better fit; log-likelihood ratio test [LRT], where a significant comparison indicates the model with a higher number of parameters has significantly better fit; and entropy with values approaching 1 indicating better classification of individuals into profiles; Celeux & Soromenho, 1996; Nylund, Asparouhov, & Muthén, 2007) in conjunction with theory-based decision making and interpretability influenced the profile model chosen.

LPA variables were collected when ADHD probands were 25 years old (see Table 2 for variable scales). Mean differences between ADHD profiles and control participants on profile variables were evaluated via one-way analysis of variance, and significant differences between controls and ADHD profiles indicate impairment. Baseline and Wave 1 variables were included in the LPA as auxiliary variables, allowing them to influence profile membership and be evaluated as predictors of profile membership within a single model that accounts for measurement error in profile membership (Lanza, Tan, & Bray, 2013). Group differences on auxiliary variables were explored via Wald chi-square tests using 20 pseudoclass draws of profile membership to account for the probabilistic assignment of individuals to profiles (Clark & Muthén, 2009). Pairwise comparisons were evaluated when the overall Wald chi-square value was significant at $p < .01$ due to multiple comparisons.

RESULTS

Latent Profiles

Fit indices for one-profile to six-profile solutions are presented in Table 3. The six-profile solution was difficult to interpret due to the high number of profiles, and the distinctions between additional individual profiles lacked theoretical relevance. We therefore discontinued investigating models with a higher number of profiles. The three-profile and five-profile models optimally classified individuals into profiles (entropy ≥ .90), and the LRT and BIC continually indicated improved model fit for models with a higher number of profiles. Important to note, both the BIC and LR model fit indices take parsimony into account and include a "penalty" for increasing the number of profiles (Tein, Coxe, & Cham, 2013). As such, examination of the combination of fit indices and interpretability of profiles indicated that a five-profile model provides the best solution, entropy = 0.91, BIC = 10,312.93, LRT, $\chi^2(11) = 146.96$, $p < .001$. Although Profile 4 in the five-profile model contains only 3.15% of the sample (10 participants), this profile was consistent in the three-, five-, and six-profile models, and the four-profile model was associated with decreased entropy.

The final five-profile model is depicted in Figure 1 and Table 4 (along with control averages for reference). We labeled each ADHD profile based on the patterns of functioning across domains and differences from controls (see Table

TABLE 2
Scale for Variables in Latent Profiles (Figure 1)

Scale	*Substance Use*	*Cig Smoking*	*Peer Impairment*	*Educational Level*	*Financial Dependence*
11	Several times a day				
10	Twice a day				
9	Once a day				
8	4–6 times a week				
7	2–3 times a week	≥ 2 packs a day			
6	Once a week	1½ packs a day	Extreme problem	Partial high school	
5	2–3 times a month	1 pack a day		Completed high school	A good bit behind
4	Once a month	½ pack a day		Partial college	Somewhat behind
3	8–11 times	1–5 cig per day		Completed vocational or technical school	About where he/she should be
2	4–7 times	< 1 cig per day		Completed 4-year degree	Somewhat further ahead
1	1–3 times	Did not smoke		Partial graduate school	A good bit further ahead
0	Not at all		No problem	Completed graduate school	

Note: Substance use refers to alcohol consumption, binge drinking, and marijuana use. Variables used but not in the table include count outcomes: distinct criminal acts, maternal relationship problems (as measured by the Conflict Behavior Questionnaire and scored as the number of negative interactions and attributions the parent-child dyad have), and number of sex partners in the last year. Cig = cigarette.

Table 2 describes the scales of variables analyzed in the latent profile analysis and depicted in Figure 1 to assist in interpretation of Figure 1.

TABLE 3
Model Fit Statistics

Profiles	*Log-Likelihood*	*LRT*	*BIC*	*Entropy*
1	−5390.828		10,896.833	
2	−5195.505	$p < .001$	10,569.535	0.870
3	−5121.830	$p < .001$	10,485.535	0.932
4	−5045.658	$p < .001$	10,396.539	0.882
5	**−4972.18**	***p* < .001**	**10,312.930**	**0.905**
6	−4932.647	$p < .001$	10,297.213	0.856

Note: The Log-Likelihood Ratio Test (LRT) uses the difference of −2 times the log-likelihood between two models to evaluate whether the inclusion of additional parameters (i.e., profiles) leads to significantly improved model fit (i.e., LRT $p < .05$). A significant LRT therefore indicates that the model with a greater number of profiles fits the data significantly better than the previous model. Entropy approaching 1 indicates that individuals are well-categorized into profiles. The final model is bold for emphasis. BIC = Bayesian information criterion.

4): (a) prototypic impairment group, (b) high binge drinking group, (c) high marijuana use group, (d) high criminal activity group, and (e) high cross-domain impairment group.

Profile 1, the prototypic impairment group, contains 54% of the sample. It is labeled "prototypic impairment" due to impairment across domains commonly identified in the literature as impaired among children and adolescence with ADHD, because these impairments were mostly present in every other profile as well—that is, educational, peer, and financial impairment—and because it is the largest profile. This profile is characterized by relatively low substance use across alcohol (drinking eight to 11 times per year, binge drinking less than once per year), cigarettes (lower use than one cigarette per day), and marijuana (lower use than once per year) and relatively low to negligible criminal activity (less than one criminal act). Compared to controls, these individuals were significantly impaired in peer relationships, maternal relationship, educational attainment, and financial independence, and they engaged in significantly less substance use (see Table 4).

Profile 2, the high binge-drinking group, contains 17% of the sample. Individuals in this group were consuming alcohol once a week, binge drinking two to three times per month, and smoking one to five cigarettes per day. Yet only their frequencies of binge drinking and cigarette smoking, not frequency of any alcohol use, are significantly higher than controls (Table 4). The high binge-drinking group is not engaging in marijuana use or criminal behavior. Social impairment and financial dependence appear to be lowest in this group. This group engaged in significantly less marijuana use than controls and altogether had the lowest number of significant differences from controls (Table 4).

Profile 3, containing 10% of the sample, is the high marijuana use group. These individuals were smoking

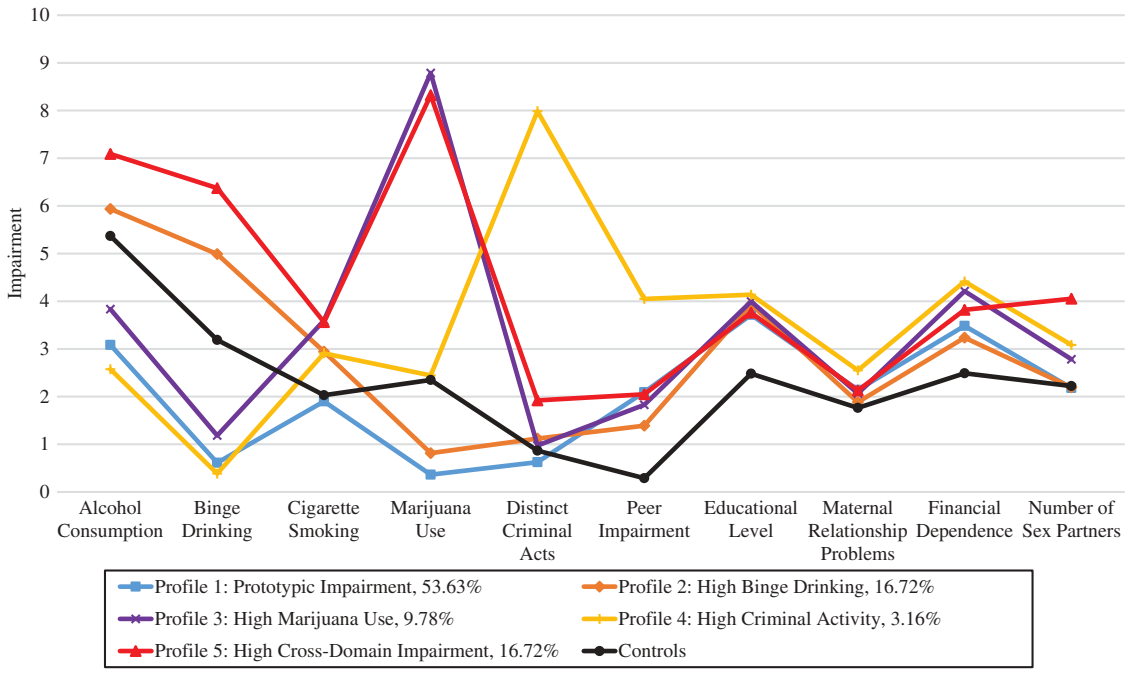

FIGURE 1 Attention-deficit hyperactivity disorder (ADHD) latent profiles and control participant mean scores at Age 25. *Note*: Estimated mean scores are presented for each of the five ADHD profiles. For reference, comparison young adult means are also presented. Higher values indicate greater impairment. Count outcomes include distinct criminal acts, maternal relationship problems (measured by the Conflict Behavior Questionnaire and scored as the number of negative interactions and attributions in the parent–child dyad), and number of sex partners. Refer to Table 2 for the scaling of remaining variables and the Results section for descriptions of each profile.

TABLE 4
Means and Standard Deviations for Age 25 Profile Variables and Mean Differences Compared to Controls

	M (SD)					
	Non-ADHD[a]	*Profile 1, Prototypic Impairment*[b]	*Profile 2, High Binge Drinking*[c]	*Profile 3, High Marijuana Use*[d]	*Profile 4, High Criminal Activity*[e]	*Profile 5, High Cross-Domain Impairment*[f]
Alcohol Use	5.37 (2.23)	3.07 (2.33)***	5.87 (1.16)	3.93 (2.10)**	2.56 (2.24)**	7.09 (1.28)**
Binge Drinking	3.19 (2.59)	.60 (.76)***	4.89 (1.17)***	1.20 (1.00)***	.38 (.52)***	6.40 (1.23)***
Cigarette Smoking	2.03 (1.34)	1.91 (1.39)	2.98 (1.72)***	3.63 (1.67)***	2.89 (1.90)	3.55 (1.54)***
Marijuana Use	2.35 (3.30)	.38 (.87)***	.81 (1.383)**	8.81 (1.80)***	2.50 (3.51)	8.33 (2.09)***
Distinct Criminal Acts	.87 (1.35)	.63 (.91)	1.14 (1.17)	.97 (1.35)	8.00 (1.94)***	1.92 (1.73)***
Peer Impairment	.29 (.95)	2.14 (2.02)***	1.31 (1.80)**	1.60 (1.78)**	4.00 (1.93)***	2.05 (1.99)***
Educational Attainment	2.48 (1.23)	3.72 (1.27)***	3.96 (1.21)***	4.00 (1.00)***	4.10 (.74)***	3.77 (.91)***
Maternal Relationship Problems	1.76 (.62)	2.16 (.86)***	1.88 (.69)	1.99 (.78)	2.56 (.92)*	2.12 (.70)*
Financial Dependence	2.49 (1.22)	3.51 (1.27)***	3.15 (1.09)	4.26 (1.20)***	4.43 (.79)**	3.83 (1.26)***
No. of Sex Partners	2.22 (2.00)	2.20 (2.58)	2.16 (1.49)	2.84 (2.17)	3.00 (4.53)	4.03 (2.90)***

Note. Differences were evaluated via one-way analysis of variance. ADHD = attention-deficit hyperactivity disorder.
[a]$n = 217$.
[b]$n = 161$.
[c]$n = 56$.
[d]$n = 37$.
[e]$n = 10$.
[f]$n = 53$.
*$p < .05$. **$p < .01$. ***$p < .001$ compared to controls.

marijuana once per day, consuming alcohol once per month, binge drinking one to three times per year, and smoking about half a pack of cigarettes per day. As shown in Table 4, the high marijuana use group engaged in significantly less alcohol and binge drinking and significantly more cigarette smoking and marijuana use than controls. They were also significantly impaired compared to controls in peer relationships, educational attainment, and financial dependence.

Profile 4, containing only 3% of this sample, is the high criminal activity group. These individuals are distinctly characterized by a relatively high number of criminal acts committed in the previous year (average of eight distinct self-reported criminal acts) and markedly high peer relationship impairment. Young adults in this group were consuming alcohol four to seven times per year, binge drinking less than once per year, smoking one to five cigarettes per day, and using marijuana less than once per month—which are all at or significantly *below* the rate of substance use in the non-ADHD group (Table 4). However, individuals in the high criminal activity group were committing more crimes, were more financially dependent, had lower educational attainment, and had more problems in peer and maternal relationships than controls.

Profile 5, containing 17% of the sample, is the high cross-domain impairment group. These individuals were consuming alcohol and binge drinking two to three times per week, smoking half a pack of cigarettes per day, and using marijuana four to six times per week. Individuals in the high cross-domain impairment group reported committing two distinct criminal acts in the last year, had maternal relationship problems, were financially dependent, and had an average of four sexual partners per year. ADHD probands in the high cross-domain impairment group were significantly impaired relative to controls on all profile variables (Table 4).

Differences on Predictor Variables

Of the 21 auxiliary variables, profiles were not significantly different on 19 variables at the p-value of .01. Biological sex was significantly different between the prototypic impairment group (82% male) and both the high cross-domain impairment and high criminal activity groups (96% and 100% male, respectively), $p < .001$. Other demographic and child baseline variables (i.e., child race, parent marital status and education, household income, IQ, and achievement scores, ADHD symptoms [inattentive and hyperactive/impulsive], oppositional behavior, anxiety, depression, and peer impairment) were not significantly different across profiles (ps >.01).

In terms of familial risk factors, maternal alcohol use during pregnancy ($p = .002$) was significantly different across groups. Specifically, the prototypic impairment group was significantly higher in maternal alcohol use during pregnancy than the high binge-drinking and high

criminal activity groups. Other familial risk variables (i.e., paternal alcohol use, alcohol problems among male relatives, smoking while pregnant, and maternal depression) were not significantly different among profiles (*p*s >.01).

DISCUSSION

This study is the first to use person-centered analyses to characterize the variability and multifinality of longitudinal outcome among children with ADHD, and specifically, focus was placed on core areas of impairment (educational/financial functioning, social functioning, substance use, and criminal behavior). Results indicated that (a) children with ADHD present with at least five distinct patterns and levels of impairment in young adulthood largely differentiated by substance use, criminal behavior, and number of clinically impaired domains; (b) all empirically derived subgroups of young adults with childhood ADHD were impaired compared to controls, specifically in terms of peer relationships, educational attainment, and financial dependence; and (c) childhood predictors of young adult functioning were rarely significant. These findings are discussed in turn next.

Profiles of impairment indicate that substance use varies systematically among young adults with childhood ADHD. The three profiles that exhibited relatively high substance use behaviors were the high marijuana use, high binge drinking, and the high cross-domain impairment groups, accounting for about 43% of young adults with ADHD histories. Important to note, for any given substance, the ADHD probands bifurcated in their use. Results suggest that childhood ADHD confers risk for heightened alcohol use for some and predicts below normative use for others, consistent with previous work in this longitudinal sample. Molina and Pelham (2014) empirically delineated two distinct developmental pathways toward alcohol use among young adults with ADHD, with a delinquency pathway conferring *increased* risk for alcohol use (i.e., high cross-domain impairment group) and a social impairment pathway conferring *decreased* risk in young adulthood (i.e., prototypic impairment group). The differing pathways may explain somewhat confusing meta-analytic findings indicating that adults with ADHD are at greater risk for alcohol use disorders than their peers but do not consume more alcohol in their lifetime, on average (Lee, Humphreys, Flory, Liu, & Glass, 2011). This is consistent with our findings that the ADHD subgroup that endorsed the least amount of alcohol use (even compared to non-ADHD young adults) also demonstrated the highest level of impairment in peer relationships (i.e., high criminal activity profile).

The profiles also indicate that, for individuals with ADHD, heightened cigarette use co-occurs with substance use (i.e., alcohol and marijuana use). This extends previous literature indicating that ADHD and drug use disorders uniquely relate to daily smoking and nicotine dependence (Lambert & Hartsough, 1998; Rohde, Kahler, Lewinsohn, & Brown, 2004) and that cigarette smoking is a risk factor for concurrent and later substance use among youth with ADHD (Biederman, Petty, Hammerness, Batchelder, & Faraone, 2012; Molina et al., 2013). Marijuana use also provided an interesting distinction among young adults with childhood ADHD, with about 26% using marijuana *more* and 70% using marijuana *less* than comparison young adults. The varying risk for later substance use is important for researchers to consider when evaluating substance use at the group level (ADHD vs. non-ADHD) as such analyses may obscure potentially important addiction-prone subgroups with unique vulnerabilities associated with ADHD or its impairments. Altogether, multifinality in ADHD substance use outcome is apparent in generalized substance use (e.g., high cross-domain impairment group) and substance-specific risk pathways (e.g., high binge-drinking group and high marijuana use group; Molina & Pelham, 2014). Finally, it also suggests potential pathways to emergence of substance use disorder at older ages when developmentally limited substance use tends to decline. Exacerbation of ADHD-related impairments from substance use, and vice versa, may partially explain the higher number of alcohol-related problems that we recently reported for the ADHD group at a mean age of 29 (Pedersen et al., 2016).

Adults in the high criminal activity group reported engaging in an average of eight distinct criminal acts in the last year, and high criminal behavior co-occurs with impaired interpersonal relationships, relatively high financial dependence, and relatively low substance use among young adults with childhood ADHD. Later aggression and criminal activity are related to disturbed peer relationships in childhood (e.g., few friends, aggression; Huesmann et al., 1984), and it follows that social impairment and criminal behavior would co-occur in adulthood. Although all ADHD profiles had peer problems, the high criminal activity group had markedly higher peer problems than did all other ADHD profiles (1 *SD* higher) and controls (2 *SD*s higher). Further, individuals who engage in criminal behavior during adulthood tend to have life-course-persistent antisocial behavior, which is costly to society (Moffitt, 2006).

Person-centered analyses identified a high cross-domain impairment group that is impaired in more domains than any other ADHD profile (i.e., educational/financial, social/interpersonal, substance use, and criminal activity) compared to controls. Highlighting a subgroup of children with ADHD who are contributing highly to the lifetime societal cost of ADHD as the impairments this group exhibits (e.g., binge drinking once per week, using marijuana daily, and engaging in risky sexual behavior and criminal activity) are the

behaviors that lead to high costs from lost productivity, health care needs, and the criminal justice system (Pelham et al., 2007). Of interest, research into the typology of alcoholism converges on a similar subset described as poly-drug users or antisocial subtype that engage in high binge drinking, nonalcohol substance use, criminal behavior, and risky sexual behavior (Moss et al., 2007; Windle & Scheidt, 2004), who may overlap to an extent with this subgroup presenting with ADHD in childhood. Further, these results align with research on the dimensionality of adult externalizing problems, which has indicated that substance use and conduct problems are related via a higher order disinhibited externalizing factor (Kotov et al., 2017).

Of particular importance for understanding long-term outcome is that children with ADHD, regardless of profile membership, have impaired peer functioning, educational attainment, and financial independence in young adulthood relative to the non-ADHD group. This is exemplified by the prototypic impairment profile (54% of the sample), as their major impairments are the same that they had in childhood and adolescence (i.e., problems in relationships with peers, relationships with parents, and academic achievement), in addition to domains that weren't relevant when they were younger (i.e., vocational functioning, financial independence), and nearly all ADHD profiles are impaired in these domains. This homotypic continuity of impairments from childhood to young adulthood extends numerous variable-centered, as opposed to person-centered, findings in the literature to underscore that even when an attempt is made to identify subgroups of children with variable outcomes, social, educational, and financial impairments appear to be universal. In other words, a low impairment group did not emerge among the young adults with ADHD histories. Very few children with ADHD are financially independent or earning bachelor's degrees in young adulthood, despite relatively high parental education in the PALS sample. These pervasively impaired areas, coupled with the long-term societal and individual cost of ADHD (Altszuler et al., 2016; Biederman & Faraone, 2006; Pelham et al., 2007), indicate that an ADHD diagnosis in childhood is clearly sufficient to indicate need for preventive interventions to address future financial, educational, and social impairment.

Childhood and familial risk factors were rarely significant predictors of adult functioning. Of the 21 auxiliary variables examined, two were significant predictors. Child biological sex was significant due to the high rates of males in the high criminal activity (100%) and high cross-domain impairment (96%) profiles compared to the prototypic impairment profile (82%). Aligning with research indicating girls with ADHD are not at heightened risk for substance use problems or delinquency (Hinshaw et al., 2012), results herein show that boys with ADHD are more likely than girls to engage in criminal activity and polysubstance use in adulthood. Further, increased maternal alcohol consumption while pregnant predicted membership in the prototypic impairment profile compared to the high binge-drinking and high criminal activity profiles. Given that the high criminal activity group includes only 10 participants, we advise caution when interpreting this effect. Although it is surprising that higher prenatal alcohol consumption predicts not belonging to the high binge-drinking profile, it is important to note that the high binge-drinking profile's alcohol use pattern is most similar to the non-ADHD controls' alcohol use pattern. In addition, it is often the case in the ADHD longitudinal literature that childhood predictors are not significant when not including controls in analyses, likely due to the restricted variability at baseline within a clinical sample (Roy et al., 2016).

LIMITATIONS AND FUTURE DIRECTIONS

Prediction from childhood may have been limited by the time gap between predictors and outcome and the developmental nonspecificity of baseline predictors. Children in the PALS sample were recruited via participation in a treatment program, and as such they varied in age at baseline and there may have been artificially limited variability due to severe baseline functioning. Future research should examine specific predictors based on each profile, and it is likely that developmentally or domain-sensitive variables, such as early parenting behavior, adolescent initiation of substance use, or association with a deviant peer group, would provide better prediction (e.g., Molina et al., 2014). For example, adolescent onset of substance-specific use may predict membership in that substance-specific profile in adulthood. Given the explicit focus of this article on functional impairment, we did not evaluate variations in internalizing comorbidities in adulthood. We did, however, examine childhood internalizing problems as a predictor of adult impairment, and the result was not significant. Future research with larger samples may be needed to investigate patterns of co-occurring diagnoses and impairment.

Further, the stability of the profiles cannot be established within the current analyses. Future research should compare profile membership across ages and samples, particularly to replicate the high criminal activity group, which includes a small subset of this sample (3%, n = 10). This profile was stable at the three-, five-, and six-profile models and associated with improved entropy, but replication is needed. Instability in profiles across periods of adulthood may be expected given that substance use largely differentiated the profiles herein and declines after young adulthood among non-ADHD individuals (Johnston, O'Malley, Bachman, Schulenberg, & Miech, 2016). Last, most profile indicators were single

items. We selected the items carefully based on previous research, and the robustness of LPA is not impacted by this. However, results may have been different if composite scores were used.

CLINICAL IMPLICATIONS

Using person-centered analyses, patterns of functional impairment outcomes among individuals with ADHD histories were derived that significantly add to the understanding of the outcomes associated with childhood ADHD. Critically, a subgroup of ADHD probands that evidenced positive outcomes was not identified. It is important for clinicians who work with families and teachers of children and adolescents with ADHD to be aware of the potential long-term outcomes for children with ADHD, as this is often a primary parental concern. Clinicians, parents, and teachers may benefit from understanding, in clear terms, that childhood ADHD is a chronic disorder that, at this time, is likely to lead to prototypic, lifetime impairments in educational, financial, and social functioning. Clearly, more research is needed regarding promoting financial, academic, and social success among individuals with ADHD at critical periods, such as entering the workforce or preparing for college. Further, substance use was elevated in specific subgroups of young adults with ADHD histories, indicating that not all adolescents with ADHD require substance use prevention or intervention programs, and collateral information associated with later substance use, such as association with a deviant peer group, should be taken into account when choosing preventive interventions.

CONCLUSIONS

By empirically deriving profiles of impairment among young adults with childhood ADHD, we are able to characterize the relationships among critical, functional outcomes in a heterogeneous clinical population. Results indicate that young adults with ADHD histories present with distinct patterns of functional impairment that vary by substance use, criminal activity, and number of clinically impaired domains. All ADHD profiles were impaired compared to controls, most commonly on measures of educational attainment, peer relationships, and financial independence as evidenced by the prototypic impairment group. Therefore, childhood ADHD diagnosis alone is sufficient to indicate long-term difficulties with academic, financial, and social competencies and need for treatment in these key domains. Three profiles, comprising 43% of the sample, were characterized by higher substance use than controls, indicating that elevated use of at least one substance is present among subgroups of, but not all, young adults with childhood ADHD. Further, a particularly concerning subgroup of young adults with childhood ADHD was empirically identified, the high cross-domain impairment profile (17% of the sample), that exhibits significantly elevated problems in all domains assessed (i.e., educational attainment, financial independence, social functioning, polysubstance use, and criminal behavior). This group therefore may have the greatest individual and societal costs, and, if replicated in a similar sample, this group is arguably the one in which intervention efforts should be targeted in young adulthood.

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The Long-Term Financial Outcome of Children Diagnosed With ADHD

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Objective: Characterize the early trajectories of financial functioning in adults with history of childhood ADHD and use these trajectories to project earnings and savings over the lifetime. ***Method:*** Data were drawn from a prospective case-control study (PALS) following participants with a rigorous diagnosis of ADHD during childhood (N = 364) and demographically matched controls (N = 240) for nearly 20 years. Participants and their parents reported on an array of financial outcomes when participants were 25 and 30 years old. ***Results:*** At age 30, adults with a history of ADHD exhibited substantially worse outcomes than controls on most financial indicators, even when they and their parents no longer endorsed any *DSM* symptoms of ADHD. Between ages 25 and 30, probands had exhibited considerably slower growth than controls in positive financial indicators (e.g., monthly income) and substantially less reduction than controls in indicators of financial dependence (e.g., living with parents), indicating worsening or sustained deficits on nearly all measures. When earnings trajectories from age 25 to age 30 were extrapolated using matched census data, male probands were projected to earn $1.27 million less than controls over their working lifetime, reaching retirement with up to 75% lower net worth. ***Conclusion:*** The financial deficit of adults with history of childhood ADHD grows across early adulthood. Projections based on early financial trajectories suggest very large cumulative differences in earnings and savings. With or without persistence of the *DSM* symptoms, the adult sequela of childhood ADHD can be conceptualized as a chronic condition often requiring considerable support from others during adulthood.

What is the public health significance of this article?
This study underscores the need for clinical interventions that can improve the financial outcomes of children with ADHD in adulthood. Left unaddressed, ADHD-related deficits in financial functioning incur substantial burden to the afflicted, their families, and social welfare programs.

Keywords: ADHD, impairment, personal finance

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Approximately 10% of children in the United States (Danielson et al., 2018) have been diagnosed with attention deficit hyperactivity disorder (ADHD), a diagnosis characterized by inattention, impulsivity, and hyperactivity. A growing literature has shown that

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children diagnosed with ADHD experience a variety of difficulties in adulthood (Barkley, Murphy, & Fischer, 2008), with most studies focusing on diagnostic symptomatology (Sibley et al., 2012), substance use (Molina & Pelham, 2014), and educational and occupational functioning (Barkley, Fischer, Smallish, & Fletcher, 2006; Kuriyan et al., 2013). Fewer studies have reported on financial functioning, even though financial independence might be considered the primary developmental goal of adulthood, just as school completion might be considered the primary developmental goal of childhood and adolescence. The literature to date suggests that adults who were diagnosed with ADHD during childhood report lower income (Hechtman et al., 2016; Klein et al., 2012), have less in savings (Barkley et al., 2008), and are more likely to receive public assistance (E. B. Owens, Zalecki, Gillette, & Hinshaw, 2017) or be financially dependent on parents (Altszuler et al., 2016; Biederman et al., 2012). Thus, poor finances may be one of the most critical and impairing deficits for adults with a history of ADHD, their parents, and their spouses.

This emergent literature has several limitations. First, all previous studies have examined financial functioning at a single point in time, leaving it unknown how ADHD-related deficits evolve over the course of adulthood. On one hand, the gap may shrink as those with ADHD eventually "catch up" to controls in financial status, consistent with a conceptualization of ADHD as a developmental delay that slows progression through important milestones but is eventually overcome. On the other hand, the gap may persist or even grow, consistent with a conceptualization of ADHD as a chronic, refractory disorder that confers lasting and potentially cumulative impairment.

Second, no previous study has evaluated the potential cumulative impact of lower income and savings rates on the accumulation of net worth over the life span. Participants in the ongoing large, prospective cohort studies will not reach retirement age until 20 to 40 years from now (Altszuler et al., 2016; Barkley et al., 2006; Biederman et al., 2012; Hechtman et al., 2016; Klein et al., 2012; E. B. Owens et al., 2017), precluding a direct test of this question in the near future. In the interim, early financial trajectories can be used to anticipate what will be observed at retirement age and inform the design of data collection during the intervening years. For example, the U.S. Census Bureau has used a synthetic approach to provide intermediate estimates of sex, ethnicity, and occupational differences in earnings over the lifetime without prospectively collecting the 40 years of requisite data (Day & Newburger, 2002; Julian, 2012; Julian & Kominski, 2011).

Third, most prior studies have examined a restricted set of just one or two financial outcomes (e.g., just income) while reporting on outcomes from several different domains. Yet without understanding participants' pattern of income, savings, credit, rent, debts, and dependence on others, it is difficult to appraise their overall financial status (Gordon & Fabiano, 2019). For example, moderate income might be offset by high debt, or low rates of dependence on public assistance might be offset by high rates of dependence on family. Fourth, prior studies have relied almost entirely on self-report of financial status. Because individuals with ADHD often exhibit a positive illusory bias (Hoza, Pelham, Dobbs, Owens, & Pillow, 2002; J. S. Owens, Goldfine, Evangelista, Hoza, & Kaiser, 2007; Sibley et al., 2012, 2017), relying on self-report is likely to underestimate the magnitude of the financial deficit associated with ADHD.

Finally, the few extensive prior studies of financial outcomes (Altszuler et al., 2016; Barkley et al., 2008) have not evaluated whether financial impairment is related to the persistence or desistance of ADHD diagnosis/symptoms. Some children with ADHD will no longer exhibit *DSM* symptoms in adulthood (Sibley et al., 2017), and it is unclear whether financial impairment remains when symptoms have remitted. Recent work (Hechtman et al., 2016; E. B. Owens et al., 2017) has reported relatively small differences in the occupational outcomes of adults whose childhood ADHD has desisted and matched comparisons, so the same may be true of financial outcomes.

The current study addresses the limitations of past literature identified above using data from the Pittsburgh ADHD Longitudinal Study (PALS), a sample of ADHD children and demographically matched controls that has been followed prospectively for nearly 20 years. Building on our earlier analysis of data from age 25 (Altszuler et al., 2016), in Analysis 1, we compare probands and controls on a broad array of self-reported and parent-reported financial indicators at age 30; evaluate whether probands continue to exhibit financial impairment when ADHD symptoms desist; and test whether proband-control differences in financial outcomes can be explained by reduced educational attainment among probands. In Analysis 2, we compare probands' and controls' trajectories of financial functioning from age 25 to age 30 to evaluate whether ADHD-related deficits grow, shrink, or remain constant over time. In Analyses 3 and 4, we combine the PALS data with matched census data to create projections of income over the life span and net worth at retirement. Together, these analyses provide the most comprehensive picture to date of the financial prognosis of adults with a history of childhood ADHD.

Method

Sample

PALS has followed a mixed-age sample of children with ADHD ($N = 364$) and children without ADHD ($N = 240$) for nearly 20 years (Faden et al., 2004; Molina, Sibley, Pedersen, & Pelham, 2016).

Probands. All attendees of a summer treatment program for ADHD at the University of Pittsburgh Medical Center between 1987 and 1996 were recontacted between 1999 and 2003 and offered enrollment as probands in the PALS study. Three hundred sixty-four of a possible 516 enrolled, amounting for 71% of the treatment program attendees during this interval. Those that enrolled exhibited lower average Conduct Disorder symptom ratings ($d = 0.30$) than those that did not enroll, but these groups were otherwise similar (Molina et al., 2016).

Participation in the summer treatment program required diagnosis of ADHD per *DSM–III–R* or *DSM–IV* symptom criteria. PhD-level clinicians conducted a semistructured interview and reviewed symptom scales completed by teachers and parents in order to confirm the diagnosis of ADHD. Exclusion criteria included a full-scale IQ below 80 and a history of seizures, neurological disorders, pervasive developmental disorder, schizophrenia, and/or other psychotic or organic mental disorders (Molina et al., 2016). Other psychiatric comorbidities (e.g., anxiety disorders) were permitted. Forty-seven percent met *DSM* symptom criteria for oppositional defiant disorder, and 36% met symptom criteria for conduct disorder.

All probands received treatment for ADHD during childhood, since they were recruited from attendees of an intensive, 8-week summer treatment program. Ninety percent reported use of stimulant medication at some time in their lifetime, for an average of 5 years medicated between ages 5 and 25. At age 25, 7% of the sample were taking stimulant medication and 8% were taking some other psychoactive medication.

Controls. A demographically similar control group was recruited between 1999 and 2001 from a variety of sources, including pediatric practices (41%), advertisements in local newspapers (28%), and local colleges (21%; Molina et al., 2016). A prospective participant was offered enrollment if his or her age, sex, race, and level of parent education would increase the control group's rolling similarity to the probands on these characteristics. Table S1 compares baseline characteristics of probands and controls, which are similar except for probands exhibiting lower intelligence quotients ($M = 101$) than controls ($M = 111$). This difference is expected based on past literature (Frazier, Demaree, & Youngstrom, 2004; Jepsen, Fagerlund, & Mortensen, 2009), and adjusting for intelligence had minimal impact on findings (see online supplemental material).

Overall sample. In the overall sample, 89% of children were male. Eighty-two percent of children were White, 10% were Black, 5% were Mixed Race, and 1% were Hispanic. These proportions were broadly representative of the population of Allegheny County, Pennsylvania (84.3% White, 12.4% Black, 1.1% Mixed Race, 0.9% Hispanic; U.S. Census Bureau, 2000). Twenty-nine percent of children were in single parent households. Median parental income was ~$64,000, and at least one parent had graduated college in 55% of families. See prior reports (Faden et al., 2004; Molina et al., 2016) for further information about the PALS sample. This report uses data from two follow-up visits: the target age-25 visit ($M = 25.2$, $SD = 0.5$) and the target age-30 visit ($M = 29.6$, $SD = 0.8$). Of relevance to financial outcomes, 18% of these visits occurred within the Great Recession (i.e., December 2007 to June 2009)—this proportion was similar in probands and controls. The institutional review board approved all procedures.

Measures

Finances questionnaire. Participants and their parents independently completed questionnaires asking about participants' earnings, savings, dependence on family or others, credit cards, debt, and other relevant financial habits. Items included a mix of binary responses (e.g., "Do you own a home?"), categorical responses ("Mark the interval indicating how much debt you are in"), and open-ended responses ("How much money do you have in savings?"). The self-report form included 28 items and the parent-report form included 16 items, with some items overlapping across these two forms. Parents did not report on outcomes of which they were unlikely to have knowledge (e.g., balance of participant's savings account). See online supplemental material for more detail about this questionnaire.

***DSM* symptoms of ADHD.** Some analyses required identifying which probands no longer met *DSM* symptom criteria for ADHD as adults (i.e., "desisters"). Both participants and their parents rated *DSM–IV* symptoms of ADHD at age 30 via the Adult ADHD Scale (Barkley, Fischer, Smallish, & Fletcher, 2002), with a symptom counted as endorsed when rated as occurring "pretty often" or "very often." Following Hechtman et al. (2016), probands were classified as desisters when neither they nor their parents endorsed five or more *DSM* symptoms of either inattention or impulsivity/hyperactivity. Nonmissing parent report was required in order to be classified as a desister. Furthermore, in this report, probands were classified as *complete* desisters when they exhibited zero *DSM* symptoms of ADHD per both self- and parent-report. Seventy-seven percent of probands were classified as desisters ($N = 227$), and 35% of probands were classified as complete desisters ($N = 103$).

Educational attainment. Participants reported educational attainment at the age-25 visit. They used a six-point ordinal scale: 1 (*no high school diploma*), 2 (*graduated high school or obtained GED*), 3 (*some college*), 4 (*associate degree*), 5 (*bachelor's degree*), 6 (*graduate degree*). Table S2 lists the proportion of probands and controls in each category.

Analyses

Analyses were conducted in the R statistical software environment (v3.6.1; R Core Team, 2019) unless otherwise specified. Self-report of financial outcomes was present for 474 participants at age 25 and for 435 at age 30. Parent-report of financial outcomes was present for 383 participants at age 25 and for 386 at age 30. Missing data were addressed using multiple imputation by chained equations (White, Royston, & Wood, 2011; see online supplemental material); $N = 604$ unless otherwise specified.

Analysis 1: Proband/control differences at age 30. We compared controls and probands at age 30 by regressing each financial outcome on a dummy indicator of ADHD status. Logistic regression was used for binary outcomes, and ordinary least squares regression was used for nonbinary outcomes. Next, we checked if these results changed when comparing controls to just the probands identified as exhibiting desistant (i.e., less than five) or completely desistant (i.e., zero) *DSM* symptoms of ADHD. Finally, we conducted statistical mediation analysis (MacKinnon, Fairchild, & Fritz, 2007) to test whether educational attainment at age 25 mediated the effect of childhood ADHD (i.e., proband vs. control) on financial outcomes at age 30. Educational attainment was identified as a potential mediator because previous analyses have shown that it predicts financial functioning in this sample (Altszuler et al., 2016). To reduce the number of statistical tests, we fit mediation models for four key financial outcomes at age 30: monthly income, money in savings, living with parents/family, and regularly receiving money from parents/family. The latter two outcomes were combined across informants—if either participant or parent endorsed them, they were counted as positive. For each outcome, a path analysis model was fit in Mplus (v7.4; Muthén & Muthén, 2015) with educational attainment at age 25 mediating the effect of childhood ADHD (i.e., proband vs. control) on financial outcome at age 30 (Figure S3). The statistical significance of the indirect effect was evaluated using the joint significance test (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002).

Analysis 2: Proband/control differences in change from age 25 to age 30. We next tested whether the probands and controls differed in financial trajectory from age 25 to age 30. For nonbinary outcomes, change scores were computed and then regressed on a dummy indicator of ADHD status and the value of the outcome at age 25 (Kim & Steiner, 2019). For binary outcomes,

each participant contributed two rows to the data set (one for each age of data), and the binary outcome was regressed on dummies indicating ADHD status, timepoint, and the interaction thereof.

Analysis 3: Proband/control differences in projected lifetime income. Projections of lifetime income and net worth at retirement were restricted to the White, male portion of the sample ($N = 444$). This restriction focused results on the comparison of ADHD and non-ADHD groups (rather, e.g., than effects of child rearing status on income) and ensured adequate census coverage for age, education, and employment strata (see online supplemental material). We implemented the synthetic work-life earnings approach of Day and Newburger (2002) using person-level data from the Census' American Community Survey (ACS; Ruggles, Genadek, Goeken, Grover, & Sobek, 2017). The income of PALS participants was projected in two ways. In Method A, each member of the sample was assigned the synthetic lifetime income of respondents in the ACS with the same education and employment status as the PALS participant at age 30. This method treats the probands and controls as exchangeable within employment and education strata. In Method B, we relaxed this assumption by estimating how closely the proband and control groups tracked their census-projected growth in income from age 25 to age 30, then rescaling future growth in income based on this correspondence. See online supplemental material for more detail.

Analysis 4: Proband/control differences in projected net worth at retirement. Net worth at retirement was also projected in two ways. The first method of projection (Method A) used data from Wave 1 of the 2014 Survey on Income and Program Participation (SIPP) panel to calculate the mean net worth at ages 65–69 of Americans at different levels of education. Total net worth was computed in the SIPP using a broad definition of assets, including savings, equities, bonds, businesses, home equity, real estate, and retirement accounts. Each member of the PALS sample was assigned the net worth projection created using respondents in the census sample with the same education as the PALS participant at age 30. However, this procedure does not account for known ADHD/control differences in employment status (Kuriyan et al., 2013), annual income (Hechtman et al., 2016), or savings behavior (Barkley et al., 2008). The second method of projection (Method B) addressed these limitations by combining the more detailed ACS income data with three assumptions: (a) the savings rate in the control group, (b) the savings rate in the ADHD group, and (c) the annual return on savings (i.e., interest rate). We projected the group difference in net worth at retirement across a range of values for these assumptions.

Results

Analysis 1: Proband/Control Differences at Age 30

Table 1 reports financial outcomes at age 30 for the ADHD and control groups. By self-report, probands were more likely than controls to be unemployed (22% vs. 13%) and living with parents/family (33% vs. 12%), were earning 37% less per month (mean of ~$2,211 vs. $3,530), and had 66% less money in savings ($3,990 vs. $9,970). Probands were also spending less than controls in monthly rent ($490 vs. $852), had fewer credit cards (1.5 vs. 2.7), had been rejected for a credit card more frequently, and were less likely to own a home (22% vs. 42%).

By parent report, probands were more likely than controls to be living with parents/family (30% vs. 9%), to be regularly receiving money from parents (23% vs. 8%), to be receiving financial assistance from a nonparent adult (21% vs. 7%), and to have ever moved back in with parents after first leaving home (41% vs. 27%). Probands were also more likely than controls to have ever received emergency funds from parents and had received them more than twice as often in the past year. Finally, when the same questions were asked of the participants and their parents, probands reported lower rates of financial dependence than did their parents (see Figure 1). There was no such difference among controls.

Controls versus probands with desistant childhood ADHD. Follow-up analyses examined whether the observed proband/control differences remained significant even when the probands' childhood ADHD had desisted. When comparing controls to only the probands with desistant childhood ADHD (i.e., less than five symptoms), nearly all the significant probands/control differences (14 of 17) remained statistically significant (Figure S1). When comparing controls to only the probands with *completely* desistant childhood ADHD (i.e., zero symptoms), several of the significant proband-control differences (8 of 17) remained statistically significant (e.g., differences on living with parents/family, regularly receiving money from parents/family, receiving financial assistance from a nonparent adult, and having less money in savings account). Thus, even probands who no longer met *DSM* symptom criteria for ADHD (or exhibited no symptoms whatsoever) showed substantial and pervasive deficits in financial functioning relative to controls. See Table S3 for financial outcomes by symptom status and which specific differences remained statistically significant.

Educational attainment as mediator of proband-control differences in financial outcomes. Table S4 reports estimated effects from path analysis models with educational attainment mediating the effect of childhood ADHD on financial outcomes. The indirect (i.e., mediated) effect was in the expected direction and statistically significant for all four outcomes: monthly income ($p < .001$), money in savings ($p < .001$), living with parents/family ($p < .001$), and regularly receiving money from parents/family ($p < .10$). Probands had lower educational attainment at age 25, which in turn was associated with worse financial functioning at age 30. The direct effect was in the expected direction for all four outcomes and statistically significant for three of the four (the exception being money in savings). Thus, there remained a significant direct effect of childhood ADHD on financial outcomes at age 30 that was *not* mediated by educational attainment at age 25.

Analysis 2: Proband/Control Differences in Change From Age 25 to Age 30

Table 1 reports the change in each group from age 25 to age 30. Figure 2 illustrates four key trends. By self-report, the ADHD group had exhibited a significantly smaller reduction than the control group in the proportion living with parents or family, dropping from 40% to 33% (ADHD) versus from 28% to 12% (control). Probands had increased their monthly income (+$285 vs. +$974), monthly rent (+$103 vs. +$340), and savings (+$1,508 vs. +$3,722) significantly less than had controls. Probands had acquired fewer additional credit cards than had controls and had been rejected for more new credit card applications. Finally, while the proportion of controls owning a home had

Table 1
Financial Trajectories of Controls and Probands From Ages 25 to 30

Informant	Outcome	Descriptive statistics: Mean (or proportion) at age 25 — Controls	Mean (or proportion) at age 25 — Probands	Mean (or proportion) at age 30 — Controls	Mean (or proportion) at age 30 — Probands	Change in mean from age 25 to 30 — Controls	Change in mean from age 25 to 30 — Probands	Inference: Diff. at age 30 significant?	Inference: Diff.-in-diff. significant?
Adult	Currently employed full-time	72%	50%	80%	65%	+8%	+15%	*	
	Currently unemployed	17%	28%	13%	22%	−4%	−6%	*	
	Living with parents/family	28%	40%	12%	33%	−16%	−7%	*	*[a]
	Regularly receives money from parents/family	11%	12%	5%	11%	−6%	−1%	*	
	Monthly rent/housing expenses	$ 512 [183, 719]	$ 387 [0, 638]	$ 852 [436, 1204]	$ 490 [0, 707]	+340	+103	*	*
	Receiving welfare/government assistance	2%	12%	6%	11%	+3%	−2%		
	Monthly income	$2,556 [974, 3485]	$1,926 [810, 2832]	$3,530 [1724, 4548]	$2,211 [809, 2927]	+974	+285	*	*
	Money in savings account	$6,247 [0, 4720]	$2,482 [0, 1400]	$9,970 [13, 8545]	$3,990 [0, 2191]	+3,722	+1,508	*	*
	Number of credit cards	2.36 [1, 3]	1.38 [0, 2]	2.68 [1, 4]	1.51 [0, 2]	+.32	+.13	*	*
	Number of times rejected for credit card	1.11 [0, 1]	1.60 [0, 2]	.83 [0, 1]	2.13 [0, 2]	−.28	+.53	*	*
	Number of times credit card cancelled by issuer	.26 [0, 0]	.29 [0, 0]	.25 [0, 0]	.31 [0, 0]	−.01	+.01		
	Ever moved back home after first leaving	23%	29%	28%	30%	+6%	+1%		
	How many times moved back home after first leaving	.27 [0, 0]	.38 [0, 1]	.36 [0, 1]	.43 [0, 1]	+.09	+.04		
	Has debt	38%	41%	41%	39%	+3%	−3%		
	Money in debt	$ 1842 [0, 3513]	$ 1889 [0, 3477]	$ 2299 [0, 3400]	$ 2163 [0, 3277]	+458	+274		
	Ever received emergency funds from parents	31%	38%	35%	37%	+4%	−0%		
	Number of times in past year received emergency funds from parents	.47 [0, 0]	.68 [0, 1]	.40 [0, 0]	.71 [0, 1]	−.06	+.03		
	Money in emergency funds received in past year from parents	$ 270 [0, 0]	$ 518 [0, 201]	$ 414 [0, 0]	$ 506 [0, 0]	+144	−13		
	Owns a home	38%	33%	42%	22%	+4%	−11%	*	*
Parent	Living with parents/family	28%	35%	9%	30%	−18%	−5%	*	*
	Regularly receives money from parents/family	13%	20%	8%	23%	−5%	+2%	*	
	Ever received emergency funds from parents	46%	55%	37%	56%	−9%	+1%	*	
	Number of times in past year received emergency funds from parents	1.06 [0, 2]	1.54 [0, 2]	.95 [0, 1]	2.11 [0, 3]	−.10	+.56	*	*
	Money in emergency funds received in past year from parents	$ 427 [0, 348]	$ 590 [0, 376]	$1,169 [0, 210]	$1,259 [0, 568]	+742	+668		
	Parent ever cosigned loan	11%	8%	7%	9%	−4%	+0%		
	Other adult provides financial assistance	13%	20%	7%	21%	−6%	+1%	*	
	Ever moved back home after first leaving	21%	33%	27%	41%	+6%	+8%	*	
	How many times moved back home after first leaving	.24 [0, 0]	.49 [0, 1]	.37 [0, 1]	.80 [0, 1]	+.13	+.31	*	*

Note. Values in "Descriptive statistics" section are either percentage of sample responding "yes" to criterion or mean [25th percentile, 75th percentile]. Rightmost two columns indicate statistical significance of (a) the difference between ADHD and control groups at age 30 and (b) of the difference-in-differences from age 25 to 30 ($\alpha = .05$, all tests two-sided). Coefficients and confidence intervals corresponding to the statistical tests in the rightmost columns are reported in Table S6. $N = 604$ throughout.
[a] Significant per logistic regression but not per linear probability model (see online supplemental material for discussion).
* $p < .05$.

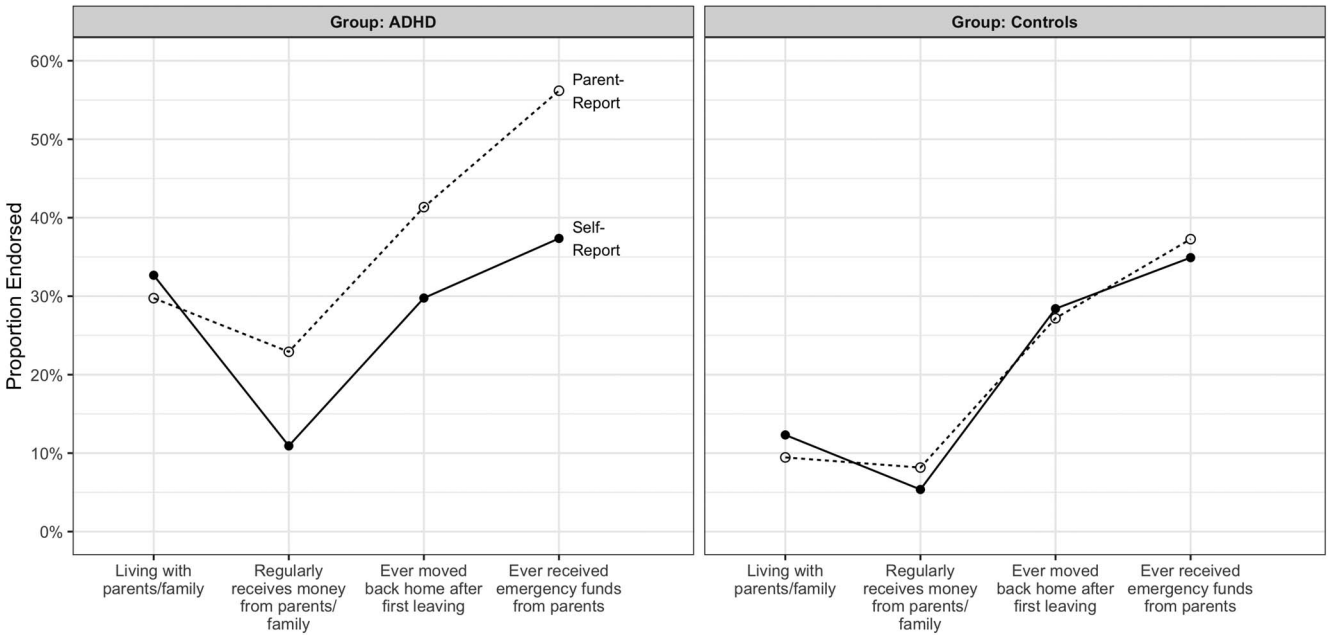

Figure 1. Self-report and parent-report were discrepant for probands but not controls. Four binary financial status indicators were reported by both participants and their parents. On more subjective indicators (cf. living with parents), adults with a history of childhood ADHD (left panel) provide more positive report than do their parents. No such gap is observed for control adults (right panel). ADHD = attention deficit hyperactivity disorder.

increased from 38% to 42%, the proportion of probands owning a home had *decreased* from 33% to 22%. By parent report, probands had exhibited a significantly smaller reduction than controls in the proportion living with parents/family and a significantly greater increase than controls in the number of times they moved back in with parents after first moving out. Probands had also increased the number of times they received emergency funds from parents in the past year, while the controls exhibited a slight decrease.

Analysis 3: Proband/Control Differences in Projected Lifetime Income

Projections based on education and employment status at age 30 (Method A) suggested that males in the control group would earn $1.10 million more than those in the ADHD group over their lifetime ($2.26 million vs. $3.36 million), or 49% more. Examining trajectory from age 25 to age 30, whereas the controls captured most (80%) of the increase in income expected based on their education and employment, the probands captured only half (49%) of the expected increase, displaying flatter income growth than expected (see Figure 3). After rescaling each group's projected earnings trajectory accordingly (Method B), the overall deficit associated with ADHD grew to $1.25 million. Controls ($3.06 million) were expected to earn 70% more than ADHD adults ($1.80 million) over their lifetime. Figure 4 shows the projected mean income for the ADHD and control groups across the life span.

Analysis 4: Proband/Control Differences in Projected Net Worth at Retirement

Projections based on the Census' SIPP data (Method A) suggested that male probands would reach retirement age with a mean net worth 35% lower than that of controls ($410,000 vs. $630,000), reflecting a deficit of $220,000. Estimates based on the projected lifetime income (Method B) accounted for group differences in employment patterns and growth in income but required further assumptions. Group differences in projected net worth at retirement varied greatly as a function of the assumed savings rates and return on investment, ranging from $70,000 to $1.45 million. Assuming savings rates of 5% in both groups and an annual return on investment of 7%, the ADHD group was projected to have 40% lower net worth at retirement (deficit of $270,000). When the savings rate was assumed to be lower in the ADHD group (i.e., 3% in ADHD group vs. 5% in control group), the ADHD group was projected to have 64% lower net worth (deficit of $431,000). Results under other combinations of assumptions are shown in Table S5 and Figure S2.

Discussion

We used a prospective, longitudinal, case-control design to compare the early trajectories of financial functioning in (a) persons diagnosed with ADHD during childhood and (b) demographically matched controls with no history of ADHD. At age 30, adults with a history of childhood ADHD showed deficits across almost all financial indicators, including income, savings, employment status, and dependence on parents and other adults. Substantial and pervasive deficits were apparent even when probands no longer met *DSM* symptom criteria for ADHD (or exhibited no *DSM* symptoms whatsoever). Moreover, the magnitude of several key ADHD-related deficits had increased from age 25 to age 30. While the control group increased income and savings, moved out from parents' homes, and transitioned to supporting themselves independently, the ADHD group achieved only small increases in

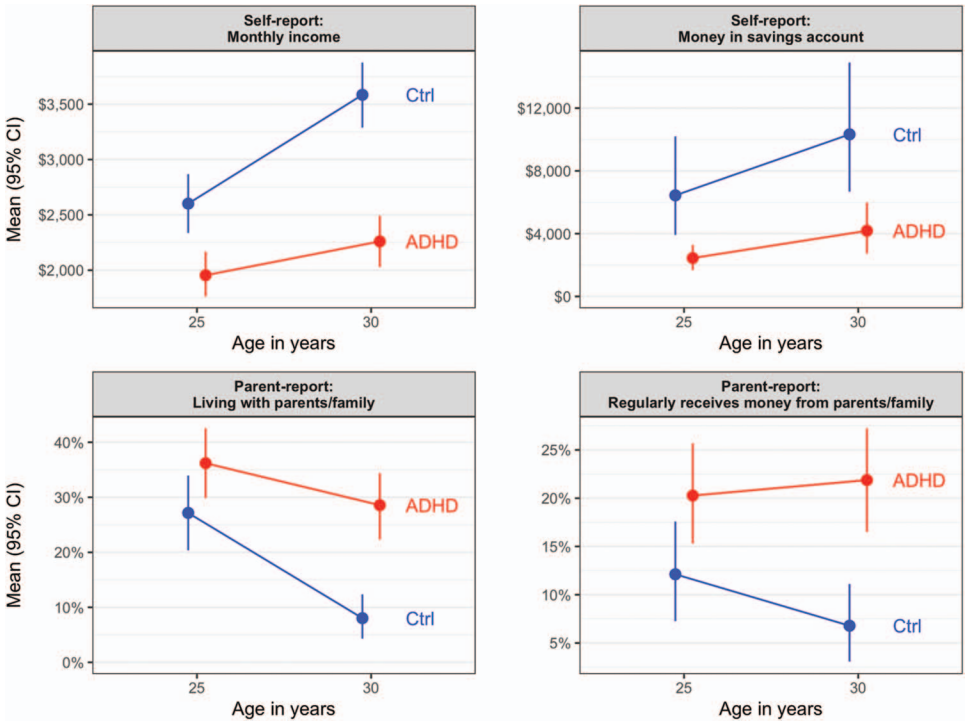

Figure 2. Probands and controls diverged between age 25 and age 30. Confidence intervals of 95% about the means were constructed using nonparametric bootstrap resampling (5,000 resamples). Dollar amounts in 2018 USD. Based on available data for each group at each age. ADHD = attention deficit hyperactivity disorder. See the online article for the color version of this figure.

earnings and savings and sustained their financial dependence on parents, family, and other adults. Projections of lifetime income suggest that males with childhood ADHD were expected to earn $1.25 million less than controls over the duration of their working life, reaching retirement with 40–75% lower net worth. Taken together, results suggest a poor financial prognosis for the clinic-referred children with ADHD that were followed in this study.

Modal Outcome of Probands at Age 30 Was Financial Dependence on Others

The financial status of the ADHD group at age 30 significantly lagged that of the control group at age 25 (see Table 1). Even with five additional years of opportunity for occupational development, the adults with a history of childhood ADHD were still reporting lower monthly income, less money in savings, and higher rates of unemployment, living at home, and regularly receiving financial support from others. Combining across informants, two thirds of the probands exhibited some form of financial dependence at age 30 (cf. 30% of controls). Half were unemployed and/or living with parents (cf. 25%). Nearly half were regularly receiving money from parents, other adults, and/or the government (cf. 20%). Moreover, these statistics may obscure reliance on sources not included in our questionnaire (e.g., spouses, siblings). For example, considering only those in the ADHD group that remained single at age 30, 76% were living with parents and/or regularly receiving money from others.

Probands' reliance on their parents for housing and income at age 30 may be particularly damaging because parents are nearing retirement age and, thus, have fewer resources of their own to share. Continued care is a common burden for parents of children with autism and other developmental disabilities, with findings indicating adverse impact on the physical health, mental health, and finances of parents as these children enter adulthood but remain dependent (Fujiura, 2010; Lunsky, Tint, Robinson, Gordeyko, & Ouellette-Kuntz, 2014; Seltzer, Floyd, Song, Greenberg, & Hong, 2011). Our results suggest that children with ADHD may be on dependence trajectories like those of children routinely viewed as having more serious "childhood" developmental disabilities.

Findings should not be mistaken as indicating that *all* children with ADHD have poor financial outcomes. While somewhat arbitrary, suppose that we define a "good enough" financial outcome at age 30 as (a) being employed full-time, (b) having more than $400 in savings (i.e., enough to handle an emergency expense; Federal Reserve Board, 2018), and (c) not being reliant on parents, family, other adults, or welfare programs for regular financial support. At age 30, 15% of probands met these criteria for a "good enough" financial outcome (cf. 45% of controls).

Large Financial Deficits Even When *DSM* Symptoms of ADHD Have Desisted

Unfortunately, even probands who no longer met *DSM* symptom criteria for ADHD at age 30 still exhibited substantial and pervasive financial deficits relative to controls (Table S3). In other words, *remission of DSM symptoms did not imply remission of impairment*. Even completely desistant probands still reported significantly lower

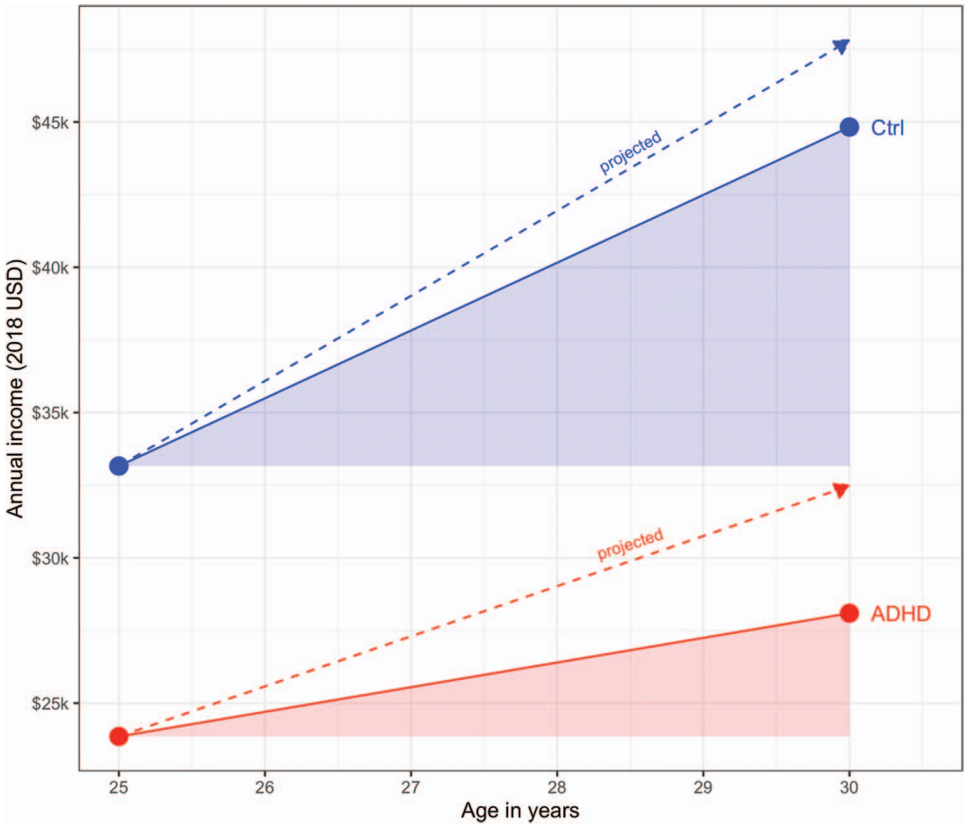

Figure 3. Male probands captured only half of projected increase in income from age 25 to age 30. Solid lines indicate actual growth in income observed in Pittsburgh ADHD Longitudinal Study (PALS) data, and dotted lines indicate projected growth in income based on census data. Male probands increased their income from age 25 to age 30 substantially less than expected, capturing only 49% of anticipated gains in income (i.e., only the shaded part of triangle beneath dotted red line). In contrast, male controls captured most of anticipated gains in income (i.e., the shaded part of triangle beneath dotted blue line). Census projections are based on employment status and education of participants at age 25. Performance relative to census projections must be interpreted with geographical and secular effects in mind (i.e., participants were seeking work in the Western Pennsylvania economy, and the mean age of participants at start of Great Recession was 25.3; see online supplemental material for further discussion). See the online article for the color version of this figure.

income than controls ($2,704 vs. $3,530), had fewer credit cards (2.7 vs. 5.2), and were more likely to be living with parents (25% vs. 9%) and receiving financial assistance from other adults (19% vs. 7%). While these individuals no longer exhibited any *DSM* symptoms of ADHD (by self- and parent- report), their poor financial outcomes relative to controls make it difficult to argue they were no longer experiencing the condition (Patterson, 1993). Rather, the *DSM* symptoms originally written to identify ADHD in childhood (American Psychiatric Association, 1980; Conners, 1969) may fail to capture the nature of ADHD-related deficits in adulthood. Our data show that clinicians should expect residual impairment in a critical area of life functioning (i.e., personal finances) even when adults with a history of ADHD and their parents endorse no current *DSM* symptoms of ADHD whatsoever (Merrill et al., 2019).

Gap Between Probands and Controls Grows Over Time

Comparison of the age 25 and age 30 data shows that the gap between the ADHD and control groups is growing as the participants become older. Adults with a history of ADHD displayed flatter growth than controls in earnings and savings and sustained (rather than decreased) financial dependence on parents and others (see Figure 2). By age 30, adults with a history of ADHD were already earning 37% less than controls, a reduction similar to that associated with serious mental illness (42%; Kessler et al., 2008) and exceeding those associated with early onset chronic depression (12–18%; Berndt et al., 2000) or post-traumatic stress disorder (16%; Savoca & Rosenheck, 2000). Projections using the matched census data (Figure 4, Method B) suggest that the ADHD-control gap will widen to an eventual 45% reduction in income at age 50.

We estimated that the probands will reach retirement with a mean net worth 40% lower than that of controls, even when accounting only for differences in education accrued by age 30. Yet adults with a history of childhood ADHD save a smaller percentage of their salary (3% vs. 11%; Barkley et al., 2008) and are less likely to be saving for retirement (29% vs. 55%; Barkley et al., 2008). Estimates accounting for differences in savings and employment patterns suggested the reduction in net worth at

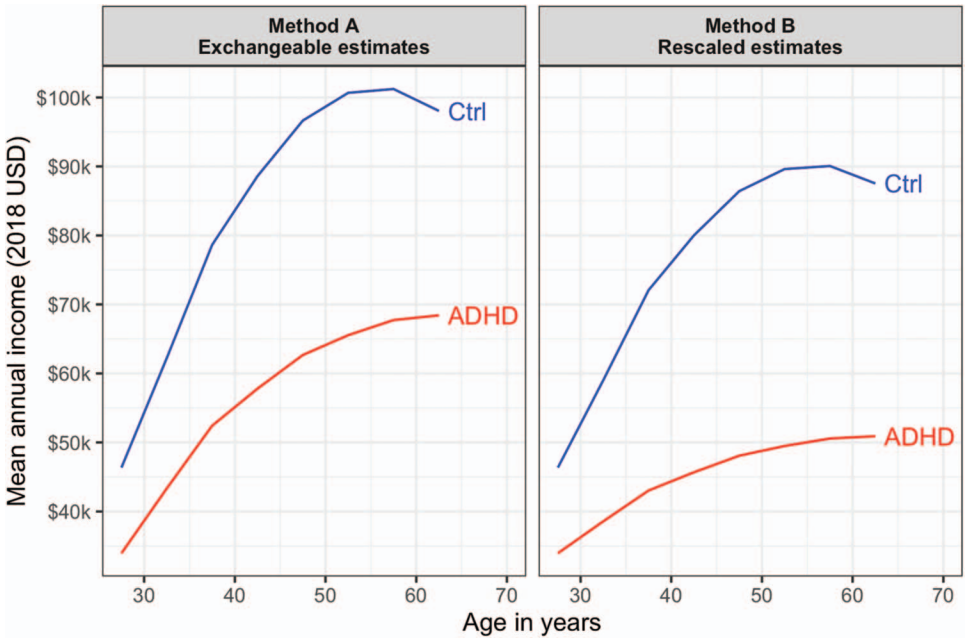

Figure 4. Projected income of control and proband males across life span. Based on individuals in census data matched to ADHD and control groups on employment status and education at age 30. Left panel (Method A) shows estimates treating ADHD and control adults as exchangeable, conditional on education and employment. Right panel (Method B) shows estimates that rescale projections based on the observed degree to which ADHD and control groups tracked their census projections between ages 25 and 30. Curves in right panel are lower than curves in right panel since both groups underperformed census projections between ages 25 and 30 (see Figure 3). ADHD = attention deficit hyperactivity disorder. See the online article for the color version of this figure.

retirement is arguably closer to 64% and quite plausibly as high as 75%. The combination of reduced earning potential and impulsive, present-focused financial decision-making (Barkley et al., 2008) seems likely to produce a high rate of financial difficulties and reliance on others when those with childhood ADHD reach retirement age.

Assuming a prevalence rate of 8.4% (Danielson et al., 2018), our data suggest that the adult sequela of childhood ADHD is associated with $301 billion in annual lost income in the United States (see online supplemental material for back-of-the-envelope calculations). Nonetheless, analyses have likely underestimated the magnitude of the economic deficit associated with childhood ADHD. First, ADHD conveys a substantial positive bias in self-evaluation (Hoza et al., 2002; J. S. Owens et al., 2007; Sibley et al., 2012), and this bias was indeed present in report of financial dependence (see Figure 1). Thus, on financial outcomes for which we did *not* obtain parent report (e.g., income, savings), we likely underestimated the ADHD-related deficit. Second, existing literature suggests that ADHD adults are more likely than controls to quit or lose their jobs and hold jobs for a shorter duration of time (Barkley et al., 2006; Hechtman et al., 2016; Kuriyan et al., 2013). Since our income projections assumed that employment status was constant beyond age 30, they likely underestimated the ADHD-related deficit.

Clinical Implications

Taken together, results suggest there is great need for interventions that can improve financial functioning as children with ADHD reach young adulthood. However, there has been very little work in this area (Gordon & Fabiano, 2019). Paradigms such as vocational training, supported employment, and counseling on personal finances (Drake, Skinner, Bond, & Goldman, 2009; Marshall et al., 2014; Wehman, Chan, Ditchman, & Kang, 2014) may be of use in developing clinical approaches that can help those with ADHD increase income and savings, improve personal finance habits, and reduce dependence on parents, other adults, and public assistance.

In addition, mediation analyses suggested that lower educational attainment may be a key mechanism driving ADHD-related deficits in long-term financial functioning. Probands were more likely to have dropped out of high school (9% vs. 1%) and less likely to have completed a bachelor's degree (14% vs. 53%), two educational milestones that are associated with significant increases in earnings (Day & Newburger, 2002). Thus, educational supports and interventions that can help those with ADHD attain these milestones may be an important means of improving long-term financial outcomes (Evans, Langberg, Egan, & Molitor, 2014; Sibley, Kuriyan, Evans, Waxmonsky, & Smith, 2014). Unfortunately, educational supports for children with ADHD tend to decrease in intensity as they grow older, even as dropout is becoming a more salient possibility (e.g., Wagner, Marder, & Blackorby, 2002).

Strengths and Limitations

This is the first prospective study of the financial outcomes of childhood ADHD to characterize how the deficits associated with ADHD evolve over time. It is also the first study to use early

financial trajectories to project net worth at retirement. Our sample size is 2–4 times larger than all prior longitudinal studies except the MTA (Hechtman et al., 2016), our inclusion of parent report is the most extensive to date, and our mean age of follow-up is older than all but one previous study (Klein et al., 2012).

Generalizability of findings may be limited by the sample, which consisted of children with ADHD from treatment-seeking, primarily Caucasian families from a single geographic region. These limitations are endemic to the existing prospective, longitudinal studies with a large cohort of *DSM*-diagnosed children with ADHD (Barkley et al., 2006; Biederman et al., 2012; Hechtman et al., 2016; Klein et al., 2012; E. B. Owens et al., 2017). Relative to community samples, clinic-referred samples like PALS may (a) exaggerate proband-control differences if families of children with more severe ADHD are more likely to present for treatment or (b) attenuate proband-control differences due to exclusion criteria (e.g., IQ below 80). While participants were recruited from a single geographic region, the only comparable study that has included children recruited in multiple geographical regions (i.e., the Multimodal Treatment of ADHD Study) has generally failed to find that results vary by site (e.g., Molina et al., 2009). Especially reassuring is that one of these sites was at Pittsburgh, the same location of the PALS sample. Nonetheless, we emphasize that the current results are most justifiably generalized to Caucasian boys with ADHD. Generalizability is also stronger when focusing on the *relative* financial functioning of probands and controls (e.g., ratio of incomes) since participants' absolute level of financial functioning may be in part driven by economic conditions in Western Pennsylvania.

In addition, the use of a case-control design limits causal inference. While controls were recruited to match the probands in age, sex, race, and level of parent education, they could not be equated on all features. A portion of the difference in outcome between probands and controls might be caused by differences in factors besides ADHD (Rothman, Greenland, & Lash, 2008), such as psychiatric comorbidities in childhood or adulthood (e.g., SUD, CD). While it is conceptually difficult to separate the effects of related forms of psychopathology (Meehl, 1971; Miller & Chapman, 2001), we emphasize the need for caution in attributing the observed differences solely to ADHD. Similarly, mediation analyses were correlational—the apparent relation between educational attainment and financial outcomes could be driven by other factors (Valente, Pelham, Smyth, & MacKinnon, 2017).

Additional limitations stem from the measurement of financial outcomes. We did not have access to objective financial records (e.g., tax returns, credit reports, bank statements) that could overcome the positive bias of participants with self-reported ADHD, produce more accurate income and net worth projections, and reduce our dependence on modeling assumptions. More frequent data collection (e.g., several waves per year) with more granular measures (e.g., expenses separated by spending category, job application behavior among the unemployed, planfulness in money management) would shed light on the specific mechanisms contributing to probands' poor financial functioning and facilitate the design of supportive interventions (Gordon & Fabiano, 2019).

Conclusion

The financial prognosis of those diagnosed with ADHD during childhood is poor, with the modal outcome at age 30 being dependence on others. Trajectories from age 25 to age 30 indicate sustained or growing deficits relative to controls on nearly all financial measures, suggesting that as participants in the prospective cohort studies grow older, an increasingly negative picture will emerge. Just as children with ADHD may take longer than peers to reach developmental milestones such as staying seated in the classroom, adults with a history of ADHD may take longer than peers to reach financial independence. Interventions for teens and young adults should focus on the development of functional life skills (e.g., with vocational training) rather than just the reduction of *DSM* symptoms, since substantial deficits were present even for those adults whose symptoms had apparently remitted. The literature on developmental delay or serious mental illness has long regarded vocational training and support as a primary component of effective treatment of young adults (Burns et al., 2007; Campbell, Bond, & Drake, 2011; Moore & Schelling, 2015; Wehman et al., 2014). Our results suggest that ADHD should likewise be conceptualized as a chronic condition often requiring considerable, potentially lifelong support from others (e.g., family, spouses, social service agencies). Parents may benefit from being informed of this prognosis and its implications for their own financial planning (Zhao et al., 2019).

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ORIGINAL ARTICLE

Costs of attention deficit–hyperactivity disorder (ADHD) in the US: excess costs of persons with ADHD and their family members in 2000

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Key words: ADHD – Cost – Economics – Family burden – Healthcare – Work loss

ABSTRACT

Objective: The objective of this study is to provide a comprehensive estimate of the cost of ADHD by considering the healthcare and work loss costs of persons with ADHD, as well as those costs imposed on their family members.

Methods: Excess per capita healthcare (medical and prescription drug) and work loss (disability and work absence) costs of *treated* ADHD patients (ages 7 years–44 years) and their family members (under 65 years of age) were calculated using administrative claims data from a single large company; work loss costs are from disability data or imputed for medically related work loss days. Excess costs are the additional costs of patients and their family members over and above those of comparable control individuals. The excess costs of *untreated* individuals with ADHD and their family members were also estimated. All per capita costs were extrapolated using published prevalence and treatment rates and population data; the prevalence of persons with ADHD was based upon the literature.

Results: The total excess cost of ADHD in the US in 2000 was $31.6 billion. Of this total, $1.6 billion was for the ADHD treatment of patients, $12.1 billion was for all other healthcare costs of persons with ADHD, $14.2 billion was for all other healthcare costs of family members of persons with ADHD, and $3.7 billion was for the work loss cost of adults with ADHD and adult family members of persons with ADHD.

Conclusion: The annual cost of ADHD in the US is substantial. Both treated and untreated persons with ADHD, as well as their family members, impose considerable economic burdens on the healthcare system as a result of this condition. While these first estimates of the cost of ADHD to the nation are suggestive of its substantial economic burden, future research needs to refine and build on this analysis, particularly in the context of a model to control for related co-morbidities. Similarly, since these results are based on data from a single company for the period 1996–1998, the analysis should be validated with more representative, current data.

Introduction

There is considerable epidemiological research regarding the prevalence and correlates of attention deficit–hyperactivity disorder (ADHD)[1–4]. Research on the cost of ADHD is more limited, particularly regarding the cost of adults with ADHD and the burden imposed on the family members of persons with ADHD.

ADHD is a childhood-onset condition requiring at least some symptoms to be present by age 7 years[2,5,6]. Published prevalence estimates of ADHD among children range between 3% and 5% based on the *Diagnostic and Statistical Manual of Mental Disorders* criteria, though estimates based on less restrictive criteria are as high as 16%[1–3,5,7,8]. Among children, boys are more likely than girls to have ADHD[2,4,9]. Few epidemiological studies of adult prevalence are available. Instead, most adult ADHD studies estimate that the persistence of ADHD from childhood to adulthood ranges between 30% and 70% of cases[10–14]. Published adult ADHD prevalence rates, often derived from these persistence estimates, range between 1% and 7%[2,11,13,15,16].

The symptoms of ADHD (e.g., distractibility, impulsivity, hyperactivity) can interfere with a person's ability to conduct normal daily activities at work, school, and home[2,7,10,17]. In addition, a number of health outcomes are more common among persons with ADHD. For example, accidents (e.g., automobile collisions, poisoning, and fractures) are more likely among children and adults with ADHD[18–23]. A substantial share of persons with ADHD also have mental health conditions such as oppositional defiant disorder, conduct disorder, anxiety disorder, and/or depression[1,2,4,10,16,24–28]. Furthermore, as children with ADHD age into adolescence and adulthood they are more likely to exhibit delinquent behavior or symptoms of antisocial personality disorder[2,10]. Not surprisingly, persons with ADHD utilize a greater than average share of healthcare, mental health, social, and special education services[4,29–31].

ADHD can also affect the health and work outcomes of family members. Increased rates of conduct, mood, and anxiety disorders have been documented among family members of persons with ADHD[32,33]. These tendencies and any incremental work loss experienced by these individuals are likely attributable, in part, to the burden of living with a person who has ADHD. Such outcomes would be consistent with published literature regarding the family burden of other mental health conditions[34–36]. It is also likely that at least some of the familial aggregation of psychological disorders associated with ADHD is due to the fact that ADHD is a marker of genetic risk for psychopathology among family members[37].

Several studies describe the medical care and prescription drug utilization patterns of those with ADHD. Most of the studies that depict the economic burden of ADHD consider the *per capita* medical costs of children treated for ADHD, while few studies have estimated the cost of adult ADHD[31,38–43]. Several studies extrapolate costs to the nation. For example, research by Chan *et al.*, using the Medical Expenditure Panel Survey, concluded that the excess medical expenditures for ADHD children were approximately $1 billion in 1996[40]. Marchetti *et al.* used a decision analysis model to estimate the total annual per patient cost of children with ADHD[42]. Extrapolated to the national level, their research suggested that the total expected cost of treating children with ADHD in the US ranged from $2 billion to $11 billion in 2001. However, neither study considered the cost of adults with ADHD or the burden on caregivers and other family members. Likewise, neither study considered the workplace burden of ADHD.

Patient level research by Swensen *et al.* estimated both the excess healthcare costs of treated ADHD children and their family members as well as the ADHD related work loss costs of adult family members of children with ADHD[41]. Building upon the Swensen approach and other similar claims data research designs[44,45], we present a more comprehensive estimate of the total excess cost of ADHD in the US in 2000. Specifically, we estimated the per capita healthcare costs of persons between the ages of 7 years and 44 years with ADHD (i.e., both children and adults), as well as the associated healthcare costs for their family members under the age of 65 years. We also estimated the work loss cost of ADHD adults and adult family members of persons with ADHD.

Methods

The prevalence based, human capital approach used here to profile the costs of ADHD in the US has been used in numerous cost of illness studies[46–49]. In this study, the human capital approach measured the value of work loss in terms of an employee's salary. This approach integrated data from a number of sources noted below. Per capita direct costs were based on administrative health insurance claims; per capita indirect work loss costs were based on disability and imputed medically related missed days from work, based on employee disability claims. In order to extrapolate to the national level, the per capita direct and indirect costs were multiplied by the appropriate prevalence rate and population figures, using population statistics from the US Census[50,51], and prevalence and treatment rate data published in the literature for treated and untreated ADHD[1–5,7–16,52–54]. The excess cost estimates were generated using the same administrative claims data and a similar case-control methodology as that of the Swensen study, which also provides descriptive statistics on the sample demographics[41]. All estimates were measured as excess costs, calculated as the difference between the costs of

those affected by ADHD and matched controls. Data sources and definitions of key measures are provided below and are summarized in Table 1.

Cost data

Cost estimates were based on administrative claims data collected between 1996 and 1998 for a national Fortune 100 company (total population, including non-claimants, ~300 000). The data include all medical and prescription drug claims for each beneficiary, as well as disability claims made by company employees. Beneficiaries were in managed fee-for-service (non-capitated) plans.

ADHD sample and matched controls

Using a case-control methodology, from among the ~300 000 claimant population, we identified 1219 diagnosed (i.e., 'treated') ADHD patients between the ages of 7 years and 44 years with at least one medical claim for ADHD (i.e., an *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis code of 314.0x) in the period 1996–1998. Patients were limited to those between the ages of 7 years and 44 years to correspond to available prevalence and treatment rate data. Matched controls were identified as those of the same age, gender, employment status, and geographical location who did not have a claim for ADHD.

ADHD family members and matched controls

Family members were identified in the eligibility file of each ADHD patient. For each ADHD family member, we also identified a matched control (i.e., person of the same age, gender, employment status, and geographical location who did not have an ADHD claim or a family member with an ADHD claim). This process insured we did not double-count persons.

Per capita healthcare and work loss costs

Cost data for ADHD patients, family members, and matched controls are from the most recent year for which data were available, 1998. Healthcare costs were calculated based on payments from medical and prescription drug claims. These costs were calculated in two parts: ADHD treatment costs, defined as either a medical claim for ADHD or a claim for a prescription drug used to treat ADHD, and all other healthcare costs. Similarly, we calculated indirect work loss costs as employer payments for disability and imputed medically-related work absence time based upon a widely used approach[55]. Work absence costs were based on the employer payments for disability claims and imputed wages for medically related work absence days (e.g., days in the hospital, physician visits).

Excess costs

The difference between the per capita cost of ADHD patients (and similarly, of family members) and their controls was defined as the excess cost of ADHD. Excess costs were measured separately for ADHD treatment and all other healthcare services; and also for work loss costs. By definition, the entire cost of ADHD treatment (identified by claims with ADHD diagnoses or stimulant drugs) was considered excess.

Table 1. *Key statistics used to extrapolate per capita estimates to the national population*

	Prevalence rates	Treatment rates	Population
Male children (age 7–18)	8.1%	73%	25 238 027
Female children (age 7–18)	4.0%	66%	23 946 777
Male adults (age 19–44)	5.2%	24%	54 363 303
Female adults (age 19–44)	3.4%	28%	53 768 804
Number of other children per family of a person with ADHD			1.5
Number of other adults per family of a person with ADHD			1.5
1998 US average female health expenditures/research sample average female health expenditure			114%
1998 US average male health expenditures/research sample average male health expenditure			115%
1997 US average weekly wage/1996–1998 research sample average weekly wage			76%
Male adult employment rate (ages 18 years–44 years)			85%
Female adult employment rate (ages 18 years–44 years)			72%
Overall adult employment rate (ages 18 years–44 years)			78%
Medical inflation rate, 1998–2000			1.08
Wage inflation rate, 1998–2000			1.07

Costs of persons with treated vs. untreated ADHD

Administrative claims data provide an estimate of per capita costs of *treated* ADHD patients and their family members. We estimated the costs of people with *untreated* ADHD and their family members based upon assumption. By definition, untreated individuals do not incur ADHD treatment costs. We assumed that persons with untreated ADHD experienced the same excess healthcare costs for other conditions and the same excess work loss costs as did those who were treated for ADHD. Similarly, we assumed that the family members of those untreated for ADHD experienced the same excess healthcare and work loss costs as did the family members of those treated for ADHD. We recognize that persons with untreated ADHD and their family members may have higher costs than the treated group due to the impact of treatment for undiagnosed ADHD. Alternatively, they may have lower excess healthcare costs than the treated group because they experience milder, less burdensome cases of ADHD that result in less medical utilization. Consequently, we conducted sensitivity analyses to evaluate the impact of our equivalence assumption.

Statistical tests

To account for variation in the excess cost and prevalence rates of ADHD across demographic groups, we calculated per capita costs by age group (i.e., for children from 7 years to 18 years and adults from 19 years to 44 years) and by gender. We performed statistical *t*-tests on the resulting cost differences (between the relevant ADHD and demographic comparison group) to determine which were not statistically significant. For female adults, work loss estimates based on the claims data analysis were statistically insignificant (as reported in Table 2). For this parameter, we relied on findings of Kessler *et al.*, and imputed female per capita work loss costs equivalent to males[43].

Standardized costs

Since we relied on the administrative claims data of a single, albeit large, national employer, we made adjustments to standardize to national healthcare cost averages by increasing the costs by 14% for females and 15% for males[56,57]. The adjustment was based on the ratio of the costs from the research sample to US per capita health care costs. Similarly, work loss costs were adjusted downward by 24% to reflect the average US wage rate[58]. The sensitivity of this normalization process was tested and results are presented below. Moreover, all cost data were inflated to 2000 dollars using the medical consumer price index and the growth rate of weekly earnings from the US Census Bureau[57,59].

Prevalence rates

Published estimates of the prevalence of ADHD among children aged 7 years–18 years range from 3% to 16%, with boys more likely to suffer from ADHD than girls. Based on this literature, we selected a set of prevalence rates for use in our analysis that was confirmed by the implied prevalence rates from our administrative claims dataset: 8% for boys and approximately half that for girls. A study by Rowland *et al.*, consistent with the other published literature, found that the treatment rate of ADHD was 73% for boys and 66% for girls[60].

Adult ADHD prevalence rate data come from Kessler's recent National Co-morbidity Survey Replication (NCS-R) epidemiologic survey[16,43]. Data from the NCS-R on patterns of adult ADHD show a 4.4% prevalence rate in the adult general US population. These data are consistent with the literature and with our claims data. We used prevalence rates of 3% for females and 5% for males, ages 19 years–44 years. Adult treatment rates used were 24% and 28% for men and women, respectively.

National projections

To extrapolate costs, we used population statistics for 2000 from the US Census Bureau[50,51]. Estimates of average family composition were also obtained from the Census. Employment rates from the Bureau of Labor Statistics were used to extrapolate the excess work loss costs of adults[61].

Results

Table 2 presents excess annual per capita ADHD treatment, other healthcare, and work loss costs by demographic groups. It shows that the cost differences between ADHD and control patients in all three categories are statistically significant across most demographic groups. Similarly, excess per capita costs among family members of ADHD patients are statistically significant. Additional data on cost drivers by type of service from a similar analysis are presented elsewhere[41].

Figure 1 illustrates the progressive summation of the excess costs associated with ADHD in the US in 2000 for persons with ADHD (aged 7 years–44 years) and their family members (under 65 years of age). First, we estimated that the cost of ADHD treatment was $1.6 billion. In addition, we estimated the excess cost of other healthcare treatment incurred by people with ADHD

Table 2. *Per capita excess costs of ADHD**

	ADHD treatment costs‡			
	Mean¶,§	*t*-test	dfs**	*p*-value
Children†				
Female ADHD patients (*N* = 268)	$507.47	8.27	528	< 0.0001
Male ADHD patients (*N* = 780)	$560.31	17.54	1542	< 0.0001
Family members of ADHD children (*N* = 1015)	N/A	N/A	N/A	N/A
Family members of ADHD adults (*N* = 147)	N/A	N/A	N/A	N/A
Adults†				
Female ADHD patients (*N* = 49)	$310.09	5.56	94	< 0.0001
Male ADHD patients (*N* = 122)	$398.43	8.18	238	< 0.0001
Family members of ADHD children (*N* = 2243)	N/A	N/A	N/A	N/A
Family members of ADHD adults (*N* = 287)	N/A	N/A	N/A	N/A
	All other healthcare costs‡			
	Mean¶,§	*t*-test	dfs**	*p*-value
Children†				
Female ADHD patients (*N* = 268)	$650.19	3.81	522	0.0002
Male ADHD patients (*N* = 780)	$743.83	7.20	1526	< 0.0001
Family members of ADHD children (*N* = 1,015)	$137.94	2.40	2328	0.0165
Family members of ADHD adults (*N* = 147)	$466.44	3.45	317	0.0006
Adults†				
Female ADHD patients (*N* = 49)	$1962.24	3.44	92	0.0009
Male ADHD patients (*N* = 122)	$2272.21	4.07	234	< 0.0001
Family members of ADHD children (*N* = 2243)	$999.25	8.03	4581	< 0.0001
Family members of ADHD adults (*N* = 287)	$829.07	2.77	570	0.0058
	Work loss costs‡			
	Mean¶,§	*t*-test	dfs**	*p*-value
Children†				
Female ADHD patients (*N* = 268)	N/A	N/A	N/A	N/A
Male ADHD patients (*N* = 780)	N/A	N/A	N/A	N/A
Family members of ADHD children (*N* = 1015)	N/A	N/A	N/A	N/A
Family members of ADHD adults (*N* = 147)	N/A	N/A	N/A	N/A
Adults†				
Female ADHD patients (*N* = 49)	N/S	(0.73)	92	N/S
Male ADHD patients (*N* = 122)	$690.08	2.66	234	0.0084
Family members of ADHD children (*N* = 2243)	$112.30	2.89	4581	0.0039
Family members of ADHD adults (*N* = 287)	$137.89	2.19	570	0.0289

*N/A indicates a cost category not applicable to the cohort. N/S indicates a value that was not statistically significant

†Persons with ADHD include children aged 7–18 years and adults aged 19–44 years. Family members include children aged 0–18 years and adults aged 19–64 years

‡Healthcare costs include medical and prescription drug costs. Workplace costs include the cost of time on disability and medically-related work absences

¶Means are adjusted for differences in average healthcare costs nationwide and those of healthcare beneficiaries in the employer claims dataset and inflated to 2000 US dollars

§Statistical significance calculated from unadjusted means

**dfs is degrees of freedom

($12.1 billion). Next, we included the excess healthcare costs of family members of those with ADHD ($14.2 billion). Finally, the work loss costs of adults with ADHD and adult family members was $3.7 billion. Combining these costs, our broadest (i.e., upper bound) estimate of the cost of ADHD was $31.6 billion.

Of the total $31.6 billion associated with ADHD, approximately half was attributable to persons with ADHD and half to their family members (see Table 3). Adults accounted for 77% of the total ADHD cost while children represented 23%. Among adults, persons with ADHD accounted for $12.9 billion (53%) of the $24.4 billion in costs while family members (aged 19 years–64 years) accounted for the remaining $11.4 billion (47%). Among children, family members (aged 18 years and under) of ADHD adults accounted for the largest share (45%) of the $7.2 billion in total costs of ADHD.

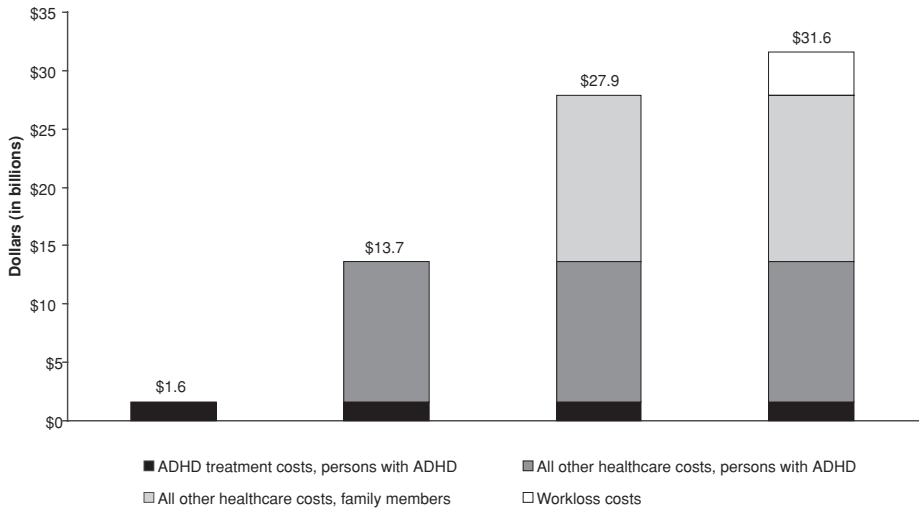

Figure 1. *Excess costs associated with ADHD in the US in 2000. Dollars in billions. Work loss costs are calculated for adults with ADHD (aged 18–44 years) and adult family members of persons with ADHD (aged 18–64 years) only*

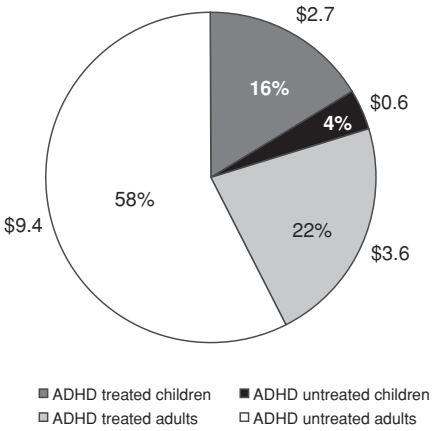

Figure 2. *Excess costs of persons with ADHD in the US in 2000. Total costs $16.3 billion. ADHD children include persons aged 7–18 years; ADHD adults include persons aged 19–44 years*

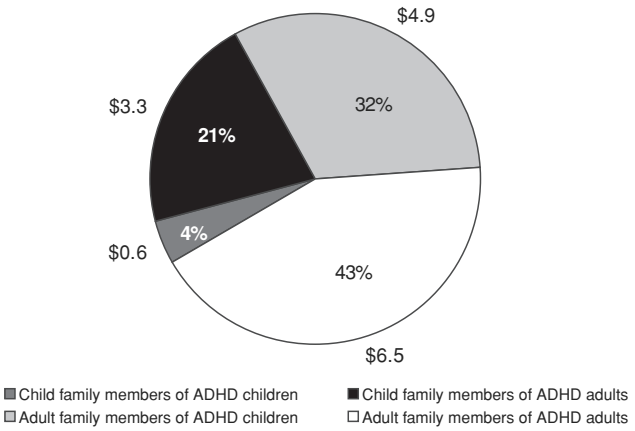

Figure 3. *Excess costs of family members of persons with ADHD in the US in 2000. Total costs $15.3 billion. Child family members include persons aged 0–18 years; adult family members include persons aged 19–64 years*

Figure 2 displays the composition of the costs incurred by persons with ADHD (i.e., excluding their family members), with attention to both treated and untreated children and adults. Of the total $16.3 billion, $3.3 billion (20%) was attributable to children with ADHD and $13.0 billion (80%) to adults with ADHD. Costs for adults with ADHD were greater in part due to their work loss costs.

Family members incurred a total excess cost burden of $15.3 billion (see Figure 3). Adult family members of ADHD children (parents or caregivers) accounted for 32% of the total costs associated with family members while child family members of ADHD children (siblings) accounted for 4%. The remaining 64% was attributable to the family members of ADHD adults, 21% from child family members (children) and 43% from adult family members (spouses or partners).

Sensitivity analyses

Several of the input variables and assumptions were key drivers of the estimated costs associated with ADHD, particularly as the study is based only on a single large company. To determine the extent to which these assumptions and variables influenced our estimates, we performed a variety of sensitivity analyses.

Table 3. *Excess costs of ADHD in the US in 2000*

	ADHD treatment costs		All other healthcare costs		Work loss costs		Total costs	
	Billions of dollars	Percentage of total	Billions of dollars	Percentage of total	Billions of dollars	Percentage of total	Billions of dollars	Percentage of total
Children*								
ADHD females	$0.4	32%	$0.6	10%	N/A	N/A	$1.0	14%
ADHD males	$0.8	68%	$1.5	25%	N/A	N/A	$2.3	32%
Family members of ADHD children	N/A	N/A	$0.6	10%	N/A	N/A	$0.6	9%
Family members of ADHD adults	N/A	N/A	$3.3	54%	N/A	N/A	$3.3	45%
Total	$1.2	100%	$6.0	100%	N/A	N/A	$7.2	100%
Adults*								
ADHD females	$0.1	27%	$3.6	18%	$0.9	25%	$4.6	19%
ADHD males	$0.3	73%	$6.4	32%	$1.7	45%	$8.4	34%
Family members of ADHD children	N/A	N/A	$4.5	22%	$0.4	11%	$4.9	20%
Family members of ADHD adults	N/A	N/A	$5.8	29%	$0.7	19%	$6.5	27%
Total	$0.4	100%	$20.3	100%	$3.7	100%	$24.4	100%
ADHD females	$0.5	30%	$4.2	16%	$0.9	25%	$5.6	18%
ADHD males	$1.1	70%	$7.9	30%	$1.7	45%	$10.7	34%
Family members of ADHD children	N/A	N/A	$5.1	19%	$0.4	11%	$5.5	17%
Family members of ADHD adults	N/A	N/A	$9.1	35%	$0.7	19%	$9.8	31%
Total	$1.6	100%	$26.3	100%	$3.7	100%	$31.6	100%

*Persons with ADHD include children aged 7–18 years and adults aged 19–44 years. Family members include children aged 0–18 years and adults aged 19–64 years

The administrative claims file used to estimate direct per capita costs represents a large employer (~300 000 lives). However, we considered the possibility that our per capita direct cost estimates could range ± 10%. A 10% increase in per capita direct costs resulted in a total cost of ADHD of $34.6 billion. A 10% decline in per capita direct costs resulted in a total cost of ADHD of $28.3 billion.

As reported, the literature provides a range of prevalence and treatment rates for ADHD. Note that since the prevalence data are based on the literature, the use of company specific data does not affect this aspect of the research. We performed sensitivity analyses to determine to what extent our results would change upon variation of these rates. A 10% increase in the prevalence and treatment rates (for both children and adults) resulted in a total cost of ADHD of $34.8 billion, while a 10% decrease generated a total cost of $28.5 billion.

Another assumption in the model was that untreated individuals with ADHD experience excess healthcare costs and work loss costs of equal value to the excess costs of treated ADHD patients (excluding ADHD treatment costs). As an alternative formulation to evaluate the lower bound cost estimate, we considered the possibility that the excess costs of those untreated for ADHD could be as much as 10% less than the excess costs of those treated for ADHD. The result of this simulation decreased the total cost of ADHD from $31.6 billion to $33.5 billion.

An additional assumption in the model was that the indirect costs calculated based on the administrative claims file imply an average daily wage 24% greater than the US average. While we made an adjustment to correct for this difference, we also tested the sensitivity of this assumption by allowing the indirect costs to range ± 10% around the US average. This simulation generated a range of total ADHD costs from $32.0 to $31.3 billion in 2000. Also, as noted above, we normalized the healthcare cost data to the level of average US healthcare expenditures. Had we not normalized our data in this way the total cost associated with ADHD in 2000 would have been $28.1 billion.

Discussion

ADHD is associated with significant costs for both those treated and untreated for the condition, which underscores its considerable burden in the US. Estimates here of the costs of treating children with ADHD are consistent with the literature[40,42]. The contribution of our research is to also include the healthcare costs of adults with ADHD, as well as the healthcare costs of family members, and the work loss costs associated with ADHD. Based upon this definition, the total cost associated with ADHD in the US in 2000 was estimated at $31.6 billion.

Of the total costs, persons with ADHD incurred $16.3 billion (52%). While 10% of this $16.3 billion was directly related to ADHD treatment, a substantial portion (nearly 75%) was attributable to the excess costs of treating other medical conditions. These excess costs were likely associated with the treatment of conditions more common among ADHD patients than their matched controls (e.g., anxiety disorder, depression)[41]. The result here is consistent with other administrative data analysis findings regarding the prevalence of co-morbidities among persons with ADHD, as well as the higher rates of sickness absence among employed adults with ADHD than their controls[31].

The current study estimated that 16% of the $16.3 billion cost estimate for persons with ADHD was attributable to work loss costs. However, this result likely underestimates the workplace burden of ADHD because it omits costs associated with reduced productivity[62]. Moreover, the work loss estimates reported here also are low relative to those based on analysis of self reported NCS-R data that include short-term absenteeism as well as presenteeism costs[43]. Recent research by Biederman *et al*.[63], considers lost household income, based on a telephone survey of persons who reported a diagnosis of ADHD, also suggests that our work loss estimates may be low.

Family members of persons with ADHD incurred the remaining 48% of the $31.6 billion costs associated with ADHD. In particular, adult family members experienced substantial excess healthcare and work loss costs, in part as a result of caring for a family member with ADHD. These costs were likely associated with higher than average rates of conduct, mood, and anxiety disorders among the family members of people with ADHD, as well as resultant incremental work absence. However, because persons with ADHD may have a family member with undiagnosed ADHD, some of the family costs estimated here may be more appropriately attributable to the cost of persons with ADHD.

While these first estimates of the cost of ADHD to the nation are suggestive of its substantial economic burden, future research needs to refine and build on this analysis. Selecting a sample of patients that had a *single* claim with an ADHD diagnosis is very broad, although this ICD-9 strategy is consistent with other research[64,65]. This approach may have included more patients than those with true ADHD, since some may be rule-out diagnoses; however, an opposing tendency was also present since some persons with ADHD likely were misdiagnosed with another or no

condition. A related clinical point is the uncertainty about the extent to which an aggregation of costs from non-ADHD conditions is actually related to ADHD itself, as well as uncertainty in allocating these costs to family members. These uncertainties derive from several sources, including the fact that ADHD may not itself be the cause of excess costs. Family units with widespread mental health problems may experience a host of related conditions, any of which can result in additional healthcare treatment costs. Similarly, undiagnosed ADHD may result in misallocation of costs to family members. Children or adults with ADHD may have other family members who suffer from the condition unknowingly. As a result, the excess costs of these family members are not properly attributed to ADHD. One additional reason for uncertainty is the use of claims data that inherently contain ambiguities in the coding of diagnoses, as well as the role of related co-morbidities. Future research should address these issues particularly in the context of a model to control for other related co-morbidities. Similarly, since these results are based on data from a single company for the period 1996–1998 the analysis may not be generalizable and should be validated with more representative, current data.

Additional societal burdens imposed by ADHD were not included here. For example, students with ADHD impose a burden on the school system as they may require customized lesson plans. Moreover, ADHD is also associated with a higher likelihood of delinquent behavior, adding to the costs of law enforcement and social service systems[66,67]. ADHD is also likely to negatively impact the earnings of adults with the condition. Children with ADHD may achieve less academic success and have more adjustment problems as they age when compared with other young adults[68,69]. Research regarding other mental health conditions, including those associated with ADHD, has found similar results[70].

Conclusion

Although ADHD is primarily recognized as a childhood condition, adults can continue to experience symptoms. Adults with ADHD have greater healthcare costs than children with ADHD, and as adults they incur work loss costs. To the extent that timely diagnosis and effective treatment of children with ADHD helps mitigate the severity of this condition, its economic burden will be reduced. Furthermore, as these children age, ADHD-related conditions such as driving-related accidents and alcoholism may also be reduced. These observations suggest that appropriate treatment of ADHD among children may lead to future cost savings to society. While appropriate treatment of adults could potentially reduce costs, saving from the reduction in the number of adults with ADHD also potentially makes treating children (i.e., before they become adults and incur these costs) an effective strategy.

Acknowledgment

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EXHIBIT 83

Economic Impact of Childhood and Adult Attention-Deficit/Hyperactivity Disorder in the United States

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Objective: Attention-deficit/hyperactivity disorder (ADHD) is one of the most prevalent mental disorders in children in the United States and often persists into adulthood with associated symptomatology and impairments. This article comprehensively reviews studies reporting ADHD-related incremental (excess) costs for children/adolescents and adults and presents estimates of annual national incremental costs of ADHD. **Method:** A systematic search for primary United States-based studies published from January 1, 1990 through June 30, 2011 on costs of children/adolescents and adults with ADHD and their family members was conducted. Only studies in which mean annual incremental costs per individual with ADHD above non-ADHD controls were reported or could be derived were included. Per-person incremental costs were adjusted to 2010 U.S. dollars and converted to annual national incremental costs of ADHD based on 2010 U.S. Census population estimates, ADHD prevalence rates, number of household members, and employment rates by age group. **Results:** Nineteen studies met the inclusion criteria. Overall national annual incremental costs of ADHD ranged from $143 to $266 billion (B). Most of these costs were incurred by adults ($105B–$194B) compared with children/adolescents ($38B–$72B). For adults, the largest cost category was productivity and income losses ($87B–$138B). For children, the largest cost categories were health care ($21B–$44B) and education ($15B–$25B). Spillover costs borne by the family members of individuals with ADHD were also substantial ($33B–$43B). **Conclusion:** Despite a wide range in the magnitude of the cost estimates, this study indicates that ADHD has a substantial economic impact in the United States. Implications of these findings and future directions for research are discussed. J. Am. Acad. Child Adolesc. Psychiatry, 2012;51(10):990–1002. **Key Words:** ADHD, cost of illness, societal costs, children, adults

Attention-deficit/hyperactivity disorder (ADHD) is defined by the *DSM-IV-TR* as a persistent set of inattentive, hyperactive, and impulsive symptoms that impairs function in at least two settings (e.g., home, work, and/or school).[1] It has been reported to be one of the most prevalent mental disorders in children in the United States,[2] with a current prevalence rate of 5.5% to 9.3%[3] in children and adolescents 4 to 17 years old. Children and adolescents with this disorder experience educational difficulties,[4] problems with self-esteem,[5] significantly impaired family and peer relationships,[6] and an overall decrease in quality of life.[7]

Although traditionally thought of as a condition of childhood, ADHD often persists into adulthood with associated symptomatology and impairments. Prevalence rates in U.S. adults 18 to 44 years old are reported to be 4.4%[8] and highlight the chronicity of this disorder. ADHD-related impairments may underlie subsequent problems in adulthood such as occupational dif-

This article is discussed in an editorial by Dr. A. Reese Abright on page 987.

Clinical guidance is available at the end of this article.

Supplemental material cited in this article is available online.

ficulties, criminal activity, substance abuse problems, and traffic accidents and citations.[9] Moreover, the difficulties faced by children and adults with ADHD may have spillover effects and can negatively affect the health and work productivity of family members.[10]

Although hundreds of studies have reported on the negative outcomes of ADHD in childhood and adulthood in areas such as health, education, occupation, and antisocial behavior, few have monetized these outcomes to provide an estimate of the economic impact of ADHD in the different sectors of society. For instance, the two most recent systematic reviews of the economic costs of ADHD found only 12 to 13 original research studies addressing this topic[11,12] compared with 351 original research studies found in a recent review of long-term outcomes of ADHD.[9] A comprehensive understanding of the incremental costs of ADHD (i.e., excess costs over and above those of individuals without ADHD) from a societal perspective is important to inform, plan, and justify policies and interventions to help alleviate the numerous negative consequences associated with this disorder. In addition to being dated, prior systematic reviews of the economic impact of ADHD have been limited in scope, examining a restricted population or a few sectors of the economy.[11-13] Pelham et al.[12] (2007) only reviewed costs in children and adolescents with ADHD. Leibson and Long[13] (2003) considered only health care costs. Matza et al.[11] (2005) examined children and adults and additional cost sectors besides health care, but studies of education costs were not available. Furthermore, results reported across the reviewed studies were not consolidated to present an overall estimate of incremental costs of individuals with ADHD at the national level.

The present study uses a societal perspective, comprehensively reviews studies reporting ADHD-related incremental costs for children/adolescents and adults, and computes estimates of overall annual national incremental costs of ADHD in the United States. Estimates are also stratified by age group, cost sectors, and patient versus family member.

METHOD

A systematic review was conducted using guidelines from the Cochrane Handbook for Systematic Reviews of Interventions.[14] Four large databases (MEDLINE, EMBASE, ERIC, and PsycINFO) were searched for articles published from January 1, 1990 through June 30, 2011 using the following abstracted search strategy: (*terms describing ADHD*) AND ((*terms describing cost analysis or economic impact*) OR (*terms describing areas of cost due to ADHD*)). An extensive list of terms describing cost areas of interest was used to identify studies on health care resource use, productivity losses, accidents, education, substance abuse, and criminal behavior (Table S1, available online). Studies were also identified by examining the reference lists of prior publications and by follow-up directly with the study authors. This identification method deviated from strict Cochrane guidelines but was in line with international systematic review guidelines.[15]

A primary screen retained all articles published in English and classified as original research studies of human participants conducted in the United States that included a study group of participants with ADHD and monetized ADHD-related outcomes. In a final screen, the full text of the articles were reviewed to exclude studies in which mean annual incremental costs of individuals with ADHD compared with a control group of patients without ADHD were not reported (or could not be derived).[16-18] Studies using specific disease groups (e.g., asthma or depression) as the only control group were excluded.[19,20] Studies not reporting mean costs (e.g., only median costs reported[21]) and studies from which it was not possible to separately estimate contributions from different cost categories (e.g., combined costs of health care and productivity losses[22]) were also excluded.

Study characteristics and cost measurements were extracted and tabulated for the included studies. For one study,[23] numeric data underlying the published graphs were obtained from the study author. A few calculations and adjustments were made on the data reported in the studies. Per-person annual costs were computed by dividing the aggregate annual national costs by the estimated size of the population in one study.[24] Weighted average estimates for the overall population were calculated for two studies that reported only cost estimates stratified by patient gender.[10,25] Costs were annualized for three studies estimating costs over 1 month or multiple years.[23,26,27] All cost estimates across the included studies were inflated to 2010 U.S. dollars using the consumer price index from the U.S. Bureau of Labor Statistics.[28] The medical care component of the consumer price index was used to inflate reported health care cost estimates.

For the national incremental cost calculations, the studies were compiled by age group (children/adolescents versus adults) and cost category (health care, productivity and income losses, education, and justice system). The health care and productivity cost categories were separated into subcategories of costs incurred by patients with ADHD versus those by family members of patients with ADHD. Except for the minimal requirements that each study had to meet for inclusion

in the review as outlined earlier in the selection criteria, this review did not identify and adjust for differential quality of studies. The number of studies in each age group and cost category combination was too small, often only a single study, to permit such an approach. Instead, for each age group and cost category, the lowest and highest reported incremental cost estimates across all included studies were identified. For the cost categories with a sufficient number of studies, namely those examining costs related to health care in children/adolescents (n = 9) and adults (n = 6) with ADHD and productivity losses in adults with ADHD (n = 7), reported adjusted estimates were used to identify the range of incremental cost estimates. For all remaining cost categories, the number of relevant studies was three or fewer and, hence, estimates adjusted by regression or matched controls or unadjusted estimates were used to identify the range. The range of per-person incremental cost estimates within each age group and cost category were then converted to a range of annual national incremental costs of ADHD using 2010 U.S. Census population estimates, ADHD prevalence rates, number of household members, and employment rates by age group as described below.[29,30]

First, the national counts of individuals with ADHD within each age group and cost category in the United States were estimated as the product of the nationwide U.S. population count reported by the 2010 U.S. Census[31] corresponding to the age range of the patients with ADHD across the studies specifically examining that age group (i.e., children/adolescents or adults) and cost category and the ADHD prevalence rate corresponding most closely to this age range. For children/adolescents, prevalence rates of current ADHD diagnosis reported by the Centers for Disease Control and Prevention were used.[3] For adults, a published and commonly cited rate of 4.4% in 18 to 44 year olds[8] was applied given that the Centers for Disease Control and Prevention has not reported ADHD prevalence rates in adults. For the category of productivity (i.e., absenteeism and low productivity while at work, referred to as "presenteeism" in some studies) costs in adult patients with ADHD, which is applicable only to employed patients, an employment rate of 67.6% was applied, assuming employment rates similar to those in the general 18- to 64-year-old population reported by the 2010 U.S. Bureau of Labor Statistics.[32]

Second, the national counts of family members of individuals with ADHD who would be affected under each of the subcategories of health care and productivity costs in family members of patients with ADHD was estimated. For the subcategory of health care costs among family members of the patients with ADHD, the national count of patients with ADHD was multiplied by 2.92 to compute the total number of family members (adults and children) affected by ADHD. This figure obtained from the 2010 U.S. Census[33] represents the average size of the U.S. household less one (representing the one patient with ADHD in the household.) For the subcategory of productivity costs among adult family members of children/adolescents with ADHD, the national count of patients with ADHD was multiplied by 2.0, which represents the average number of adult household members in the United States in 2010. Similarly, for the subcategory of productivity costs among adult family members of adults with ADHD, the national count of patients with ADHD was multiplied by 1.0. For the two categories related to productivity costs, the same employment rate of 67.6% was applied.[32]

Third, the range of national incremental costs of ADHD was estimated by multiplying the lowest and highest reported per-person incremental cost estimates for each age group and cost category by the corresponding national counts of individuals. Overall national incremental costs of ADHD in 2010 were computed by summing the costs across age groups and categories. The estimates were also stratified by age group, cost sectors, and patient versus family member.

RESULTS

The initial literature search identified 4,580 citations. After the screening process, only 19 studies met all inclusion criteria (Figure S1, available online). Table 1[10,23-27,34-45] lists the key characteristics of these 19 studies. Eleven studies examined costs incurred by children with ADHD or their family members and 10 studies examined costs incurred by adults with ADHD or their family members (two studies examined children/adolescents and adults). Most studies evaluated health care costs (n = 13). Nine studies examined costs related to income and productivity losses. Only three studies examined education costs and two studies examined justice system costs. None of the studies meeting the inclusion criteria evaluated costs related to traffic accidents or substance abuse problems.

Table 2[3,8,10,23-26,31,33-37,41-46] presents the analysis resulting in the range of national incremental costs of ADHD under each combination of cost category and age group of interest. The range of ages considered across all studies was 0 to 64 years old, including individuals with ADHD and their family members. In the health care cost category, wide ranges of per-person incremental cost estimates were reported across the studies evaluating children/adolescents ($621 to $2,720) and adults ($137 to $4,100) with ADHD. This variability was a function of the characteristics

TABLE 1 Key Characteristics of Studies Meeting Inclusion Criteria

Study	Design, Setting, and Sample Size	Year of Data Collection	Identification of ADHD Patients	Age Group (and Age Range Considered) of Patients with ADHD	Cost Categories Evaluated	Regression Adjustment or Matched Controls
Guevara et al., 2001[37]	retrospective analysis of Group Health Cooperative of Puget Sound HMO data (n = 14,960)	1997	*ICD-9* 314.xx or ≥1 prescription for a stimulant	children/adolescents (3–17 yo)	health care (patient)	regression and matched controls
Chan et al., 2002[38]	cross-sectional analysis of Medical Expenditure Panel Survey (n = 5,439)	1996	*ICD-9-CM* 314.xx or ≥2 prescriptions for neurostimulant	children/adolescents (5–20 yo)	health care (patient)	regression
Burd et al., 2003[39]	retrospective analysis of North Dakota Department of Health claims (n = 129,138)	1996–1997	*ICD-9* diagnosis of 314.00, 314.01, 314.8, 314.9	children/adolescents (0–21 yo)	health care (patient)	none
Mandell et al., 2003[27]	retrospective analysis of pediatric Medicaid patients in Philadelphia, PA (n = 76,662)	1993–1996	≥2 claims associated with *ICD-9* 314.xx or parental report of symptoms at diagnostic interview	children/adolescents (3–15 yo)	health care (patient)	regression
Swensen et al., 2003[25]	retrospective analysis of a random sample of health plan enrollees of a large Fortune 100 company (n = 2,172)	1998	*ICD-9* 314.0x with ≥1 ADHD medical or disability claim	children/adolescents (0–18 yo)	health care (patient), health care (family), productivity (family)	matched controls
Swensen et al., 2004[40]	retrospective analysis of a random sample of health plan enrollees of a large Fortune 100 company (n = 2,616)	1998	*ICD-9* 314.0x with ≥1 ADHD medical or disability claim	children/adolescents (0–18 yo) and adults (18–64 yo)	health care (patient), productivity (patient)	matched controls
Birnbaum et al., 2005[10]	retrospective analysis of health plan enrollees in 1 large company and associated disability data (n = 9,822)	1998	*ICD-9-CM* 314.0x with ≥1 ADHD medical claim	children/adolescents (7–18 yo) and adults (19–44 yo)	health care (patient), health care (family), productivity (patient), productivity (family)	matched controls

TABLE 1 Continued

Study	Design, Setting, and Sample Size	Year of Data Collection	Identification of ADHD Patients	Age Group (and Age Range Considered) of Patients with ADHD	Cost Categories Evaluated	Regression Adjustment or Matched Controls
Kessler et al., 2005[41]	retrospective analysis of 2 large health care claims and employer-reported productivity databases (n = 2,399)	2001–2003	*ICD-9-CM* 314.0, 314.00, or 314.01 with ≥1 evaluation or claim for ADHD diagnosis	adults (18–44 yo)	productivity (patient)	regression
Secnik et al., 2005[42]	retrospective analysis of claims from six Fortune 200 employers (n = 4,504)	1999–2001	*ICD-9* 314.00 or 314.01	adults (18–64 yo)	health care (patient) productivity (patient)	regression and matched controls
Biederman and Faraone, 2006[34]	cross-sectional analysis using nationwide, random, telephone-administered survey (n = 1,001)	2003	self-report of prior adult diagnosis	adults (18–64 yo)	income losses due to unemployment and wage differences (patient)	regression
Fischer and Barkley, 2006[26]	patients receiving psychology service within Milwaukee Children's Hospital (n = 223)	1992–1996	*DSM-III-R*	adults (19–25 yo)	income losses due to wage differences (patient)	regression
Ray et al., 2006[43]	Kaiser Permanente (Northern CA) HMO (n = 11,356)	1996–2004	*DSM-IV*, *ICD-9-CM* 314.0	children/adolescents (2–10 yo)	health care (patient)	regression and matched controls
Fishman et al., 2007[44]	group health coop and group health options members in WA and ID (n = 249,874)	2001	*ICD-9-CM* 314.xx and ≥1 AD[H]D inpatient or outpatient encounter	adults (≥18 yo)	health care (patient)	regression
Fletcher and Wolfe, 2009[24]	nationally representative sample during school years 1994–1995, 1995–1996, and 2001–2002 (n = 13,572)	1994–2002	*DSM-IV* (inattentive, hyperactive, and combined subtypes included)	adults (18–28 yo)	justice system (patient)	regression

TABLE 1 Continued

Study	Design, Setting, and Sample Size	Year of Data Collection	Identification of ADHD Patients	Age Group (and Age Range Considered) of Patients with ADHD	Cost Categories Evaluated	Regression Adjustment or Matched Controls
Jones and Foster, 2009[23]	longitudinal analysis of a cohort of kindergartners from Durham, NC; Nashville, TN; Seattle, WA; and central PA (n = 650)	1997–2004	parental self-report of child's symptoms on the Diagnostic Interview Schedule for Children (identified hyperactivity/ impulsivity or inattention)	children/adolescents (12–17 yo)	health care (patient), education (patient), justice system (patient)	regression
Kessler et al., 2009[41]	large U.S. manufacturing firm (n = 8,563)	2005–2006	*DSM-IV* criteria for adult ADHD	adults (40–51 yo IQR)	health care (patient), productivity (patient)	regression
Marks et al., 2009[35]	68 preschools within greater New York City area (n = 206)	2004–2005	*DSM-IV* criteria for pediatric ADHD	children/adolescents (3–4 yo)	education (patient)	regression
Hodgkins et al., 2011[45]	2 large health care claims and productivity databases, 100 large employers throughout US (n = 127,008)	2006	*ICD-9* 314.0, 314.00, or 314.01 with ≥1 evaluation or claim of ADHD diagnosis with continued treatment	adults (18–64 yo)	health care (patient), productivity (patient)	regression and matched controls
Robb et al., 2011[36]	Western Psychiatric Institute and Clinic, Pittsburgh, PA (n = 604)	1999–2008	*DSM-III-R* or *DSM-IV*, childhood diagnosis	children/adolescents (5–18 yo)	education (patient)	none

Note: ADHD = attention deficit/hyperactivity disorder; CA = California; DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders—3rd Edition (Revised); DSM-IV = Diagnostic and Statistical Manual of Mental Disorders—4th Edition; HMO = health maintenance organization; ICD-9 = International Classification of Diseases, Ninth Edition; ICD-9-CM = International Classification of Diseases, Ninth Edition, Clinical Modification; IQR = interquartile range; ID = Idaho; NC = North Carolina; PA = Pennsylvania; TN = Tennessee; US = United States; WA = Washington; yo = years old.

TABLE 2 National Incremental Costs of Attention-Deficit/Hyperactivity Disorder (ADHD) by Cost Category and Age Group

Cost Category	Age Group of Patients with ADHD	Number of Studies	Age Range across Studies	Population corresponding to Age Range[31,33]	ADHD Prevalence for Age Range	Other Multipliers[a]	Population Incurring Cost	Per-Person Incremental Cost, 2010 U.S. Dollars	National Incremental Cost, 2010 U.S. Dollars (Billions)
Health care									
Health care (patient)	children and adolescents	9	0–21	92,140,979	7.2%[3]	—	6,634,150	$621[37]–$2,720[23]	$4.12–$18.04
Health care (patient)	adults	6	18–64	194,296,087	4.4%[8]	—	8,549,028	$137[(NS)46]–$4,100[42]	$1.17–$35.05
Health care (family)	children and adolescents	2	0–18	74,181,467	7.2%[3]	2.92	15,595,912	$1,088[10]–$1,658[25]	$16.97–$25.86
Health care (family)	adults	1	19–44	108,305,787	4.4%[8]	2.92	13,915,128	$1,051[10]	$14.62
								subtotal	$37B–94B
Productivity and income losses									
Income losses (lower wages)	adults	1	19–25	30,433,583	4.4%[8]	—	1,339,078	$(3,744)[26]	$(5.01)
Income losses (unemployment and lower wages)	adults	1	18–64	194,296,087	4.4%[8]	—	8,549,028	$10,532[34]–$12,189[34]	$90.04–$104.20
Productivity losses (patient)	adults	6	18–64	194,296,087	4.4%[8]	67.6%	5,779,143	$209[45]–$6,699[41]	$1.21–$38.71
Productivity losses (family)	children and adolescents	2	0–18	74,181,467	7.2%[3]	2.0, 67.6%	7,221,121	$142[10]–$339[25]	$1.03–$2.45
Productivity losses (family)	adults	1	19–44	108,305,787	4.4%[8]	1.0, 67.6%	3,221,447	$174[10]	$0.56
								subtotal	$88B–$141B
Education	children	1	3–4	8,182,210	5.5%[3]	—	450,022	$12,447[35]	$5.60
	children and adolescents	2	5–18	58,480,960	7.2%[3]	—	4,210,629	$2,222[23]–$4,690[36]	$9.36–$19.75
								subtotal	$15B–$25B
Justice system	adolescents	1	13–17	21,238,249	9.3%[3]	—	1,975,157	$267[(NS)23]	$0.53
	adults	1	18–28	47,550,861	4.4%[8]	—	2,092,238	$1,204[24]–$2,742[24]	$2.52–$5.74
								subtotal	$3B–$6B
								total	$143B–$266B

Note: B = billions; NS = difference was not statistically significant in the original study.
[a]*Figures used in "Other Multipliers" are described in the Method section.*

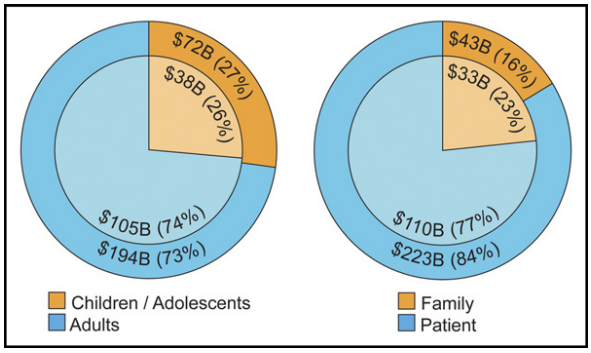
of the studies including setting, design, and cost components included. Conversely, for health care costs incurred by family members of patients with ADHD, there was little variability in these estimates, given that there were only one or two relevant studies. The estimates across the 13 studies evaluating health care costs translate into annual national incremental costs ranging from approximately $37 billion (B) to $94B among individuals with ADHD and their families.

For costs due to income losses, two studies examined costs to patients with ADHD owing to lower wages and/or unemployment. One study found that young adults (19-25 years) with current or childhood ADHD had a significantly higher incremental mean annual salary ($3,744) than non-ADHD controls, likely because a significantly smaller proportion was enrolled in college and thus more likely employed.[26] The second study reported that the annual household income was lower by $10,532 to $12,189 per adult with ADHD when examined across the entire typical working age range of 18 to 64 years.[34]

Productivity losses for adults with ADHD owing to absenteeism, poor performance while at work, disability payments, and/or worker's compensation ranged from $209 to $6,699 annually per 18- to 64-year-old employee across six studies. Although the cost components included across these studies varied, poor performance while at work was clearly the major driver of costs to employers. Per-person incremental cost estimates were smaller in magnitude for productivity losses for family members of children/adolescents ($142 to $339) and adults ($174) with ADHD across the one or two relevant studies. The estimates across the nine studies on income and productivity losses translated to annual national incremental costs ranging from approximately $88B to $141B.

For the category of education costs, one study reported the annual ADHD-related incremental costs of education in 3 to 4 year olds at $12,447 per student and included costs related to special education, occupational, speech, and physical therapy.[35] The annual incremental costs in 5 to 18 year olds ranged from $2,222 to $4,690 per student across two studies; the former estimate included costs related to special education, grade retention, and school counseling,[23] whereas the latter included costs related to special education, grade retention, and disciplinary incidents.[36] The estimates across the three studies on education costs translated to annual national incremental costs ranging from approximately $15B to $25B in 3 to 18 year olds.

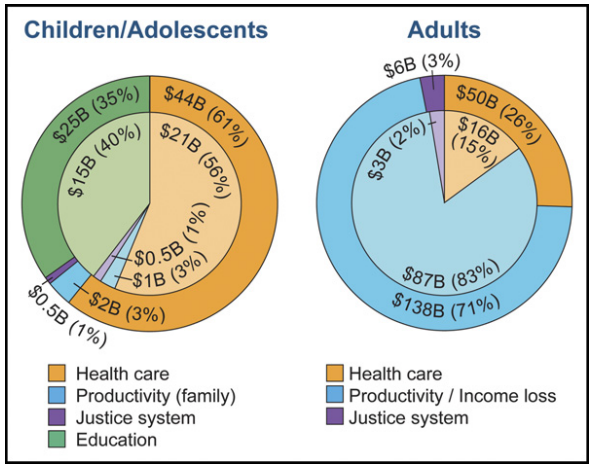
FIGURE 1 Annual national incremental costs of attention-deficit/hyperactivity disorder (ADHD) (in billions) by population groups. Note: The inner circle represents the lower end of the range of costs ($143B). The outer circle represents the higher end of the range of costs ($266B).



For justice system costs, two studies reported costs related to criminal offenses by individuals with ADHD. The per-person annual incremental costs of detention center and arrest expenditures derived from one study of 13- to 17-year-old adolescents with ADHD was $267.[23] Another study of 18- to 28-year-old young adults reported annual incremental costs ranging from $1,204 to $2,742 to the victim and society owing to burglary, robbery, larceny, arrests/convictions, and selling of drugs.[24] The estimates across these two studies translated to annual national incremental costs ranging from approximately $3B to $6B in 13 to 28 year olds.

Summing the estimates across the various cost categories resulted in overall national incremental costs of ADHD ranging from $143B to $266B in 2010. Figure 1 (left) highlights that $105B to $194B (73%–74%) of these overall costs were attributable to adults with ADHD or to adult family members of patients with ADHD. Spillover costs borne by the family of children and adults with ADHD ranged from $33B to $43B (16%–23%; Figure 1 [right]). For adults with ADHD, the largest cost component was productivity and income losses ($87B–$138B, 71%–83%; Figure 2 [left]). For children with ADHD, the largest cost components were health care ($21B–$44B, 56%–61%) and the educational sector ($15B–$25B, 35%–40%; Figure 2 [right]).

FIGURE 2 Annual national incremental costs of attention-deficit/hyperactivity disorder (ADHD) (in billions) by cost sectors within age groups. Note: The inner circle represents the lower end of the range of costs. The outer circle represents the higher end of the range of costs.



DISCUSSION

This review included 19 studies examining the incremental costs of ADHD in the United States. Recognizing the variance introduced by heterogeneous methodologies across these studies, the range of costs rather than point estimates was calculated. Despite a wide range in the annual national incremental costs computed in the present analysis (overall $143B–$266B), the lower end estimate alone indicates that ADHD has a substantial economic impact in the United States. Although large in magnitude, these results may be an underestimate of the true societal costs of ADHD in the nation for several reasons. First, there were no studies identified in the literature reporting analyzable cost information within the cost categories of substance abuse and traffic accidents, and patients with ADHD have been shown to have a higher risk of these problems.[47-51] Second, within the remaining cost categories, some included studies did not capture all relevant cost components within that sector wherein individuals with ADHD or their families may have incurred higher costs. Third, within cost categories of the justice system, education, and health care and productivity losses of family members of adult patients with ADHD, only studies for a restricted age group were found and thus the national incremental cost estimates do not include costs incurred by individuals with ADHD beyond that limited age range. Fourth, within the cost category of education, the period, study samples, and cost components in the included studies may have underrepresented the increased use of special educational services by children with ADHD under the Individuals with Disabilities with Education Act and Section 504 of the Rehabilitation Act.

Although these limitations point to an underestimation of the cost figures, a few caveats that may influence the present computed estimates in either direction also deserve mention. First, because studies varied in whether and how they controlled for comorbidities commonly associated with ADHD (i.e., anxiety, depression, mania, and oppositional-defiant disorder[52]), estimates of the cost of "pure" ADHD in the absence of comorbidities were not derivable for every study and thus the costs of ADHD alone may have been overestimated. Nevertheless, the early age of onset of ADHD makes the majority of these comorbidities secondary in terms of temporality. To the extent that ADHD affects the risk, persistence, or severity of these comorbidities, the costs associated with these comorbidities may be considered long-term indirect effects associated with ADHD and thus appropriately considered costs of patients with ADHD.[53,46] Thus, use of adjusted estimates, where available, from studies that controlled for such comorbidities may have indeed resulted in an underestimate of the true costs associated with ADHD. Second, most of the included studies did not provide sufficient information on the prevalence and length of treatment for ADHD in their study subjects. The economic burden of ADHD may be higher or lower based on treatment status. Third, the present results reflect clinical practice in the settings and time observed within the included studies. For example, several studies predated the emergence of newer ADHD treatments or increased off-label usage, which may have resulted in the true costs associated with ADHD being overestimated (if such new treatments and/or usage save costs) or underestimated (if such new treatments and/or usage do not offset all their additional costs). Furthermore, the prevalence of ADHD has been reported to be increasing over time.[3] It is unclear whether this is because the incidence of ADHD itself has increased or if the recognition and diagnosis of ADHD has increased over time in the U.S. population.[3] If the former, then the total incremental costs associated with ADHD in the United States

may have also increased over time (because the population with ADHD times the mean incremental costs equals the total incremental costs). If the latter, then the incremental costs of ADHD may be lower than estimated to the extent that previously undiagnosed patients had less severe ADHD (and, hence, went unrecognized) or higher than estimated if these patients indeed had more severe ADHD (because their ADHD was not recognized and treated early on). Fourth, the prevalence of ADHD has been reported to vary considerably across the United States. The present study estimated the average economic impact of ADHD at the national level; however, the costs in individual states (and counties) may be higher or lower.

Nevertheless, the present results underscore that the economic cost of ADHD is substantial. The magnitude of this burden can be put into perspective by comparing it with the burden imposed by other chronic conditions, although such comparisons should be made with caution because methodologies differ across studies and other studies do not always include all costs outside the health sector. Greenberg et al.[54] estimated that major depression costs $83.1B annually (~$124B in 2010 U.S. dollars). Wittchen[55] estimated that generalized anxiety disorder costs range from $42B to $47B (~$139B–$155.5B in 2010 U.S. dollars). Weiss and Sullivan[56] estimated the total societal cost of asthma as $12.7B (~$20.4B in 2010 U.S. dollars).

Several noteworthy findings of this study have important clinical and policy implications. Unlike many other conditions, health care costs constitute only one fourth to one third of the overall incremental costs associated with ADHD. The remainder of the costs occurred in non-health care sectors. Thus, the decreases in the cost burden of ADHD owing to additional investments in improving the diagnosis and management of this condition are not all accrued by the third-party payer or health insurer, thus decreasing their incentive to bear the entire cost of such investments. Given the substantial societal costs of ADHD incurred in the workforce, education, and justice system sectors, it is necessary to develop public policies to lessen the burden associated with this condition.

The present results are also the first to highlight the magnitude of the large share of costs associated with ADHD as it progresses into adulthood. Notably, the national incremental costs for adults were almost three times higher than those for children and adolescents. This is due to a combination of a larger absolute number of adults than children and adolescents and the differences in cost sectors wherein the costs are incurred by these groups. The latter point suggests that a "one size fits all" approach to decreasing the burden of ADHD is unlikely to be successful and one should consider the age group and cost sector and target policies or initiatives accordingly.

Workforce productivity costs in adults with ADHD are the single largest contributor to the economic burden associated with the condition, amounting to $87B to $138B and accounting for more than 70% to 80% of the overall adult ADHD costs. The vast majority of these costs were attributable to income losses owing to lack of full time employment and/or lower wages when employed, as estimated by Biederman and Faraone.[34] The same study also reported that individuals with ADHD were significantly more likely to report poorer grades in high school, less likely to graduate from high school or college, or less likely to have completed a postgraduate degree compared with control subjects.[34] This implies that the lack of an early or accurate diagnosis of ADHD or medical treatment and educational interventions during childhood or adolescence extracts a substantial economic burden in adulthood. Appropriate policies or interventions need to be targeted in childhood/adolescence to increase the potential for improving educational milestones and decreasing workforce productivity losses in adulthood.

The remainder of the workforce productivity costs were largely incurred owing to decreased productivity at work in employed adults with ADHD compared with healthy controls without ADHD. Despite the substantial toll of ADHD on the workplace, some private insurers do not cover any costs for ADHD treatments for adult patients.[57] Such policies create barriers to care and may decrease workplace productivity. Ideally, policies should be created that incentivize third-party payers to consider all types of economic costs of adult ADHD when evaluating the cost-effectiveness of coverage and treatments. Self-insured employers in particular should consider these various economic effects, because increases in health care costs that effectively diagnose and treat ADHD may decrease losses in worker productivity. Because most economic costs are incurred by adults with ADHD within the workplace, efforts to decrease the overall economic burden of ADHD should focus within this area. Opportunities to create partnerships between payers, employers, and patients would be an

effective first step and would better align all parties toward the goal of reducing ADHD burden.

The study is also the first to highlight that family spillover costs are a substantial proportion of total ADHD costs (16%–23%). The vast majority of these costs (~95%) are incurred within the health care system and point to the larger potential benefits of improved diagnosis and management of ADHD. Swensen et al.[25] suggested these family members use more office services, outpatient services, and mental-disorder-specific care. Further, the symptomatology associated with improperly treated ADHD can carry an emotional burden to the patient[7,58] and the patient's family[59] beyond the economic burden described here.

Educational costs amounting to $15B to $25B were a large contributor of incremental costs in children/adolescence after health care-related costs. Although these amounts are likely underestimates for the reasons noted earlier, the vast majority of the incremental costs of education identified in the included studies were still due to special education. Thus, research is clearly needed to examine whether early diagnosis and evidence-based medication and behavioral treatments in childhood decrease the future need for special education services and downstream costs. Moreover, research to identify appropriate interventions within the educational settings could provide an evidence base to better understand whether such programs save or increase costs in children and adolescents with ADHD, and if such programs do increase costs, whether the benefits to education produce downstream savings through adult ADHD worker productivity and/or salary gains. Research to provide educators and parents the information to better identify early signs of ADHD would be helpful to limiting the impact of the illness in early life and possible future life trajectory.

Future research should also focus on better understanding the ADHD costs and the costs and benefits of interventions in targeted age groups and cost sectors. Specifically, research is needed to better understand the economic impact of ADHD in unstudied or understudied areas such as substance abuse, traffic accidents, and justice system use. In addition, studies using more recent data are needed to capture costs in light of the increasing prevalence and/or diagnosis of ADHD over time[3] and current ADHD treatment patterns including the increasing use of newer ADHD medications, adjunctive therapy, and off-label prescribing. Further research is also needed to understand how the early diagnosis and treatment of ADHD can ameliorate these costs and inform future policies and interventions.

In conclusion, this comprehensive review points to the large economic burden of ADHD in the United States and to the multifaceted nature of ADHD costs. Given the substantial societal costs of ADHD, public policy to address the burden of the condition is warranted. Moreover, further research to better understand ADHD costs and the costs and benefits of interventions is warranted. Programs to facilitate collaboration among payers, patients, employers, and educational institutions may provide opportunities to create strategies to consider the societal impact of ADHD and strategies to mitigate its burden. &

CG Clinical Guidance

- Overall, the national annual incremental costs of ADHD were substantial, ranging from $143B to $266B. Patients with ADHD and families of patients with ADHD incurred costs associated with ADHD.
- The present results highlight the societal costs of ADHD as it progresses into adulthood. Most of these costs were incurred by adults ($105B–$194B) compared with children/adolescents ($38B–$72B).
- The societal costs of ADHD were multifaceted, including four major cost categories: health care, education, productivity, and justice system costs. For adults, the largest cost category was productivity and income losses ($87B–$138B). For children, the largest cost categories were health care ($21B–$44B) and education ($15B–$25B).
- Given the substantial and multifaceted societal costs of ADHD, the development of public policies to address the burden of the condition is warranted.

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Table S1Search Terms

Outcomes of Interest	Search Terms to Capture Outcomes
ADHD subjects in all countries	ADHD or ADD or attention deficit or hyperkine* or TDAH or DAH or DAA
Cost analysis or economic impact	cost* or burden or econom* or expen* or budget or financ* or pharmacoeconom*
Productivity losses	productiv* or absen* or presen* or inefficien* or efficien* or work performance or job performance or work loss or lost work or human capital or income or employ* or unemploy* or socioeconomic status or SES or occupational scale or public assistance or disability benefit* or *term disability or workm?ns comp* or workers comp*
General services use	resource use or resource utili* or service*
Health care use	care or physician visit* or doctor visit* or physician encounter* or doctor encounter* or outpatient visit* or inpatient visit* or inpatient admission* or emergency or hospital* or day case or *care
Accidents	accident* or injur* or casualty or traffic behave* or traffic violation
Education	special education or special need* or Section 504 or IDEA or education plan or school psych* or remedial education or special class*
Drug abuse	drug rehab* or Substance-Related Disorders/epidemiology/psychology/rehabilitation or treatment seek* or seeking treatment or substance abuse treatment facilit* or substance abuse program or (illicit drug or substance abuse or substance-related disorders and treatment)
Criminal behavior	justice system or juvenile or incarcerat* or delinquen* or institution* or prison* or offender pathway or criminal behavior

Note: ADD = attention-deficit disorder; ADHD = attention deficit/hyperactivity disorder; DAA = déficit de l'attention/activité in French or déficit de atención y actividad in Spanish; DAH = déficit de l'attention/hyperactivité in French or déficit de atención con hiperactividad in Spanish; IDEA = Individuals with Disabilities Education Act; TDAH = trouble déficit de l'attention/hyperactivité in French or trastorno por déficit de atención con hiperactividad in Spanish.

Figure S1Consort diagram of articles meeting inclusion criteria. Note: ADHD = attention deficit/hyperactivity disorder.

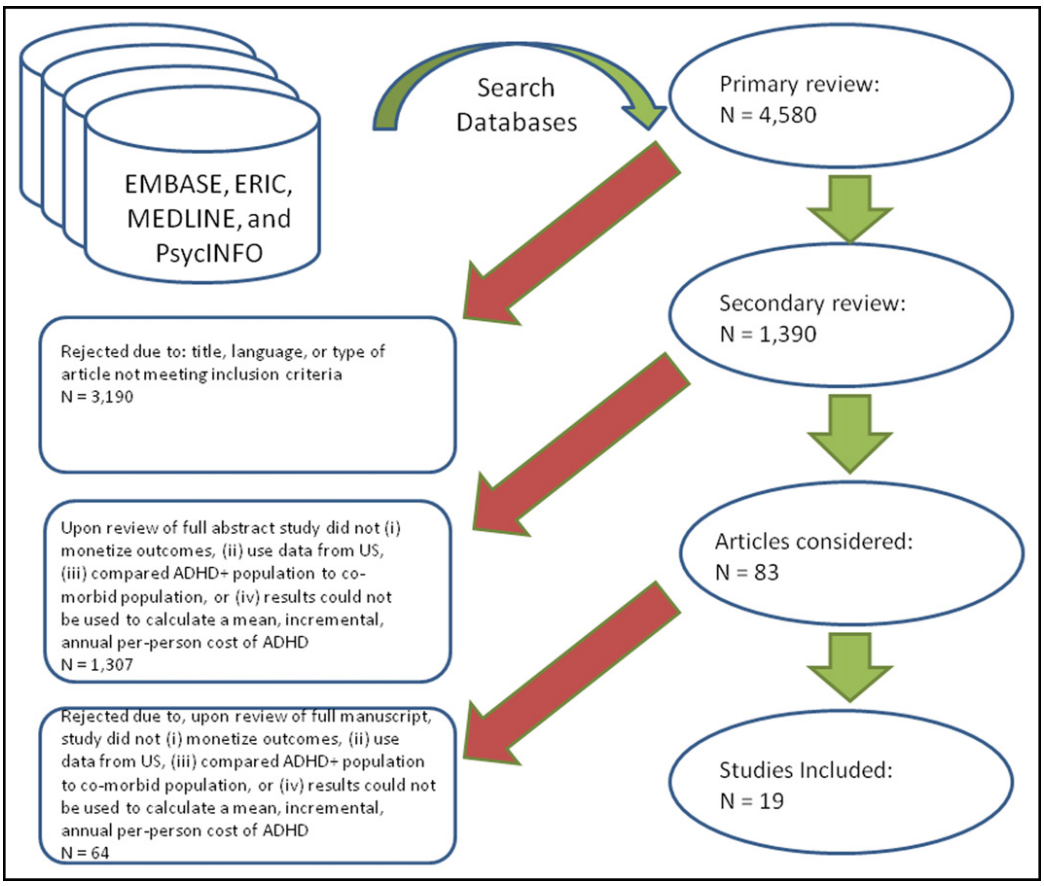

EXHIBIT 84

Cost Effectiveness and Resource Allocation

BioMed Central

Review

Open Access

A review of the economic burden of ADHD

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Abstract

Attention-deficit hyperactivity disorder (ADHD) is a common disorder that is associated with broad functional impairment among both children and adults. The purpose of this paper is to review and summarize available literature on the economic costs of ADHD, as well as potential economic benefits of treating this condition. A literature search was performed using MEDLINE to identify all published articles on the economic implications of ADHD, and authors were contacted to locate conference abstracts and articles in press that were not yet indexed. In total, 22 relevant items were located including published original studies, economic review articles, conference presentations, and reports available on the Internet. All costs were updated and presented in terms of year 2004 US dollars. A growing body of literature, primarily published in the United States, has demonstrated that ADHD places a substantial economic burden on patients, families, and third-party payers. Results of the medical cost studies consistently indicated that children with ADHD had higher annual medical costs than either matched controls (difference ranged from $503 to $1,343) or non-matched controls (difference ranged from $207 to $1,560) without ADHD. Two studies of adult samples found similar results, with significantly higher annual medical costs among adults with ADHD (ranging from $4,929 to $5,651) than among matched controls (ranging from $1,473 to $2,771). A limited number of studies have examined other economic implications of ADHD including costs to families; costs of criminality among individuals with ADHD; costs related to common psychiatric and medical comorbidities of ADHD; indirect costs associated with work loss among adults with ADHD; and costs of accidents among individuals with ADHD. Treatment cost-effectiveness studies have primarily focused on methylphenidate, which is a cost-effective treatment option with cost-effectiveness ratios ranging from $15,509 to $27,766 per quality-adjusted life year (QALY) gained. As new treatments are introduced it will be important to evaluate their cost-effectiveness to provide an indication of their potential value to clinicians, patients, families, and third-party payers.

Introduction

Attention-deficit hyperactivity disorder (ADHD) is characterized by a persistent and developmentally inappropriate pattern of inattention, hyperactivity, and/or impulsivity [1]. Children with ADHD tend to have difficulty organizing tasks and sustaining attention during schoolwork or play activities. Typical disruptive behaviors include failing to remain seated, talking excessively, playing noisily, and blurting out answers before questions have been completed. ADHD is relatively common, with prevalence rates

among school-age children in the United States ranging from roughly 4% to 12%, depending on the diagnostic approach [2-4]. Furthermore, the percentage of children treated for ADHD in the United States increased dramatically from the 1980s to the 1990s [5,6].

ADHD is associated with impairment in many areas of children's lives, including academic performance, social functioning, and overall quality of life [7-12]. Children with ADHD are frequently rejected by their peers as early as the first day of contact, likely as a result of their tendency toward disruptive and aggressive behavior [13]. ADHD also has long-term negative outcomes for many children, including decreased educational attainment, work performance, and occupational stability compared to individuals without ADHD [14,15].

Because of the broad impact of ADHD, the disorder is likely to have serious economic implications for children, families, and society. Research has only recently begun to examine these economic costs, but the initial studies suggest that ADHD leads to increased costs in healthcare and other domains. The purpose of this paper is to review and summarize available literature on the economic costs of ADHD, as well as potential economic benefits of treating this condition. In addition, recommendations for additional research on the economic implications of ADHD are provided.

Methods

A literature search was performed using MEDLINE, accessed through PubMed, to identify all published articles on the economic implications of ADHD. Searches were conducted using both the term and medical subject heading "ADHD" (in addition to the full term "attention-deficit/hyperactivity disorder" as well as individual words including "attention" and "hyperactivity"), along with economic terms including "cost," "costs," "economic," and "economics." Reference sections of relevant articles, including one review article that summarized eight economic studies [16], were reviewed to identify additional studies that may not have been included in MEDLINE. Finally, authors were contacted to locate conference abstracts and articles in press that were not yet indexed. In total, 22 relevant items were located including published original studies, unpublished conference presentations, and reports available on the Internet. Articles that discussed resource use patterns for ADHD but did not attach costs to these patterns [17] are not included in this review. All costs were updated to year 2004 US dollars based on the medical component of the Consumer Price Index [18].

Results

Direct Medical Costs of ADHD in Children and Adolescents

Formal cost of illness studies measure the "economic" burden resulting from disease and illness across a defined population (e.g., patients in the US), including both direct medical costs and indirect (e.g., lost productivity) costs [19]. Although no formal cost of illness estimates incorporating both direct and indirect costs of ADHD have been published, several studies have presented estimates of the direct medical costs of treating children and adolescents with ADHD (see Table 1). In three of the studies [20-22], annual costs of care for children with ADHD were compared to annual costs for matched (on age and sex) controls. Three other studies included a similar comparison, but utilized non-matched controls [23-25]. Studies by Chan et al. [26] and Kelleher et al. [27] compared treatment costs for childhood ADHD with childhood asthma. Leslie et al. [28] examined trends over time in costs for children with ADHD, and Marchetti et al. [29] compared costs by type of ADHD treatment. Birnbaum et al. [30] used the data set previously analyzed by Swensen et al. [21,22] to estimate total excess costs for the US population, defined as the difference between ADHD patients and matched controls.

A majority of the medical cost studies used insurance claims data from private insurers [20-22,28,30], from state Medicaid agencies [25,27], or from both sources [23,24]. The cost estimates reported by Chan et al. [26] were based on nationally representative household survey data, while the study by Marchetti et al. [29] relied on literature review and clinical expert opinion. The time period for the health care resource data used in the various studies ranged from 1987 to 1998.

The results of the medical cost studies were consistent in indicating that children with ADHD had higher annual medical costs than either matched controls (difference ranged from $503 to $1,343) or non-matched controls (difference ranged from $207 to $1,560) without ADHD (Table 1). The higher costs for ADHD patients were due to increased use of hospitalizations, primary care office visits, outpatient mental health visits, and pharmacy fills. For example, children with ADHD were 9.02 and 8.75 times more likely than other children (matched on age and sex) to have outpatient mental health visits and pharmacy fills, respectively [20]. When compared with cohorts of children with asthma (who were more likely to be female and African-American), children with ADHD had slightly higher annual treatment costs; but the differences were not statistically significant [26,27]. When Birnbaum and colleagues [30] used claims data to estimate excess costs of ADHD across the US population, the excess ADHD-related treatment costs were $0.53 billion for girls and

Table 1: Studies of the Direct Costs of ADHD

Citation	Sample	Data Sources (Time Period)	Findings[1]
Birnbaum et al. 2005	Treated ADHD patients aged 7–44 (N = 1219) and their family members under age 65 (N = 3692); controls without ADHD matched to both patients (N = 1219) and family members (N = 3692) on age, gender, employment status, geographical location age, gender, state of residence, and employment status)	Claims data from large Fortune 100 company (1996–1998)	This study estimated total excess costs for the US population, defined as the difference between ADHD patients/family members and controls. Annual mean direct ADHD treatment costs (2004 US $) were $674/$745 for girls/boys with ADHD (excess costs = $0.53/$1.06 billion) and $412/$529 for female/male adults with ADHD (excess costs = $0.13/$0.40 billion). Annual other direct treatment costs (2004 US $) were $865/$990 for girls/boys (excess costs = $0.80/ $2.0 billion) and $2609/$3022 for female/male adults with ADHD (excess costs = $0.67/$1.46 billion).
Burd et al. 2003a	Children aged 0–21 years with ADHD (N = 3,872) and non-matched controls (N = 95,119) without ADHD	North Dakota Health Claims Database (1996–1997)	Annual, mean direct treatment costs (2004 US $) were $870 for ADHD patients versus $663 for controls; 1.9% of total annual health expenditures in North Dakota attributable to ADHD.
Chan et al. 2002	Children aged 5–20 years with ADHD (N = 165), asthma (N = 322) or neither diagnosis (N = 4,952)	Nationally representative household survey data (1996)	Annual, incremental direct treatment costs (2004 US $) were $661 for children with ADHD ($P < 0.001$) and $603 for children with asthma ($P < 0.01$) (relative to costs for children with neither diagnosis)
Guevara et al. 2001	Children aged 3–17 years with ADHD (N = 2992) and matched (on age and sex) controls (N = 11,968) without ADHD	Health maintenance organization in western Washington State (1997)	Annual, incremental direct treatment costs (2004 US $) were $503 (95% CI: $450–552) for children with ADHD alone and $1088 (95% CI: $899–$1,304) for children with ADHD plus coexisting mental health disorders (relative to costs for children with no ADHD)
Kelleher et al. 2001	Children aged 7–20 years with ADHD (N = 1,602) and with asthma (N = 1,411)	Medicaid claims data for patients in Pittsburgh, PA and surrounding counties (1994–1995)	Annual, mean (± SD) direct treatment costs (2004 US $) were $2,567 ± $2,959 for the ADHD group versus $2,382 ± $2,664 for the asthma group (difference not statistically significant)
Leibson et al. 2001	Children aged 5–19 years with ADHD (N = 309) and non-matched controls (N = 3,810) without ADHD	Rochester, Minnesota medical facility-linked billing data system (1987–1995)	Long-term (9 year), median direct treatment costs (2004 US $) for ADHD patients compared with those without ADHD were more than double ($6,158 vs. $2,780; $P < 0.001$), even for the subset with no hospital or emergency room admissions ($183 vs. $93; P < 0.001)
Leslie et al. 2001	Children aged ≤ 17 years with use of mental health services, including patients with hyperactivity (N~10,000)	Health care claims for privately insured population (MarketScan®) (1993–1996)	Annual inpatient costs (2004 US $) per treated hyperactive patient declined from $26,550 in 1993 to $8,644 in 1996 ($P < 0.001$); there was also a significant decline in outpatient treatment costs ($931 and $659, respectively, $P < 0.001$)
Mandell et al. 2003	Children aged 3–15 years with ADHD (N = 4,306) and with no psychiatric disorder (N = 60,975)	Medicaid claims data for patients in Philadelphia, PA (1993–1996)	Long-term (3 year), mean direct treatment costs (2004 US $) were $4,891 for ADHD patients versus $221 for patients with no psychiatric disorder
Marchetti et al. 2001	Hypothetical cohort of school-aged children with ADHD	Literature review, managed care survey, clinical experts (2000–2001)	Average, total annual expected cost (2001 US $) per treated patient was $1,710 for Metadate CD, $1876 for Concerta, $2,061 for methylphenidate immediate-release/extended release (MPH IR/ ER), $2,122 for MPH IR, $2,392 for Ritalin, and $2,567 for Adderall.
Secnik et al. 2005b	Adults aged 18–64 with ADHD (N = 2,252) and matched controls without ADHD (N = 2252; matched on age, gender, metropolitan statistical area, and type of insurance coverage)	Health care claims for privately insured population (MarketScan®) (1999–2001)	Controlling for the impact of comorbidities, adults diagnosed with ADHD had significantly ($P < 0.0001$) higher outpatient costs ($3,009 vs. $1.491), inpatient costs ($1,259 vs. $514), prescription drug costs ($1,673 vs. $1,008) and total annual medical costs ($5,651 vs. $2,771) compared with matched controls without ADHD

Table 1: Studies of the Direct Costs of ADHD *(Continued)*

Swensen et al. 2003	Children aged 0–18 years with ADHD (N = 1,086) and matched (on age, gender, and state of residence) controls (N = 1,086) without ADHD	Claims data from large Fortune 100 company (1996–1998)	Annual, mean (± SD) direct treatment costs (2004 US $) were $2,046 ± $3,474 for the ADHD group versus $703 ± $2,215 for matched controls without ADHD ($P < 0.0001$).
Swensen et al. 2004	Individuals aged 0–64 with ADHD (N = 1,308) and matched (on age, gender, state of residence, and employment status) controls (N = 1,308) without ADHD	Claims data from large Fortune 100 company (1996–1998)	Annual, mean direct treatment costs (2004 US $) were $1,797 for children with ADHD versus $577 for matched controls without ADHD ($P < 0.05$); $2,230 for adolescents with ADHD versus $783 for matched controls without ADHD ($P < 0.05$); and $4,929 for adults with ADHD versus $1,473 for matched controls without ADHD ($P < 0.05$).

[1]All costs updated to Year 2004 US $ using the Medical Services component of the Consumer Price Index (for US-based studies). For non-US studies, all country-specific costs first updated to Year 2004 currency values based on country-specific inflators; and then converted to Year 2004 US$ based on currency exchange rates.
MPH = methylphenidate
IR = immediate release
ER = extended release

$1.06 billion for boys, and the excess overall healthcare costs were $0.80 billion for girls and $2.00 billion for boys.

Marchetti et al. [29] examined the costs of six different ADHD drug therapies: generic and branded (Ritalin) MPH immediate release (IR) therapies, two branded MPH extended release (ER) therapies (Concerta and Metadate CD), generic MPH IR/ER, and a combination therapy of amphetamine salts (Adderall). The annual expected cost of treatment with each drug therapy, including costs incurred with physician visits and lab exams, was highest for Adderall at $2,567 (2004 US $) and lowest for Metadate CD at $1,710. The cost for the other therapies ranged from $2,061 (Concerta) to $2,392 (Ritalin).

Direct Medical Costs of ADHD in Adults

Although ADHD is often perceived as a disorder of childhood and adolescence, there is growing awareness that many children continue to demonstrate symptoms in adulthood, although many adults with ADHD remain undiagnosed and untreated [31]. Limited prevalence data on adult ADHD are available, but estimates generally indicate that 30% to 70% of children with ADHD continue to have symptoms in adulthood [32,33]. Adult symptom presentation is likely to be somewhat different from the common symptoms of childhood, with less hyperactivity, but with continued problems with organizational tasks and distractibility. ADHD is known to have a broad range of negative outcomes for adults, including relatively high rates of criminality, poor job performance, lower occupational status, problems in social skills, poor driving records, and comorbid psychiatric disorders [14,15,34].

Despite the continuing impact of ADHD in adulthood, only three studies were located that examined economic costs of adults with ADHD (Table 1) [22,30,35]. Secnik et al. and Swensen et al. compared costs of care for adults with ADHD with matched controls (matched on age, sex, metropolitan statistical area, and type of insurance coverage), and both utilized privately insured claims data for the analysis. The two studies both indicated that adults with ADHD have significantly higher annual medical costs (ranging from $4,929 to $5,651) than matched controls (ranging from $1,473 to $2,771), even after controlling for patient comorbidity [35]. Birnbaum and colleagues used the same sample as Swensen et al. to estimate total excess costs for adults in the US population (i.e., the difference between ADHD patients and matched controls). The excess ADHD-related treatment costs were $0.13 billion for women and $0.40 billion for men, and the excess overall healthcare costs were $4.79 billion for women and $8.51 billion for men.

Costs to Families

The relationship between children and their families is complex and bi-directional, involving simultaneous mutual influence [36,37]. Children are shaped by their experiences with parents, while simultaneously influencing their parents' behavior and emotions [38,39]. This mutual influence between parents and children has been well-documented among families with a child who has been diagnosed with ADHD. Family environment and parent-child interaction has been shown to be a key causal factor in the development of ADHD and related conduct problems in longitudinal studies [40]. Conversely, the symptoms of ADHD have profound effects not only on the child, but also on the child's parents. For example, children's ADHD is frequently linked with strain in the

parent-child relationship, disturbance in parents' marital functioning (e.g., less marital satisfaction and more conflict than parents of children without ADHD), and extremely high parental stress [40,41].

A recent study conducted by Swensen and colleagues [21] suggests that childhood ADHD also places an economic burden on parents and other family members. This analysis was conducted using 1996–1998 data from a national sample of over 100,000 beneficiaries of a large US company that include industrial, service, and professional employees. Family members of individuals affected with ADHD had 1.6 times as many medical claims as matched control individuals without a family member diagnosed with ADHD (matching based on age, gender, geographical location, and employment status). This greater healthcare utilization resulted in increased costs. Annual direct per-capita medical costs were twice as much for family members of ADHD patients ($2,740) than for family members of control patients ($1,365). Indirect costs related to disability and absenteeism followed a similar pattern (family members of ADHD patients, $888; family members of controls, $551). Birnbaum et al. [30] used the same data set to estimate excess healthcare costs across the US population (i.e., the difference between family members of ADHD patients and family members of matched controls), which were $6.78 billion for family members of children with ADHD and $12.10 billion for family members of adults with ADHD.

There are several possible reasons for the higher indirect costs of parents whose children have ADHD. For example, children with ADHD are likely to require energy and attention that might otherwise be focused on work-related responsibilities. Furthermore, these parents may often be required to miss work in order to meet with teachers or take their children to appointments with physicians or mental health professionals. These high indirect costs suggest that ADHD has a financial impact not only on family members, but also on employers who might be affected by family members increased disability and absenteeism.

A nationally representative US survey conducted in 1998 suggests that mothers of children with ADHD perceive the financial impact of their children's disorder [42]. Compared with mothers whose children were not diagnosed with ADHD, mothers of children with ADHD were 3.3 times as likely to say that the family could not afford prescription medication for the child and 7.4 times as likely to say the family could not afford mental-health care for the child. Another study of parent perceptions clearly demonstrates the substantial economic burden of ADHD [43]. In this study, parents were asked whether they perceive their child's hyperactivity as a serious problem. The strongest predictor of whether parents considered ADHD to be a serious problem was the financial impact related to work, defined as the impact of the child's behavior on either parent's employment patterns or chances of a career (e.g., leaving work to pick up the child). Compared with parents who did not think ADHD was a serious problem, parents who perceived their child's ADHD to be a serious problem were 17.6 times more likely to say that there child's ADHD had a financial impact related to their work. Taken together, Swensen's study of family medical costs and these two studies of parent perceptions indicate that ADHD has a substantial impact on family finances.

Given the impact of a child's ADHD on parents' absenteeism and productivity, it may be beneficial for employers and human resource specialists to consider strategies for minimizing this impact. A recent survey of 41 employers in four American cities found that the participants knew little about ADHD prevalence or its potential effects on parents, despite their responsibility for purchasing employees' health insurance [44]. However, employers did offer several benefits and policies that could be helpful to parents whose children have ADHD, including on-site parent training programs, assistance with child care, flexible work/leave policies, and referral services that linked parents with community programs. When asked about benefits that could be targeted specifically for families of children with ADHD, employers suggested lunch seminars about ADHD and flexible hours for employees to meet with schools or physicians. As employers gain greater awareness of the economic impact of ADHD, it is hoped that such programs and benefits may be implemented at more companies.

Costs of Criminality

Several longitudinal studies have shown that childhood ADHD is associated with criminality in adolescence and adulthood. For example, a study conducted in Los Angeles found that children diagnosed with ADHD between the ages of 6 and 12 years old had significantly higher juvenile (46% versus 11%) and adult (21% versus 1%) arrest rates compared to normal control subjects [45]. A similar study conducted in New York found that children with ADHD were more likely than controls to later be arrested (39% versus 20%), convicted (28% versus 11%), and incarcerated (9% versus 1%) [46]. Another study, conducted with 17–18 year old adolescents in San Francisco, found that the ADHD group was more likely than the control group to be on probation, in jail, or assigned to a social worker by the court [47].

One study has estimated the economic impact of criminality associated with ADHD [48]. Data were from a sample of children (4–12 years old) identified in 1979 and 1980. Follow-up interviews were conducted between 1991 and 1996 with 149 children diagnosed with ADHD

and 76 control children when a sample ranged in age from 19 to 25 years. Criminal history was assessed through self-report, including crimes (e.g., stealing, assault), juvenile detention, probation, and jail. The costs of crimes incurred by victims and costs to the criminal justice system were estimated based on information from the Bureau of Justice Statistics, the Federal Bureau of Investigation, and the Criminal Justice Institute. Compared with the control group, the ADHD patients were more than twice as likely to have been arrested (48% versus 20%). The mean total criminal costs were dramatically greater for ADHD patients than for controls ($12,868 versus $498). All differences were statistically significant. Although this study should be considered a rough estimate, findings strongly suggest that criminality associated with ADHD results in a significant cost to society.

Costs of Comorbidities

Children with ADHD tend to have elevated rates of other psychiatric conditions [21,49,50] For example, about 30% of children with ADHD meet criteria for an anxiety disorder, compared to about 10% of the general population. Behavioral problems such as conduct disorder and oppositional defiant disorder are particularly common among children with ADHD, with comorbid rates of roughly 50%. Other conditions that are commonly comorbid with ADHD include learning disabilities, depression, and possibly bipolar disorder. When estimating the impact of ADHD, it is important to consider these comorbidities because comorbid conditions can influence children's long-term course and response to treatment.

One study has estimated the incremental increase in costs of treatment for ADHD with comorbid conditions, compared with treatment of ADHD alone [51]. Analyses were conducted using 1996 and 1997 data from the North Dakota Department of Health's Claims Database. Generally, comorbid psychiatric disorders substantially increased the costs of treating children with ADHD. For example over the two years, comorbid depression increased costs by an average of $358 per patient per year. Increases were also observed with oppositional defiant disorder ($258), bipolar disorder ($541), conduct disorder ($488), anxiety ($499), nondependent drug use ($868), tics ($198), and personality disorders ($247). Non-psychiatric medical disorders also resulted in increased costs, including respiratory illness ($630), acute sinusitis ($670), general injuries ($972), and allergies ($507).

In the North Dakota sample, the only comorbid conditions that were associated with lower costs compared to children without comorbid conditions were learning disabilities (-$759) and epilepsy (-$777). However, another recent study focusing on comorbid epilepsy in an administrative claims database from 1998 to 2001 found contrasting results [52]. In a sample, the average annual treatment costs for children with ADHD and comorbid epilepsy were $5,194, compared with $4,246 for children with ADHD but not epilepsy. Despite the mixed results relating to learning disabilities and epilepsy, initial findings suggest that the common comorbid conditions of ADHD may contribute to elevated treatment costs among this population.

Costs of Accidents

Children with ADHD have been shown to be more accident prone than other children [53], likely because of their tendencies toward impulsive, overactive behavior. They are also more likely than other children to experience injuries due to accidents, such as broken bones, lacerations, head injuries, bruises, lost teeth, or accidental poisonings [54,55]. One study has estimated the incidence and cost of accidents among individuals with ADHD using an administrative database of medical, pharmaceutical, and disability claims for national manufacturers' employees, spouses, dependents, and retirees [22]. Analyses were conducted for the whole population, adults alone, children under age 12, and adolescents aged 12 to 18 years. ADHD patients in all age groups were more likely than a matched control group to have at least one accident claim: children, 28% versus 18%; adolescents, 32% versus 23%, and adults, 38% versus 18%. Among adults, the accident-specific direct medical costs were significantly higher among ADHD patients than among the control group ($642 versus $194). Among children and adolescents, there were not significant differences in accident-specific costs between the ADHD groups and the control groups.

Costs of Work Loss

ADHD is associated with work-related problems in adulthood such as poor job performance, lower occupational status, less job stability, and increased absence days in comparison to adults without ADHD [15,34,35,56]. This poor performance and work loss is likely to have profound economic implications. One study quantified this impact by estimating the excess costs (i.e., the difference between adult ADHD patients and matched controls) related to work loss [30]. Indirect work loss costs were calculated based on employer payments for disability claims and imputed wages for medically-related work absence days (e.g., days in the hospital, physician visits). The excess costs were $1.20 billion for women with ADHD and $2.26 billion for men with ADHD.

Cost-Effectiveness of Treatments for ADHD

Three published studies have utilized decision analytic modeling techniques to assess the cost-effectiveness of

Table 2: Studies of the Cost-Effectiveness of Treatment for ADHD

Citation	Comparators	Study Design	Findings[1]
Gilmore & Milne 2001	MPH, placebo	• Decision analytic model assessing cost-utility	Cost per each additional QALY gained with MPH treatment (versus no treatment) ranged from $15,509 to $19,281 when considering short-and medium-term benefits of MPH. Cost per QALY gained ranged from $9,850–$59,101 in sensitivity analyses
Novartis data on file (2000; referenced in Lord & Paisley 2000)	MPH, placebo	• Decision analytic model assessing cost-utility	Cost per each additional QALY gained with MPH treatment (versus no treatment) was $27,766.
Zupancic et al. 1998	MPH, placebo	• Decision analytic model assessing cost-effectiveness	Cost per each additional point in the Conners Teacher Rating Scale gained with MPH treatment (versus no treatment) was $93, or $560 for a 6-point (1 SD) gain.

[1]All costs updated to Year 2004 US $ using the Medical Services component of the Consumer Price Index (for US-based studies). For non-US studies, all country-specific costs first updated to Year 2004 currency values based on country-specific inflators; and then converted to Year 2004 US$ based on currency exchange rates.
MPH = methylphenidate
QALY = quality-adjusted life years

drug therapy (i.e. methylphenidate [MPH]) for ADHD [57-59] (see Table 2). Each of these studies represented "complete" economic evaluations (i.e. estimated both the incremental costs and incremental effects associated with treatment). In two of the studies [57,58], the effectiveness of treatment was measured in terms of "quality-adjusted life years" (QALYs), an outcome measure that incorporates quality of life benefits and time [60]. These quality of life benefits are quantified using utility scores, which have been shown to be feasible and valid for assessment of children with ADHD [61-63]. In the third study [59], treatment effectiveness was based on gains in the Conners Teacher Rating Scale, a commonly used teacher-report questionnaire for assessing children's classroom behavior [64].

Overall, results of the three modeling analyses indicate that MPH is a cost-effective treatment option for children with ADHD. The cost per QALY gained in the Gilmore and Milne [57] study ranged from $15,509 to $19,281 when considering the short-and medium-term benefits of MPH. The authors note that evidence of cost-effectiveness beyond 6 months is poorer, and it is uncertain whether the effects of MPH persist into adolescence and adulthood. In the Novartis study, the cost per QALY gained was $27,766.

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

A growing body of literature has demonstrated that ADHD places a substantial economic burden on patients, families, and third-party payers. However, all available published studies on the economic implications of ADHD are relatively recent, and there are many additional questions to be examined in future research. Thus far, studies have identified several aspects of ADHD that are likely to have economic implications, including direct treatment costs, increased rates of comorbid psychiatric disorders, high accident rates, work loss, and criminality. There are many other well-documented outcomes of ADHD that are likely to have economic implications. For example, ADHD frequently has detrimental effects on a child's academic performance and behavior in school. These difficulties are likely to place an economic burden on school systems, as there is an increased need for school-based services such as in-school medication administration; special education services; child and possibly parent counseling; educational testing; development of individualized educational programs; and efforts to address disruptive classroom behaviors [65,66]. Research is needed to quantify these costs and identify strategies for implementing the most cost-effective services. Furthermore, it is well known that adults with ADHD tend to have poor driving records and relatively high rates of traffic accidents [14,15,34]. These driving problems are also likely to present a significant cost which is not yet been examined.

The international literature on cost of ADHD could also be expanded. Nearly all published studies identified for the current review were conducted in the US. Given international differences in medical care systems and practice patterns, it is difficult to apply the direct treatment costs from US studies to countries outside the US. It is likely, however, that the indirect cost burden of ADHD identified in US studies may be similar to the burden in other countries, although it may not be recognized to the same extent. Recognition, diagnosis, and treatment of ADHD

are increasing in Europe and Australia, and future studies may document the economic burden of ADHD in these areas.

Finally, more work is needed on determining the potential cost-effectiveness of the various treatment options for ADHD. The initial research on cost-effectiveness of treatment has focused on MPH, and results generally indicate that treatment of ADHD is cost-effective. As new treatments are introduced (e.g., the new non-stimulant atomoxetine), it is important to evaluate their cost-effectiveness to provide an indication of their potential value to clinicians, patients, families, and third-party payers. Effective treatments, while possibly increasing direct medical costs, are likely to reduce the overall burden of ADHD by controlling symptoms, improving children's functioning, and substantially reducing indirect costs to families.

List of Abbreviations

Attention-deficit hyperactivity disorder (ADHD)

extended release (ER)

immediate release (IR)

methylphenidate (MPH)

quality-adjusted life year (QALY)

Competing interests

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Authors' contributions

LM was the principal investigator. He conducted the literature search, designed the structure of the manuscript, reviewed and integrated much of the literature, and wrote and conceived most of the manuscript. CP and MP had primary responsibility for the two sections that review, integrate, and summarize studies of direct costs and treatment cost-effectiveness. They reviewed the relevant literature, wrote these two important sections of the paper, and created Tables 1 and 2.

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EXHIBIT 85

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Treatment Patterns and Costs Among Children Aged 2 to 17 Years With ADHD in New York State Medicaid in 2013

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Abstract

Objective: To identify children with ADHD enrolled in New York State (NYS) Medicaid and characterize ADHD-associated costs by treatment category. **Method:** In 2013, 1.4 million children aged 2 to 17 years were enrolled in NYS Medicaid. Medicaid claims and encounters were used to identify children with ADHD, classify them by type of treatment received, and estimate associated costs. **Results:** The ADHD cohort comprised 5.4% of all Medicaid-enrolled children, with 35.0% receiving medication only, 16.2% receiving psychological services only, 42.2% receiving both, and 6.6% receiving neither. The total costs for the ADHD cohort (US$729.3 million) accounted for 18.1% of the total costs for children enrolled in NYS Medicaid. **Conclusion:** This study underscores the importance of achieving a better understanding of children with ADHD enrolled in NYS Medicaid. A framework to categorize children with ADHD based on their treatment categories may help to target interventions to improve the quality of care and reduce costs. *(J. of Att. Dis. XXXX; XX(X) XX-XX)*

Keywords

ADHD, children, Medicaid, costs, treatments

ADHD is a neurodevelopmental disorder defined by symptoms of inattention, hyperactivity, and/or impulsivity that interferes with functioning in home, academic, and social settings (American Psychiatric Association, 2013). Children with ADHD have difficulty focusing and controlling their behaviors, and can be negatively affected in multiple ways, including increased risk of school failure, difficulties with social functioning, and increased rates of physical injury (Barbaresi, Katusic, Colligan, Weaver, & Jacobsen, 2007; Merrill, Lyon, Baker, & Gren, 2009; Pastor & Reuben, 2006; Ros & Graziano, 2018). In 2016, approximately 6.1 million children aged 2 to 17 years (9.4% of all US children and adolescents) were reported by parents as ever having been diagnosed with ADHD, with 5.4 million children (8.4%) currently having ADHD (Danielson et al., 2018). These estimates were similar to those from 2011, which capped a period of a significant increase in the prevalence of ADHD diagnosis, when estimates of ADHD prevalence rose on average by approximately 5% each year from 2003 to 2011 (Visser et al., 2014). Children enrolled in Medicaid and those receiving Supplemental Security Income (SSI) have been found to be more likely to have ADHD than children not enrolled in these programs (Gupte-Singh, Singh, & Lawson, 2017).

In 2011, the American Academy of Pediatrics (AAP; 2011) released updated guidelines regarding the diagnosis and treatment of ADHD among children aged 4 to 18 years. These recommendations included an expansion of the age range covered by previous guidelines, with treatment guidelines varying by age. For preschool-aged children (aged 4-5 years), AAP recommended that the primary care physician prescribe behavioral therapy as the first line of treatment. If significant improvement does not occur with behavioral therapy alone, the guidelines state that specific stimulant medications may be prescribed in addition to behavioral therapy. For elementary school children (aged 6-11 years) and adolescents (aged 12-18 years), AAP recommended a combination of behavioral therapy and a Food and Drug Administration (FDA)-approved stimulant or nonstimulant medication.

With an estimated one third of children retaining the diagnosis into adulthood, ADHD is recognized as a chronic health condition (Barbaresi et al., 2013; Visser et al., 2014). ADHD is the costliest chronic health condition for children and adolescents, resulting in approximately US$20.6 billion

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in health care spending in the United States in 2013 (Bui et al., 2017). Previous findings indicate that children with ADHD incur greater health care costs and utilize a greater number of health care services than children without ADHD (Guevara, Lozano, Wickizer, Mell, & Gephart, 2001; Guevara, Mandell, Rostain, Zhao, & Hadley, 2003; Leibson, Katusic, Barbaresi, Ransom, & Brien, 2001).

Although the impact on health and behavior and the evidence base for treatment of ADHD are both well understood, there is limited research available on the cost of treatment, especially for psychological services, in the United States. A review of the existing published literature found only 13 original research studies focusing on the health care costs of ADHD in the United States from January 1, 1990 through June 30, 2011 (Doshi et al., 2012). Beyond the limited number of studies on the cost of ADHD-related treatment, even fewer studies have explored both the management of ADHD among children enrolled in Medicaid and cost of their health care. As state Medicaid agencies face potential funding cuts, and in light of the ongoing transformation of health care to value-based payment (VBP) (Roby et al., 2018), fully understanding these high-cost and high-service usage populations is integral to the success of the transformation.

To address gaps in the literature, we identified and characterized children aged 2 to 17 years with ADHD in the New York State (NYS) Medicaid program in 2013 by demographic factors and types of treatment received (medication and/or psychological services). We also compared Medicaid costs for all children aged 2 to 17 years in NYS Medicaid to costs for those children identified with ADHD, including comparisons of the mean and the median costs by treatment types received.

Method

Data Source

This study's data source was the NYS Office of Health Insurance Programs Medicaid Data Mart. This administrative database contains enrollee information on Medicaid and Medicare eligibility, receipt of SSI or Temporary Assistance for Needy Families (TANF), and demographic information such as age, gender, race/ethnicity, zip code, and county of residence. In addition to eligibility and demographic information, the Data Mart also contains fee-for-service (FFS) claims, health plan submitted encounter records, and pharmacy claims for services performed between January 1, 2004, and the present.

Study Population

FFS claims and encounter records were used to identify children with ADHD, their treatment patterns, and the associated Medicaid costs among children aged 2 to 17 years who were continuously enrolled for at least 11 months during calendar year 2013. Children in NYS Medicaid were identified as having ADHD if they had two or more outpatient visits with an International Classification of Diseases Ninth Revision Clinical Modification (ICD-9) code for ADHD (314.XX) with dates of service $\geq$ 7 days apart during 2013, or one outpatient claim with an ADHD diagnosis code and two or more FDA-approved ADHD medications dispensed $\geq$ 14 days apart during 2013.

Using the treatment combinations recommended by the AAP guidelines, children in the ADHD cohort were divided into four mutually exclusive groups by treatment received in 2013: (1) receipt of both psychological services and medication treatment, (2) receipt of medication treatment only, (3) receipt of psychological services only, and (4) receipt of neither psychological services nor medication treatment. Children were identified as receiving medication treatment if they had one or more prescription drug claims for an FDA-approved medication to treat ADHD (amphetamine and mixed amphetamine salts, atomoxetine, clonidine, dextroamphetamine, dexmethylphenidate, guanfacine, lisdexamfetamine, and methylphenidate). Children were categorized as having received psychological services if they had one or more outpatient visits with a relevant Current Procedural Technology (CPT) or Healthcare Common Procedure Coding System (HCPCS) code (CPT: 90832-90834, 90836-90840, 90845-90847, 90849, 90853, 96152-96155, 97532-97533; HCPCS: G0409-G0411, H0004, H0017-H0019, H0035-H0037, H2012-H2022, H2027, S9480, T1027).

Cost Data and Descriptive Analyses

Total Medicaid costs were calculated for all children enrolled in Medicaid, for the ADHD cohort and for the four mutually exclusive treatment groups by summing the paid amount for all FFS paid claims and health plan reported paid amount on encounter records for all services provided in 2013. Total cost of care is an estimate of direct medical costs, including but not limited to physician services, routine and sick visits, diagnostic tests, pharmacy, and hospitalization expenses. Total cost of care does not include capitation amounts paid to managed care organizations. To estimate the proportion of the total cost of care for services related to ADHD, paid amounts on both claims and encounters for any psychological services, ADHD medication, and any service with an ADHD diagnosis code were summed across the cohort and treatment groups.

Sociodemographic characteristics were compared for all NYS children aged 2 to 17 years in Medicaid, for the ADHD cohort, and across the four mutually exclusive treatment groups. Sociodemographic characteristics included age, gender, race/ethnicity (non-Hispanic White, Black, Hispanic, Other, and Unknown), urban/rural status using rural–urban

Table 1. Sociodemographic Characteristics of All New York State Children in Medicaid Aged 2 to 17 Years, All Children in Medicaid Aged 2 to 17 Years With ADHD, and Children With ADHD Grouped by Treatment Received, 2013.

	All children in Medicaid	All children in Medicaid with ADHD				
Characteristics	Overall (n = 1,390,666) n (%)	Overall ADHD cohort (n = 75,652) n (%)	Received both psychological services and medication (n = 31,905; 42.2%) n (%)	Received medication only (n = 26,514; 35.0%) n (%)	Received psychological services only (n = 12,253; 16.2%) n (%)	Received neither medication nor psychological services (n = 4,980; 6.6%) n (%)
Age group (years)						
2-5	403,352 (29.0)	6,692 (8.9)	2,000 (6.3)	1,958 (7.4)	1,553 (12.7)	1,181 (23.7)
6-11	536,622 (38.6)	42,816 (56.6)	18,406 (57.7)	15,468 (58.3)	6,455 (52.7)	2,487 (49.9)
12-17	450,692 (32.4)	26,144 (34.6)	11,499 (36.0)	9,088 (34.3)	4,245 (34.6)	1,312 (26.4)
Gender						
Male	716,325 (51.5)	55,110 (72.9)	23,327 (73.1)	19,653 (74.1)	8,481 (69.2)	3,649 (73.3)
Female	674,341 (48.5)	20,542 (27.2)	8,578 (26.9)	6,861 (25.9)	3,772 (30.8)	1,331 (26.7)
Race						
White	379,826 (27.3)	31,889 (42.2)	13,136 (41.2)	14,743 (55.6)	2,876 (23.5)	1,134 (22.8)
Black	250,687 (18.0)	14,612 (19.3)	6,808 (21.3)	4,031 (15.2)	2,778 (22.7)	995 (20.0)
Hispanic	411,225 (29.6)	19,241 (25.4)	8,458 (26.5)	4,554 (17.2)	4,507 (36.8)	1,722 (34.6)
Other	177,014 (12.7)	5,059 (6.7)	1,937 (6.1)	1,740 (6.6)	884 (7.2)	498 (10.0)
Unknown	171,914 (12.4)	4,851 (6.4)	1,566 (4.9)	1,446 (5.5)	1,208 (9.9)	631 (12.7)
RUCA codes						
Metropolitan	1,288,195 (92.6)	62,588 (82.7)	26,522 (83.1)	20,094 (75.8)	11,325 (92.4)	4,647 (93.3)
Other[a]	102,471 (7.4)	13,064 (17.3)	5,383 (16.9)	6,420 (24.2)	928 (7.6)	333 (6.7)
SES[b] indicator						
SSI	103,181 (7.4)	21,920 (29.0)	11,229 (35.2)	6,644 (25.1)	2,813 (23.0)	1,234 (24.8)
TANF	1,287,485 (92.6)	53,732 (71.0)	20,676 (64.8)	19,870 (74.9)	9,440 (77.0)	3,746 (75.2)

Note. SSI = Supplemental Security Income; TANF = Temporary Assistance for Needy Families; SES = socioeconomic status; RUCA = rural-urban commuting area.
[a]Other includes micropolitan, small town, rural and out of state/unknown.
[b]SES: SSI and TANF.

commuting area (RUCA) codes, and socioeconomic status (SES) indicators. The SES indicators in this analysis reflect the two possible Medicaid aid categories the children qualified under (1) SSI, a program that provides financial support to people with severe physical or mental impairments (which may include but are not limited to ADHD); or (2) TANF, a program that provide cash assistance to families in need.

Results

Of the 1,390,666 children aged 2 to 17 years who were continuously enrolled in the NYS Medicaid program in 2013, 5.4% (n = 75,652) met the case definition for receipt of clinical care for ADHD (Table 1). Among this cohort, 42.2% (n = 31,905) received both psychological services and medication treatment, 35.0% (n = 26,514) received medication only, 16.2% (n = 12,253) received psychological services only, and 6.6% (n = 4,980) received neither treatment.

Table 1 shows that when compared with the overall population of children aged 2 to 17 years in NYS Medicaid, the ADHD cohort had a higher proportion of children aged 6 to 11 years (56.6% vs. 38.6%), fewer children aged 2 to 5 years (8.9% vs. 29.0%), a higher proportion of males (72.9% vs. 51.5%), a higher proportion of non-Hispanic White children (42.2% vs. 27.3%), a slightly less metropolitan population (82.7% vs. 92.6%), and a much higher proportion of children receiving SSI benefits (29.0% vs. 7.4%).

Figure 1 demonstrates a few additional notable sociodemographic differences across the four mutually exclusive treatment groups for children identified with ADHD. By age group, there was a higher proportion of the youngest children (aged 2-5 years) receiving psychological services only (23.2%) or receiving no services at all (17.6%) compared with older children, whereas older children (aged 6-11 years or 12-17 years) were more likely to receive both psychological services and medication (43.0% and 44.0%, respectively), or to receive medication only (36.1% and 34.8%, respectively). Compared to the other four race/ethnicity categories, non-Hispanic White children had the highest percentage (46.2%) receiving medication only, whereas Hispanic children were more likely to have received psychological services only (23.4%). Children from metropolitan areas had a higher proportion receiving psychological services only compared with children from other areas (18.1% vs. 7.1%) and a lower proportion receiving medication only (32.1% vs. 49.1%). A higher proportion of children with ADHD and receiving SSI received both psychological services and medication, compared to children with ADHD and receiving TANF (51.2 % vs. 38.5%).

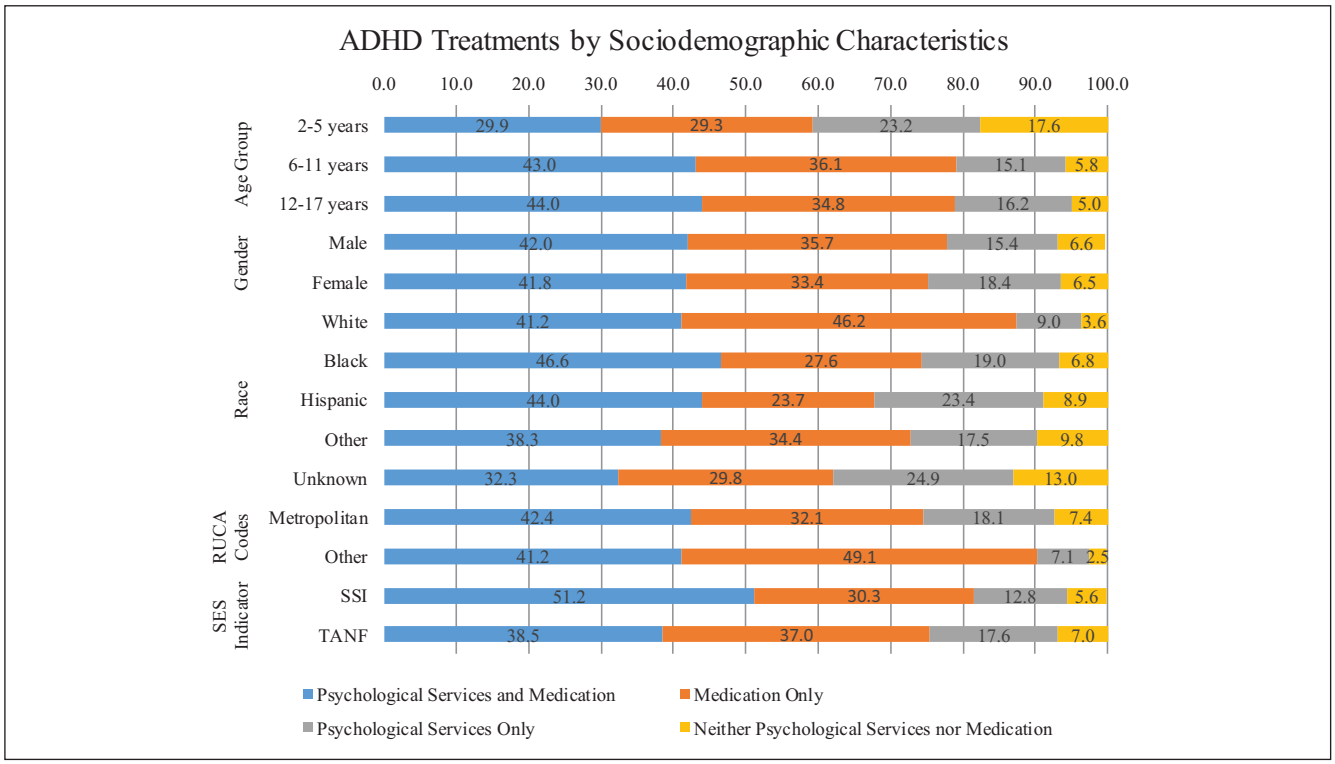

Figure 1. Proportion of New York State children in Medicaid with ADHD receiving different treatments by sociodemographic characteristics, 2013.
Note. RUCA = rural–urban commuting area; SES = socioeconomic status; SSI = Supplemental Security Income; TANF = Temporary Assistance for Needy Families.

Although the ADHD cohort comprised only 5.4% of the total Medicaid group, the total costs for the ADHD cohort accounted for 18.1% (US$729,250,258) of the total costs (US$4,026,563,864) for all children in Medicaid in 2013 (Table 2). The overall average cost per child with ADHD was US$9,640, and ranged from US$0 to US$923,678. The average cost per child for the ADHD cohort was approximately 3.2 times the average cost per child for all children in Medicaid (US$9,640 vs. US$3,042). This cost differential pattern for the ADHD cohort versus all children in Medicaid persisted across most sociodemographic groups except by SES indicators. The average cost per child among the subset of children receiving SSI who had ADHD was slightly lower than the average per child cost among all children in Medicaid receiving SSI (US$15,974 vs. US$16,194).

The majority (55%) of the total Medicaid costs for children with ADHD were expended on the treatment group that received both psychological services and medication (US$403,320,070), followed by 24% (US$175,206,898) from those who received medication only, and 14% (US$99,881,602) from the group who received psychological services only (Table 2). Children with ADHD receiving psychological services and medication had the highest average cost per child (US$12,641) of the four treatment groups. Although the overall proportion of total costs for those receiving neither psychological services nor medication (7%; US$50,841,688) was small in comparison with the total overall costs, the average cost per child with ADHD receiving neither treatment was the second highest among the four treatment groups (US$10,209), and greater than the average cost per child for children receiving medication only or psychological services only. Children with ADHD receiving psychological services and medication had the highest median costs (US$6,008), followed by those who received psychological services only (US$3,298) and those who received medication only (US$2,687), whereas children with ADHD who received neither treatment had the lowest median costs (US$2,225).

The subset of costs for ADHD-related claims (psychological services, ADHD medication, and any service with an ADHD diagnosis code) totaled US$331.5 million and accounted for 45.5% of the total Medicaid costs incurred for the ADHD cohort (Tables 2 and 3). This ranged from a high of 51.6% (US$208,197,408 out of US$403,320,070) of the total Medicaid costs for children receiving both psychological services and medication to a low of 30.1% (US$15,285,833 out of US$50,841,688) of the total Medicaid costs for children receiving neither. The average cost per child was US$4,389 (Table 3) for ADHD-related

Table 2. Total Medicaid Costs and Per Child Mean and Median Cost for All New York State Children in Medicaid Aged 2 to 17 Years, All Children in Medicaid Aged 2 to 17 Years With ADHD, and Children With ADHD Grouped by Treatments Received, 2013.

	All children in Medicaid		All children in Medicaid with ADHD													
			Overall ADHD cohort		Received both psychological services and medication			Received medication only			Received psychological services only			Received neither medication nor psychological services		
	Total costs	Per child *M*	Total costs	Per child *M*	Total costs	Per child *M*	Per child median	Total costs	Per child *M*	Per child median	Total costs	Per child *M*	Per child median	Total costs	Per child *M*	Per child median
Total	US$4,026,563,864	US$3,042	US$729,250,258	US$9,640	US$403,320,070	US$12,641	US$6,008	US$175,206,898	US$6,608	US$2,687	US$99,881,602	US$8,152	US$3,298	US$50,841,688	US$10,209	US$2,225
Age Group																
2-5 years	US$1,038,994,557	US$2,661	US$45,652,342	US$6,822	US$18,377,496	US$9,189	US$5,690	US$10,340,112	US$5,281	US$2,874	US$9,936,172	US$6,398	US$3,363	US$6,998,562	US$5,926	US$2,347
6-11 years	US$1,380,007,924	US$2,692	US$358,346,400	US$8,369	US$209,582,825	US$11,387	US$5,793	US$84,923,417	US$5,490	US$2,605	US$42,437,939	US$6,574	US$3,053	US$21,402,219	US$8,606	US$1,900
12-17 years	US$1,607,561,384	US$3,823	US$325,251,516	US$12,441	US$175,359,749	US$15,250	US$6,590	US$79,943,369	US$8,797	US$2,800	US$47,507,491	US$11,191	US$3,753	US$22,440,907	US$17,104	US$3,501
Gender																
Male	US$2,303,904,600	US$3,387	US$527,625,232	US$9,574	US$293,316,615	US$12,574	US$6,025	US$131,656,987	US$6,699	US$2,690	US$66,230,146	US$7,809	US$3,180	US$36,421,484	US$9,981	US$2,183
Female	US$1,722,659,265	US$2,678	US$201,625,026	US$9,815	US$110,003,455	US$12,824	US$5,981	US$43,549,911	US$6,347	US$2,682	US$33,651,456	US$8,921	US$3,554	US$14,420,204	US$10,834	US$2,390
Race																
White	US$1,345,408,999	US$3,683	US$294,934,588	US$9,249	US$165,354,879	US$12,588	US$6,136	US$88,733,736	US$6,019	US$2,794	US$26,597,506	US$9,248	US$3,382	US$14,248,466	US$12,565	US$2,492
Black	US$706,407,894	US$3,057	US$154,333,823	US$10,562	US$92,395,954	US$13,572	US$5,984	US$28,876,470	US$7,164	US$2,458	US$23,998,637	US$8,639	US$3,090	US$9,062,763	US$9,108	US$2,110
Hispanic	US$1,089,442,820	US$2,751	US$157,771,353	US$8,200	US$90,648,430	US$10,717	US$5,864	US$27,088,996	US$5,948	US$2,567	US$28,795,665	US$6,389	US$3,228	US$11,238,263	US$6,526	US$1,935
Other	US$432,143,018	US$2,567	US$51,193,856	US$10,119	US$29,234,470	US$15,093	US$6,181	US$10,419,899	US$5,988	US$2,549	US$7,111,635	US$8,045	US$3,406	US$4,427,852	US$8,891	US$2,112
Unknown	US$453,161,133	US$2,785	US$71,016,637	US$14,640	US$25,686,338	US$16,403	US$5,818	US$20,087,797	US$13,892	US$2,774	US$13,378,159	US$11,075	US$3,916	US$11,864,343	US$18,802	US$4,588
RUCA codes																
Metropolitan	US$3,662,798,852	US$2,988	US$620,968,436	US$9,922	US$341,251,684	US$12,867	US$6,016	US$139,985,852	US$6,967	US$2,657	US$92,670,242	US$8,183	US$3,312	US$47,060,659	US$10,127	US$2,209
Other[a]	US$363,765,012	US$3,725	US$108,281,822	US$8,289	US$62,068,386	US$11,530	US$5,965	US$35,221,046	US$5,486	US$2,764	US$7,211,360	US$7,771	US$3,097	US$3,781,029	US$11,354	US$2,471
SES[b] indicator																
SSI	US$1,591,074,254	US$16,194	US$350,141,830	US$15,974	US$200,734,553	US$17,876	US$8,060	US$86,004,801	US$12,945	US$4,034	US$39,522,051	US$14,050	US$4,628	US$23,880,425	US$19,352	US$4,585
TANF	US$2,435,489,610	US$1,987	US$379,108,428	US$7,056	US$202,585,517	US$9,798	US$5,274	US$89,202,097	US$4,489	US$2,448	US$60,359,551	US$6,394	US$3,020	US$26,961,263	US$7,197	US$1,954

Note. SSI = Supplemental Security Income; TANF = Temporary Assistance for Needy Families; SES = socioeconomic status; RUCA = rural-urban commuting area.
[a]Other includes micropolitan, small town, rural and out of state/unknown.
[b]SES: SSI and TANF.

Table 3. ADHD-Related Total Medicaid Costs and Per Child Mean and Median Cost for All New York State Children With ADHD Grouped by Treatments Received, 2013.

	All children in Medicaid with ADHD													
	Overall ADHD cohort		Received both psychological services and medication			Received medication only			Received psychological services only			Received neither medication nor psychological services		
	Total costs	Per child *M*	Total costs	Per child *M*	Per child median	Total costs	Per child *M*	Per child median	Total costs	Per child *M*	Per child median	Total costs	Per child *M*	Per child median
Total	US$331,510,569	US$4,389	US$208,197,408	US$6,526	US$3,774	US$67,882,677	US$2,560	US$1,455	US$40,144,650	US$3,297	US$1,485	US$15,285,833	US$3,099	US$413
Age group (years)														
2-5	US$18,829,873	US$2,825	US$9,510,589	US$4,755	US$3,062	US$3,536,453	US$1,806	US$1,089	US$4,135,427	US$2,684	US$1,260	US$1,647,405	US$1,412	US$380
6-11	US$181,448,925	US$4,243	US$118,587,079	US$6,443	US$3,864	US$37,384,713	US$2,417	US$1,497	US$19,112,283	US$2,977	US$1,478	US$6,364,850	US$2,579	US$394
12-17	US$131,231,771	US$5,028	US$80,099,739	US$6,966	US$3,782	US$26,961,512	US$2,967	US$1,464	US$16,896,941	US$4,009	US$1,589	US$7,273,578	US$5,608	US$515
Gender														
Male	US$245,364,441	US$4,460	US$155,603,436	US$6,671	US$3,811	US$51,629,289	US$2,627	US$1,479	US$27,380,352	US$3,250	US$1,435	US$10,751,364	US$2,974	US$414
Female	US$86,146,127	US$4,201	US$52,593,972	US$6,131	US$3,674	US$16,253,388	US$2,369	US$1,386	US$12,764,298	US$3,403	US$1,601	US$4,534,470	US$3,443	US$406
Race														
White	US$124,992,574	US$3,922	US$77,728,853	US$5,917	US$3,635	US$35,218,207	US$2,389	US$1,620	US$8,399,834	US$2,935	US$1,237	US$3,645,681	US$3,232	US$369
Black	US$77,113,410	US$5,290	US$52,403,899	US$7,697	US$4,034	US$11,586,591	US$2,874	US$1,316	US$10,013,356	US$3,637	US$1,491	US$3,109,564	US$3,157	US$435
Hispanic	US$80,137,165	US$4,174	US$52,643,241	US$6,224	US$3,843	US$10,374,967	US$2,278	US$1,239	US$13,469,725	US$3,001	US$1,563	US$3,649,232	US$2,145	US$407
Other	US$21,741,707	US$4,310	US$13,793,039	US$7,121	US$3,678	US$4,265,622	US$2,452	US$1,278	US$3,032,415	US$3,470	US$1,520	US$650,631	US$1,320	US$364
Unknown	US$27,525,713	US$5,692	US$11,628,376	US$7,426	US$3,619	US$6,437,291	US$4,452	US$1,335	US$5,229,321	US$4,361	US$1,853	US$4,230,725	US$6,769	US$591
RUCA codes														
Metropolitan	US$284,030,777	US$4,547	US$179,500,723	US$6,768	US$3,829	US$52,708,445	US$2,623	US$1,398	US$37,932,692	US$3,372	US$1,525	US$13,888,917	US$3,019	US$418
Other[a]	US$47,479,791	US$3,636	US$28,696,685	US$5,331	US$3,523	US$15,174,231	US$2,364	US$1,664	US$2,211,958	US$2,389	US$1,047	US$1,396,916	US$4,220	US$336
SES[b] indicator														
SSI	US$143,451,728	US$6,554	US$96,894,204	US$8,629	US$4,456	US$26,109,426	US$3,930	US$1,690	US$14,148,215	US$5,071	US$1,896	US$6,299,883	US$5,143	US$497
TANF	US$188,058,840	US$3,506	US$111,303,204	US$5,383	US$3,474	US$41,773,251	US$2,102	US$1,395	US$25,996,435	US$2,770	US$1,400	US$8,985,950	US$2,424	US$392

Note. SSI = Supplemental Security Income; TANF = Temporary Assistance for Needy Families; SES = socioeconomic status; RUCA = rural -urban commuting area.
[a]Other includes micropolitan, small town, rural and out of state/unknown.
[b]SES: SSI and TANF.

services among all children with ADHD, and ranged from US$0 to US$454,734. The median for ADHD-related costs ranged from US$413 among children with ADHD receiving neither medication nor psychological services to US$3,774 among children with ADHD receiving both treatment types.

Discussion

This study estimated the proportion of children receiving clinical care for ADHD and types of treatments these children received, as well as estimates of the total and ADHD-related costs for children aged 2 to 17 years covered by Medicaid in one large state (New York) in 2013. There were some noted sociodemographic differences associated with receipt of different treatment combinations among children with ADHD. Children receiving both medication and psychological services were more likely to be 6 to 17 years old, of Black race, or receiving SSI, whereas children receiving medication alone were more likely to be White, living in a nonmetropolitan area or receiving TANF; and children receiving psychological services alone were more likely to be 2 to 5 years of age, non-White, or living in a metropolitan area. These sociodemographic differences may reflect differences in presence of cooccurring conditions (particularly for children receiving SSI), family treatment preferences, or availability of treatment services (Finnerty et al., 2016; Koerting et al., 2013).

Average costs for children enrolled in Medicaid receiving clinical care for ADHD were US$9,640 in 2013, compared with average costs of US$3,042 for all children enrolled in Medicaid in 2013. This finding of higher average costs for children with ADHD is consistent with results for other populations, though the net difference in average annual cost is higher in New York Medicaid than in other published studies (Matza, Paramore, & Prasad, 2005). This may partially be explained by variations between states, such as differences in services covered by Medicaid or differences in reimbursement rates, as well as rising costs related to health care over time. The finding of higher average costs for children with ADHD compared with all children in Medicaid persisted across each sociodemographic subgroup with the exception of children receiving SSI. This is likely due to the higher medical costs associated with the physical or mental condition(s) that qualified these children for SSI, and the costs associated for children with ADHD in this group were not higher than for children without ADHD who qualified for SSI based on another condition.

Children with ADHD receiving both psychological services and medication had the highest average cost per child (US$12,641) in 2013. However, despite having no costs for ADHD-related medication or psychological services, children with ADHD who received neither treatment had higher overall mean expenditures (US$10,209) than those receiving only one type of treatment. The finding of higher overall costs for children with ADHD receiving both medication and psychological services than children with ADHD receiving medication alone was similar to results from a recently published analysis of 2002-2011 Medical Expenditure Panel Survey (MEPS) data (deJong, Williams, & Thomas, 2016). However, the group reporting neither medication nor counseling in the MEPS study had lower annual costs than the groups receiving treatment, which contrasts with the results found for the New York Medicaid population. The higher costs for children with ADHD receiving neither type of treatment in the current study may be due to the use of care related to cooccurring conditions or acute health events such as unintentional injury, though the presence of cooccurring conditions or frequency of acute events was not explored in this analysis. The median costs served as another indicator for measuring central tendency in cases when there were a few children that incurred extreme high Medicaid expenses that influenced the average expense. The median costs among children receiving neither treatment are lower than that for other treatment groups, suggesting that a small number of children with high costs drove the higher mean costs for this group.

Study Strengths and Limitations

This study provides unique and new information on childhood ADHD prevalence, treatment patterns, and their associated costs in NYS. Our findings revealed several sociodemographic differences associated with health care costs and treatment types for children receiving clinical care for ADHD, including differences by age, gender, and race/ethnicity. A major strength of the study is that it may provide a framework to identify children with ADHD and, based on their treatment categories and sociodemographics, better target interventions to them that may improve the quality of their care and reduce unnecessary utilization.

Nearly one out of 10 children (8.9%) receiving clinical care for ADHD in the New York Medicaid program was aged between 2 years and 5 years. Although this group represented a somewhat disproportionately low fraction of total expenditures for children with ADHD (6.3%), an opportunity exists to implement cost-effective approaches to treatment in this population. For example, parent behavioral training is as effective as medication for treating ADHD in this age group (Charach et al., 2011), and evidence suggests that initiating treatment with parent behavioral training incurs less cost over a school year than starting treatment with medication (Page et al., 2016). Although our analyses did not address the sequence of treatment types received by these young children receiving clinical care for ADHD (i.e., degree of alignment with AAP treatment guidelines), our study found that nearly half of children (46.9%) in this age group had not received any psychological services in 2013. This is valuable information, suggesting an opportunity to

increase the proportion of young children who receive treatment in line with clinical guidelines (AAP, 2011).

The results of this study are also subject to several limitations. This analysis only included children actively being managed for ADHD during one calendar year, and therefore, estimates do not represent the underlying prevalence of the disorder in this population because children with ADHD who did not receive the minimum services reimbursed through Medicaid claims to meet the study ADHD case definition would not be identified in this sample. Also, grouping children into mutually exclusive treatment groups based on the evidence of at least one visit for a psychological treatment service or medication received, rather than requiring a higher number of medication or psychological treatment services claims, might have led to different conclusions regarding the utilization of services for ADHD than if different thresholds were used to characterize receipt of medication or psychological treatment services. For this analysis, we focused our estimates on broad categories of treatment received for ADHD (medication and psychological services), and did not individually quantify associated costs for other ADHD-related services, such as medication management visits or diagnostic testing. Only direct medical costs over a single calendar year were used in this study. Patients' out-of-pocket costs, costs related to additional coverage outside of Medicaid, and indirect costs, such as costs related to traveling to appointments and missing work, were not included in the analysis (Guevara et al., 2001), nor were changes in service utilization or associated costs over time. Other than the identification of children in Medicaid receiving SSI (indicating that these children had a qualifying disability), we did not explicitly adjust for the presence of cooccurring conditions or severity of ADHD, both of which may have affected the types and amount of treatment received and the magnitude of associated payments. Finally, even though this study concluded that the 5.4% of the total Medicaid group with ADHD accounted for 18.1% of the total costs for all children in Medicaid in 2013 (Table 2), it did not consider the relationship between expenditures and effectiveness of ADHD management (i.e., whether increased expenditures resulted in better outcomes for children with ADHD). The relationship between expenditures and outcomes may warrant further investigation in future studies.

Policy Implications

In the spring of 2015, NYS' Medicaid leadership convened a group to develop a roadmap for redefining the provider payment system by advancing VBP. VBP is a strategy to structure health care provider payment to reward the quality and efficiency of health care delivery. The Medicaid program in NYS has several population groups who have complex, high-cost medical needs. Children do not usually constitute a large proportion of these population groups; however, this analysis has underscored the importance of understanding the population of children with ADHD on Medicaid. In 2013, the ADHD cohort comprised 5.4% of the total Medicaid pediatric population, but the total costs for the ADHD cohort accounted for 18.1% of the total costs for all children in Medicaid. Almost half of total Medicaid costs for the ADHD cohort (US$331.5 million) were for ADHD-related treatment and services, indicating this may be a group to consider targeting for opportunities to offer better-coordinated and more efficient care. Future work may help to determine whether investment in such treatment improvements leads to better long-term outcomes for children by reducing potentially avoidable emergency department visits or hospitalizations, as well as potentially reducing other health care utilization, therefore, resulting in overall lower medical costs compared with children who received less or no treatment. Health insurance plans, health care providers, and parents can work together to ensure that children with ADHD are receiving the most appropriate and cost-effective treatment for these children to achieve optimal outcomes.

Authors' Note

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the New York State Department of Health, the Centers for Disease Control and Prevention, the Department of Health and Human Services, or AUCD. Examples of analysis performed within this publication are only examples. They should not be utilized in real-world analytic product.

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The Estimated Annual Cost of ADHD to the U.S. Education System

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Abstract

The purpose of this study was to examine and monetize the educational outcomes of students with ADHD. Data were examined from the Pittsburgh ADHD Longitudinal Study (PALS), a follow-up study of children diagnosed with ADHD in childhood and recontacted for follow-up in adolescence and young adulthood. A comprehensive educational history was obtained for all participants from Kindergarten through 12th grade. Annual economic impact was derived from costs incurred through special education placement, grade retention, and disciplinary incidents. Results indicated that, as compared to students without ADHD, students with ADHD incurred a higher annual cost to the U.S. Education system. Specifically, a student with ADHD incurred an average annual incremental cost to society of $5,007, as compared to $318 for students in the comparison group. These results suggest that prevention and intervention strategies are greatly needed to offset the large financial impact of educating youth with ADHD.

Attention Deficit/Hyperactivity Disorder (ADHD) is a chronic mental health disorder characterized by deficits in attention span, impulse control, and regulation of activity level that impair daily life functioning (APA, 2000). Recent prevalence estimates assume ADHD to be present in up to 10% of children and adolescents in the United States (CDC, 2007). Because youth with ADHD typically demonstrate impairment across multiple domains of functioning (i.e., academics, peer relations, family conflict, delinquency; Barkley, 2006), the effects of this disorder are widespread. For years research has assessed the impact of ADHD upon the individual (e.g., peer relationship difficulties, Pelham & Bender, 1982; increased use of illicit substances, Mannuzza et al., 1991; and lower occupational rank, Mannuzza et al., 1993), and upon the family (e.g., strained parent-child relationships, Patterson & Chamberlain, 1994; Mash & Johnston, 1990). Less work has investigated the consequences of ADHD at the societal level.

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The economic impact of physical disease (e.g., for coronary heart disease; Weinstein et al, 1987) and mental health disorder (Chiles, Lambet, & Hatch, 2002) has long been used to indicate an identified illness's cumulative effect upon society. To date, very few studies have monetized the societal impact of ADHD. Although some work has examined medical costs of ADHD, such as health care system and medication utilization (Birnbaum et. al., 2005; Hakkaart-van Roijen et. al., 2007; Kelleher, Childs, & Harman, 2001), little research has monetized the societal consequences of ADHD-related impairments. Using existing data on health care and mental-health care utilization (e.g. inpatient care, outpatient care, office visits), medication utilization, education costs, juvenile delinquency costs, and work-loss costs, Pelham, Foster, and Robb (2007) estimated the annual cost of ADHD to society at approximately $14,500 per child ($42.5 billion total). Additional studies have measured and monetized the impact of ADHD in very specific sectors: annual special education service utilization [$5435 (1995 dollars); Forness & Kavale, 2002], annual utilization of public services in adolescence [i.e., inpatient mental health ≈ $1300, juvenile justice system ≈ $200, outpatient mental health ≈ $500, and special education ≈ $3000 (2000 dollars); Jones & Foster, 2009], loss of employee productivity (≈ $4,000; Hakkaart-van Roijen et. al, 2007; Kessler, Lane, Stang, & Van Brunt, 2009; Kleinman, Durkin, Melkonian, & Markosyan, 2009).

When monetizing the costs associated with ADHD, one domain of impact that deserves detailed attention is the education system. Children and adolescents with ADHD commonly experience their most salient and severe impairments in the academic setting (DuPaul & Stoner, 2003; Loe & Feldman, 2007; Robin, 1998). Observations of children with ADHD in classroom settings have documented that as compared to classmates, they are more frequently off-task, complete fewer assignments, possess poorer work accuracy, interfere more with classmates' work, violate more classroom rules, and are less likely to comply with adult requests and demands (Atkins, Pelham, & Licht, 1985, 1989). These behaviors contribute to greater utilization of special educational services by children with ADHD (Forness & Kavale, 2002), lower levels of academic achievement (Swanson et al., 2000), and higher rates of disciplinary referrals, retention, and later dropout (e.g., DuPaul & Stoner, 2003; Kent et al., in press; Mannuzza & Klein, 1999). As a result, students with ADHD are a substantial source of stress for their teachers, principals, and classmates (Greene, Beszterczey, Katzenstein, Park, & Goring, 2002).

Monetary estimates of special education utilization by youth with ADHD are available (Forness & Kavale, 2002; Jones, Foster, & CPPRG 2009); however, these estimates are limited, and must be expanded to determine a more accurate estimate of the educational costs associated with ADHD. Forness and Kavale (2002) estimated the cost of special education attributable to ADHD at $3.2 billion annually (1995 dollars), or approximately $3500 in excess costs per child with ADHD. The authors noted that their figure was likely underestimated as they did not have data on more restrictive settings or on children with ADHD in regular classroom settings (e.g., accommodations in 504 plans or disciplinary actions). Jones and colleagues (2009) examined educational service utilization in adolescence [i.e., parental report of special education utilization, participation in school counseling, and retention over a four-year period (ages 12-15)]. The authors estimated incremental education costs at approximately $3400 per ADHD child annually and ADHD

youth with comorbid Conduct Disorder accounted for a significantly higher cost—approximately $4000 per child annually. Jones and colleagues utilized data from the Fast Track sample, which over-sampled high risk children. As a result, their estimate for the incremental cost of ADHD was likely an underestimate, as the comparison group displayed above-average levels of problem behavior. Also, no index of disciplinary action was assessed and data were only collected from the secondary school years.

The present study aims to provide a more comprehensive estimate of the educational costs associated with ADHD by examining data from a prospective longitudinal study of individuals diagnosed with ADHD in childhood and a demographically similar comparison group on non-ADHD individuals. Specifically, these analyses will expand upon previous studies by including: 1) data from more restrictive settings, such as alternative school placement, 2) costs associated with disciplinary infractions in general and special education classrooms, 3) data from the entire educational history, including the secondary school years, and 4) a well-diagnosed clinical sample of children with ADHD and a demographically similar comparison group. This estimate will be derived by calculating costs associated with special education use (LD and ED categories), approved private schooling, grade retention, and disciplinary needs, using a Cost-of-Illness framework (Kenkel, 1994; Kenkel, Berger, & Blomquist, 1994; see Methods). It is hypothesized that students diagnosed with ADHD will have higher use of special education services of all types, will display higher rates of grade retention, and will receive more disciplinary actions, thereby incurring higher overall COI than the comparison group.

Method

Participants

ADHD group—The ADHD group was recruited from a pool of 516 study-eligible participants diagnosed with DSM-III-R or DSM-IV ADHD in childhood and treated in the Summer Treatment Program (STP) of the Attention Deficit Disorder clinic at the Western Psychiatric Institute and Clinic (WPIC) in Pittsburgh, PA from 1987 to 1996. Of the 516, 493 were re-contacted an average of 8.35 years later (SD = 2.79) to participate in annual interviews of the Pittsburgh ADHD Longitudinal Study (PALS). Of those contacted, 364 (70.5 %) enrolled in the PALS. At the first follow-up interview, the ADHD group ranged in age from 11 to 28 with 99% falling between 11 and 25 years of age. They were admitted to the follow-up study on a rolling basis between the years 1999-2003 and completed their first follow-up interview immediately upon enrollment. Participants in the follow-up study were compared with the eligible individuals who did not enroll on demographic (i.e., age at first treatment, race, parental education level, and marital status) and diagnostic (i.e., parent and teacher ratings of ADHD and related symptomatology) variables collected at baseline. Only one of 14 comparisons was statistically significant at the $p<.05$ significance level. Participants had a slightly lower average CD symptom rating on a four point scale as indicated by a composite of parent and teacher ratings (participants $M = 0.43$, non-participants $M = 0.53$).

Comparison Group—Comparison participants were 240 individuals without ADHD. Comparison participants were recruited for the PALS from the greater Pittsburgh community between 1999 and 2001. These individuals were recruited from several sources including pediatric practices in Allegheny County (40.8%), advertisements in local newspapers (27.5%), local universities and colleges (20.8%), and other methods (10.9%) such as Pittsburgh Public Schools and word of mouth. Comparison recruitment lagged three months behind the ADHD group enrollment in order to facilitate efforts to obtain demographic similarity (discussed below). A telephone screening interview was administered to parents of potential comparison participants to gather basic demographic characteristics, history of diagnosis or treatment for ADHD and other behavior problems, presence of exclusionary criteria as previously listed for the ADHD group, and a checklist of ADHD symptoms. Young adults in the comparison group (age 18+) also provided self-report of ADHD symptoms. ADHD symptoms were counted as present if reported by either the parent or the young adult. Participants who met DSM-III-R criteria for ADHD, either currently or historically, were immediately excluded from PALS consideration. If a potential comparison participant passed the initial phone screen, senior research staff members met to determine whether he/she was demographically appropriate for the study. Each potential comparison participant was examined on four demographic characteristics: 1) age, 2) gender, 3) race, and 4) parent education level. A comparison participant was deemed study-eligible if his/her enrollment increased the comparison group's demographic similarity to the participants diagnosed with ADHD. At the end of the recruitment process, the two groups were equivalent on the four demographic variables noted above.

Childhood Assessment

As noted above, participants in the ADHD group attended the STP at WPIC during childhood. Mean age for participants at childhood diagnostic evaluation was 9.40, *SD* = 2.27, and ranged from 5.00 to 16.92 years with 90% between 5 and 12. At the time of the STP, children with ADHD underwent a diagnostic assessment including parent and teacher Diagnostic and Statistical Manual of Mental Disorders (DSM–III–R and DSM–IV; American Psychiatric Association, 1987, 1994) symptom rating scales (DBD; Pelham, Evans, Gnagy, & Greenslade, 1992) and a semi-structured diagnostic interview administered to parents by a Ph.D. level clinician. The interview consisted of the DSM-III-R or DSM-IV descriptors for ADHD, ODD, and CD with supplemental probe questions regarding situational and severity factors. It also included queries about other comorbidities to determine whether additional assessment was needed (instrument available at http://ccf.fiu.edu). Following DSM guidelines, diagnoses of ADHD, ODD, and CD were made if a sufficient number of symptoms were endorsed (considering information from parents and teachers). Two Ph.D. level clinicians independently reviewed all ratings and interviews to confirm DSM diagnoses and when disagreement occurred, a third clinician reviewed the file and the majority decision was used.

Procedure for PALS Interviews

PALS interviews were conducted yearly beginning with the year of enrollment. Post-baccalaureate research staff conducted interviews. Informed consent was obtained, and all participants were assured confidentiality except in cases of impending danger or harm to self

or others. In cases where distance prevented participant travel to WPIC, information was collected through a combination of mailed and telephone correspondence; home visits were offered as needed. Self-report questionnaires were completed either with pencil and paper or computerized web-based versions. Confidentiality of information was supported with a Certificate of Confidentiality from the Department of Health and Human Services with certain exceptions (e.g., suicidality, child abuse), and the protocol was approved by the University of Pittsburgh Institutional Review Board. The current study utilizes longitudinal data from the first eight annual follow-up visits (gathered from 1999-2008), at which point all participants had completed high school.

Measures

The Education History Questionnaire was developed by adapting measures used in the PAARC (Pittsburgh Adolescent Alcohol Research Center) and CEDAR (Center for Education and Drug Abuse Research) studies and was used to gather educational information in the PALS. The Education History Questionnaire is a retrospective report from parents (supplemented by a self-report from probands if parents were not available) regarding educational history from kindergarten through college-level education. For each year, respondents indicated the school(s) that probands attended, their placement (e.g., special education versus regular classroom), whether probands were retained, whether they received additional services, and estimates of how many disciplinary referrals the probands had received. This measure was given during the initial follow-up assessment and updated at every subsequent follow-up visit, thereby ensuring that the most recent educational information has been gathered.

Framing the Cost of Illness Analysis

The societal perspective is recognized as the gold standard perspective for an economic analysis (Gold, Russell, Siegel, & Weinstein, 1996; Siegel, Weinstein, Russell, & Gold, 1996), as it takes into account the total effect of a disorder on all members of a society. This perspective can also be complemented by other perspectives (such as the familial, institutional, or individual), which identify who will be responsible for the costs of a program or service. The COI application in this report discusses three perspectives: 1) the ADHD individual, 2) other members within the setting affected by the ADHD individual (e.g., classmates), and 3) the education system. Additionally, a COI study involves the specification of a time frame. In this analysis, the educational lifetime of the individual is used (Kindergarten through 12^{th} grade). Finally, specification of the types of cost included in the analysis is essential to define the nature and scope of the cost-analysis. COI analyses require both an outcome that creates the costs (e.g., number of special education placements) and a per-unit cost of that behavior or outcome (e.g., per-pupil expenditure for special education services).

The first outcome of our analyses is educational placement. Many ADHD children are eligible for special education services under the Individuals with Disabilities Education Act (IDEA) and receive related services at a rate higher than children without ADHD (Forness & Kavale, 2002). The most typical category placement for students with ADHD are within the Learning Disability (LD) category, the Emotional Disturbance (ED) category, and the

Other Health Impaired (OHI) category; prevalence rates of ADHD within these categories being 26%, 43%, and 40% respectively (Forness & Kavale, 2002). The second outcome involved in our analysis is grade retention. Numerous studies have shown that students with ADHD are more likely to repeat a grade than peers (Barkley et al., 2006; Barkley, Murphy, & Fischer, 2007; Barbaresi et al., 2007; Biederman et al., 1998; Faraone et al., 1993; Molina et al., 2009). However, the economic impact of this variable has not been examined in an ADHD sample. The final outcome of our analysis is disciplinary acts committed by ADHD students. The majority of these incidents occur while the student is in a classroom and it is likely that every classroom in the U.S. includes at least one child with ADHD. Thus, the COI framework involves both the teacher's involvement with the disciplinary incident and the incident's impact on classmates. For disciplinary acts that involve school staff beyond the teacher (e.g., principal and guidance counselor office visits, suspensions, expulsions), costs increase accordingly.

Cost of Special Education Utilization—Monetary costs associated with the utilization of special education were derived from the United States Department of Education, Special Education Expenditure Project (Chambers, Shkolnik, & Perez, 2003). In our sample, type of special education [specific learning disability (SLD) vs. serious emotion disturbance, (SED)] was differentiated. In 2003 dollars, average per student cost was reported to be $10,558 for SLD placement and $14,177 for SED placement. These estimates were converted to 2010 dollars (SLD= $12,549; SED=$16,815) using the Bureau of Labor Statistic's Consumer Price Index. Cost for approved private schooling (educational day-treatment) was taken from the same report (Chambers et al., 2003) and was reported to be $25,580 (2003 dollars). This estimated was also converted to 2010 dollars ($30,406).

Cost of Grade Retention—In order to provide the most accurate estimate of the cost of grade retention, educational placement (i.e., regular, SLD, SED, approved private placement) was considered during the year in which the student was held back. The costs of education noted above (Chambers et al., 2003) and the cost of regular education ($6,556 in 2003 dollars; converted to 2010 dollars = $7,793) were used to monetize the cost of spending an additional year in the public education system.

Cost of Discipline—Disciplinary incidents were defined as the summed frequencies of times sent to the principal's or guidance counselor's office, verbal warnings, written warnings, and/or detentions. Suspensions and expulsions were examined separately, as the costs associated with these incidents are estimated to be higher. Methodology for establishing cost of discipline was derived from two sources. Estimates of administrator time spent on discipline were derived from Scott and Barrett (2004) report. These authors examined school discipline records, and estimated that the average office disciplinary referral process translated into 10 minutes of administrator time, while the average suspension translated into 45 minutes of administrator time. Using direct observation procedures, Scime and colleagues (2008, February) calculated that teachers spent an average 17 minutes on each classroom disciplinary incidents, while the target student spends an average of 60 minutes engaged in the process of each disciplinary action. Furthermore, one could reasonably presume that time spent by a teacher handling an insubordinate student is

time that is not being spent on curriculum instruction, and is therefore wasted time to the other students in a classroom. Thus, the 17 minutes spent by the teacher is extrapolated to the other children in the classroom using an average class size of 21 (Fabiano et al., 2001, April). Cost of discipline was then monetized by using average cost of employment and average costs to educate a non-special education student, using national labor statistics on teacher and principal salaries (See Table 3).

Results

For all analyses, one-way ANOVAs were conducted to compare the ADHD group and the comparison group on means and/or costs.

Cost of Special Education Utilization

Years spent in SLD placement, SED placement, and approved private placement were summed and youth with ADHD (*M*= 3.68, *SD*=4.29) received special education services for significantly more years than children without ADHD [*M*= .21; *SD*= 1.32, *F*(1,601)=147.51, *p*<.001, *d*=1.01]. Frequency and proportion rates are presented in Table 2. The incurred cost for youth with ADHD and comparison youth were calculated by multiplying previously presented cost estimates for type of special education and years in approved private schooling and summing across years of schooling (Kindergarten through grade 12). As such, average cost of special placement per year was significantly higher for the ADHD group (*M*=$4,181, *SD*=$5,009) than for comparison [*M*=$211, *SD*=$1,294, *F*(1,592)=143.57, *p*<.001, *d*=.94].

Cost of Grade Retention

Over the course of their educational careers, youth with ADHD (*M*= .40, *SD*= .70) repeated a grade at a significantly higher rate than the comparison group, [*M*= .08, *SD*=.33, *F*(1,582)=43.98, *p*<.001, *d*=.97]. Consequently, youth with ADHD (*M*=$222, *SD*=$429) incurred significantly more cost per year owing to grade retention than the comparison group [*M*=$43, *SD*=$186, *F*(1,601)=37.01, *p*<.001, *d*=.51].

Cost of Discipline

Youth with ADHD had significantly more reported acts of misbehavior that resulted in disciplinary action than the comparison group (see Table 4 & 5). Additionally, youth with ADHD, as compared to the comparison group, had significantly more disciplinary infractions that resulted in in- or out- of school suspensions or expulsion (see Table 5) Across stakeholders, youth with ADHD incurred significantly higher cost for acts of discipline, suspensions, and expulsions than the comparison group (see Table 5). These costs were then summed to compute a single disciplinary cost. On average, youth with ADHD incurred an annual cost to the education system of $604 (*SD*=$1,132) owing to disciplinary incidents. This figure was $63 (*SD*=$126.58) in the comparison group.

Discussion

Our study represents the first attempt to compute lifetime educational costs for a well-diagnosed clinical sample of children with ADHD followed through the entirety of their school years in comparison to a demographically similar non-ADHD group. Our results showed that: 1) students with ADHD had very poor school outcomes with respect to special educational services, grade retention, and school discipline and 2) these outcomes directly translated into a higher monetary cost of education as compared to comparison individuals.

Our findings are consistent with existing literature, which documents impaired school and scholastic functioning in youth with ADHD (Barkley et al., 2006; Biederman, Faraone, Milberger, & Guite, 1996; Hinshaw, 1992; Kent et al., in press; Molina et al., 2009). However, we expand upon this literature by producing a monetary estimate of the impact of these impairments. As previously noted, the existing literature on the educational cost associated with ADHD suggests incremental costs associated with special education placement (Forness & Kavale, 2002; Jones et al., 2009). Our study builds upon estimates of educational costs by examining students' entire educational history of special education expenditures, grade retention, and disciplinary incidents as compared to a comparison group.

Aggregating costs associated with special education placement ($4181), grade retention ($222), and disciplinary incidents ($604), we arrive upon an annual estimate of $5,007 in incremental costs to the education system. This estimate is consistent with previous work suggesting that the education system is the public sector that bears the greatest societal cost of ADHD (Pelham et al., 2007). This cost does not include annual funds typically apportioned for regular education ($7,793 per year; Chambers et al., 2003) and is significantly higher than the corresponding estimate in the comparison group ($318). Assuming a conservative prevalence rate of 5% for ADHD in childhood and adolescence, and extrapolating these results to the U.S. population between the ages of 5-18 (U.S. Census Bureau, 2009), the estimated annual costs associated with ADHD total $13.4 billion to the U.S. Education System. Thus, the incremental lifetime cost of educating the population of children with ADHD is approximately $174 billion over 13 years of education. This estimate is nearly 50% higher than that reported from the Fast Track study sample, and 5 to 7 times greater than Forness and Kavale's (2002) estimates.

One must note that an economic analysis does not result in a static monetary figure (Foster, Dodge, & Jones, 2003) as variability in analytical assumptions influences overall estimates. A notable example of this tenet emerges in our study. The oldest participants in the PALS began their schooling in 1980, but ADHD students became eligible for special education services under the OHI categorization during the 1992 school year (Forness & Kavale, 2002). Forness and Kavale estimated a 68% increase in the number of children with ADHD utilizing special education services following the introduction of this regulation. In the present study, data collected on special education categorization was limited to either LD or SED, even for years after the 1992 legislation. Thus, though higher than previous estimates, our estimate of special education costs may be low by modern standards. Furthermore, in our study, as well as the Fast Track study (Jones et al., 2009), the sample received treatment.

It is also possible that receiving treatment for ADHD reduces the economic impact of an individual with this disorder.

As with other educational handicaps such as physical and developmental disabilities, the cost estimates presented in our analyses are substantial. However, they likely represent only a subset of the true cost of ADHD within the educational domain. For instance, the impact of long-term failure on children's outcomes, such as vocational earnings or college entrance, was not assessed. The analyses also did not include costs of educational testing, committee hearings (e.g., for IEP contracts), tutoring, or time for parent-teacher conferencing. Further, our estimates did not assess the costs of Section 504 plan accommodations. If every ADHD child in a regular classroom received a 504 plan, the incremental administrative costs and teacher time associated with implementation would also dramatically increase the estimated total incremental costs. Unfortunately, we are not aware of any data regarding the prevalence of 504 utilization by students with ADHD.

There are several limitations to our study. First, it is possible that comorbid conditions contributed to problems that qualified participants for special education placement. In addition, this study reported on a predominately middle-class sample from one locality—Pittsburgh, PA (see Table 1). Similar studies are needed with samples possessing greater geographic and demographic diversity. It is also probable that referral practices to special education, response to disciplinary infractions. and resource availability vary as a function of locality- rural v. suburban v. urban setting- and replication of educational costs will be needed. Educational data obtained in this study were a combination of retrospective and prospective report. Thus, another limitation to this study is the utilization of retrospective data. Further, the relative proportion of educational services provided for girls as compared to boys with ADHD is unknown; however, one could speculate that because girls with ADHD are under-diagnosed, they are likely under-recognized within the educational domain as well. If this is the case, then their educational costs would be deflated. Given that approximately 10% of our sample is female, we may have underestimated educational cost within this subset of the ADHD population. Unfortunately, our subsample of girls was too small to analyze independently. Replication of this work is needed with emphasis on additional educational outcomes.

Despite its limitations, the present study offers clear evidence that students with ADHD incur a substantial cost the U.S. Education System. Future research should assess the influence of prevention efforts upon the educational costs of ADHD, as special education placement is likely a result of academic underachievement and disciplinary incidents are likely a result of treatable behavior problems. Implementing preventive disciplinary strategies and proactive academic supports may prove fruitful in offsetting high cost services such as special education and/or intensive disciplinary infractions (e.g. suspension). Furthermore, there is evidence that stimulant medication, behavior therapy, and their combination yield long-term cost-benefit in treating ADHD (Foster et al., 2007; Jensen et al., 2005). It is our hope that over the next decades, greater attention to prevention and intervention will lead to decreases in the incremental costs of educating a youth with ADHD.

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Table 1
Characteristics of the Sample at First Follow-up Visit

	Comparison	ADHD
N	**240**	**364**
Demographic Variables		
Age (M, SD)	17.17 (3.16)	17.75 (3.39)
Gender (% Female)	11.3 (.32)	10.4 (.31)
Racial Minority (%)	15.4	18.4
African-American (%)	9.2	11.0
Other (%)	6.2	7.4
Highest Parent Education[a] (M, SD)	7.41 (1.65)	7.14 (1.62)
High School Grad or GED (%)	8.1	9.1
Part College or Specialized Training (%)	30.2	39.8
College or University Grad (%)	27.2	26.0
Graduate Professional Training (%)	34.5	25.1
% Single Parent Household	23.6	33.2
Age at Assessment in Childhood (M, SD)	NA	9.4 (2.27)
Follow-Up Interval (M, SD)	NA	8.35 (2.79)

Note.

[a]Response scale for parent education ranged from 1 (<7th grade education) to 9 (graduate professional training). 4=high school graduate or GED; 5= specialized training; 6=Partial College; 7+ Associate's or 2-year degree; 8= standard college or university graduation. Ns ranged from 229 to 240 and from 328 to 364 for Comparison and ADHD respectively. (Ns for parental income are 203 for Comparison and 291 for ADHD due to subjects' willingness to provide salary information.)

Table 2

Years in Special Education or Approved Private Placement

Years	*N* ADHD	% ADHD	*N* Comparison	% Comparison
Special Education- Learning Disabled				
0	169	47.6%	232	97.1%
1-3	64	18.0%	1	.4%
4-6	43	12.2%	2	.8%
7+	79	22.2%	4	1.7%
Special Education- Emotional Disturbance				
0	324	91.3%	236	98.7%
1-3	20	5.6%	3	1.3%
4-6	5	1.5%	0	0.0%
7+	6	1.7%	0	0.0%
Approved Private Placement				
0	325	91.6%	239	100.0%
1-3	15	4.2%	0	0.0%
4-6	12	3.3%	0	0.0%
7+	3	0.9%	0	0.0%

Table 3
Estimated Cost of a School Disciplinary Act

	Involvement per Disciplinary Act	Involvement per Suspension/Expulsion	Incurred Cost
Administrators	10 minutes	45 minutes	$0.78 per minute
Guidance Staff	10 minutes	---	$0.65 per minute
Teachers	17 minutes	17 minutes	$0.57 per minute
Target Student	60 minutes	360 minutes	$0.12-$0.46 per minute
Classmates	17 minutes	---	$0.12-$0.46 per minute

Note. Cost per minute was extrapolated from annual salaries for school personnel as reported by the U.S. BLS (2010) and the annual per student cost of education as reported by SEEP (2004): Administrators = $83,880; Guidance Staff = $57,800; Teachers = $50,500; Student = $7,793 (regular education) - $30,406 (approved private placement).

Table 4
Frequency of Disciplinary Incidents across Grades K-12

	ADHD	Comparison
At least once a week	5.8%	0.0%
At least once a month	29.6%	2.5%
At least once a quarter	45.5%	7.9%
Less than once a quarter	19.1%	89.6%

Table 5
Annual Costs of Disciplinary Acts, Suspensions, and Expulsions per Student

	ADHD *Mean (SD)*	Comparison *Mean (SD)*	*Cohen's d*
Number of Disciplinary Acts	8.50(15.80)	.99(2.02)*	.62
Number of Suspensions/Expulsions	.97 (2.05)	.10(.30)*	.55
Cost to Administrators	$108.75 (312.57)	$8.83 (20.12)*	.42
Cost to Guidance Staff	$6.52(14.84)	$0.84(3.91)*	.49
Cost to Teachers	$42.65(92.12)	$3.38(10.59)*	.55
Cost to Target Student	$73.02 (135.95)	$7.09(18.18)*	.63
Cost to Classmates[a]	$380.74(674.91)	$43.29(87.17)*	.65

Note. $p<.01$ for all comparisons.

[a]Cost estimated at 21 students (Fabiano et al., 2001, April) for a class in a regular education setting ($0.12/minute).

EXHIBIT 87

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Child Development

Learning Disorders in Children

Many children may struggle in school with some topics or skills from time to time. When children try hard and still struggle with a specific set of skills over time, it could be a sign of a learning disorder. Having a learning disorder means that a child has difficulty in one or more areas of learning, even when overall intelligence or motivation is not affected.

Some of the symptoms of learning disorders are

- Difficulty telling right from left
- Reversing letters, words, or numbers, after first or second grade
- Difficulties recognizing patterns or sorting items by size or shape
- Difficulty understanding and following instructions or staying organized
- Difficulty remembering what was just said or what was just read
- Lacking coordination when moving around
- Difficulty doing tasks with the hands, like writing, cutting, or drawing
- Difficulty understanding the concept of time

Examples of learning disorders include

- Dyslexia – difficulty with reading
- Dyscalculia – difficulty with math
- Dysgraphia – difficulty with writing

Children with learning disorders may feel frustrated that they cannot master a subject despite trying hard, and may act out, act helpless, or withdraw. Learning disorders can also be present with emotional or behavioral disorders, such as attention-deficit/hyperactivity disorder (ADHD), or anxiety. The combination of problems can make it particularly hard for a child to succeed in school. Properly diagnosing each disorder is crucial, so that the child can get the right kind of help for each.

Treatment for learning disorders

Children with learning disorders often need extra help and instruction that are specialized for them. Having a learning disorder can qualify a child for special education services in school. Schools usually do their own testing for learning disorders to see if a child needs intervention. An evaluation by a healthcare professional is needed if there are other concerns about the child's behavior or emotions. Parents, healthcare providers, and the school can work together to find the right referrals and treatment.

Learn more about LD

Helping children with learning and attention issues

What every parent should know...

Children with specific learning disabilities are eligible for special education services or accommodations at school under the Individuals with Disabilities in Education Act (IDEA) and an anti-discrimination law known as Section 504.

Learn more about education services and accommodations

Read the guidelines from the U.S. Department of Justice Disability Rights Section about testing accommodations for individuals with disabilities. [263 KB / 9 pages]

Get help from your state's Parent Training and Information Center

The role of healthcare providers

Healthcare providers can play an important part in collaborating with schools to help a child with learning disorders or other disabilities get the special services they need. The American Academy of Pediatrics (AAP) has created a report that describes the roles that healthcare providers can have in helping children with disabilities, including learning disorders:

1. Identifying children in need of early intervention or special education services.
2. Sharing relevant information with early intervention or school personnel.
3. Meeting with early intervention or school personnel and parents or guardians.
4. Using early intervention or school information in medical diagnostic or treatment plans.
5. Working within an early intervention, school, or school-based health clinic.
6. Working at an administrative level to improve school functioning around children with special needs.

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EXHIBIT 88

Mental Disorders and Disabilities Among Low-Income Children

DETAILS

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AUTHORS

Thomas F. Boat and Joel T. Wu, Editors; Committee to Evaluate the Supplemental Security Income Disability Program for Children with Mental Disorders; Board on the Health of Select Populations; Institute of Medicine; The National Academies of Sciences, Engineering, and Medicine

Mental Disorders and Disabilities Among Low-Income Children

Committee to Evaluate the Supplemental Security Income Disability Program for Children with Mental Disorders

Thomas F. Boat and Joel T. Wu, *Editors*

Board on the Health of Select Populations

Board on Children, Youth, and Families

Institute of Medicine

Division of Behavioral and Social Sciences and Education

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Prevalence of Learning Disabilities

The chapter begins by reviewing recent estimates of the prevalence of learning disabilities (LDs), followed by trend estimates from the general population. The chapter concludes with a comparison of trends for LD in the Supplement Security Income (SSI) program, in the Medicaid population, and in the subpopulation of children who are enrolled in Medicaid by virtue of being SSI recipients.

ESTIMATES OF LEARNING DISABILITY PREVALENCE AND PREVALENCE TRENDS FROM THE GENERAL POPULATION

The committee identified multiple potential data sources that address the prevalence of and trends for rates of learning disabilities in the United States. From these, we identified two data sets judged (1) to be of the highest quality to examine current prevalence estimates of learning disabilities and (2) to characterize trends over the past decade. We selected the National Survey of Children's Health (NSCH) and the Early Childhood Longitudinal Study (ECLS) (Cortiella and Horowitz, 2014; Dhuey and Lipscomb, 2009) as the strongest sources of information on current prevalence. For trend data, we selected the Individuals with Disabilities Education Act (IDEA) data and the National Health Interview Survey (NHIS) (Cortiella and Horowitz, 2014; Dhuey and Lipscomb, 2009). It is notable that these four data sources have produced different forms of data, with attending strengths and limitations, discussed in Chapter 2. This includes administrative data on service receipt maintained by individual school departments (IDEA), national surveys based largely upon parent report, both by telephone (NSCH)

and in person (NHIS), and a large longitudinal research project involving direct assessment of children with high-quality research measures (ECLS). While there are certainly limitations with each of these imperfect data sources (e.g., errors in parent reports, differences in awareness and available funds across different school districts, attrition in longitudinal cohorts) we are comforted by the set of results that converge through the use of these multiple data sources, on which we base our conclusions that (1) prevalence estimates for LD in the general population range between 5 and 9 percent and (2) prevalence in the general population does not appear to be rising.

Prevalence of Learning Disabilities

Prevalence Estimates from National Survey of Parents

The purpose of the National Survey of Children's Health is to estimate the national- and state-level prevalence of a variety of physical, emotional, and behavioral child health indicators. It is a random-digit dialing telephone survey and had sample sizes for 2007 and 2011–2012 of 91,642 and 91,800 children, respectively. The question used in the 2007 and 2011–2012 surveys asked, "Has a doctor, health care provider, teacher, or school official ever told you that your child had a learning disability?" Interviews were conducted with parents or guardians of one child randomly selected from each household. There were several questions that assessed not only parent reports that the child had a learning disability, but also, for those who reported learning disabilities, the severity of and services used for this impairment. (Questions assessing the prevalence of learning disabilities were not included in the 2003 survey.) The estimate for current learning disabilities among children of ages 3–17 years in 2007 was 7.8 percent, with 3.7 percent rated as mild and 4.0 percent rated as moderate or severe (NSCH, 2007a,b). The estimate for learning disabilities in 2011–2012 was 8.0 percent for children of ages 3–17, with 4 percent rated as mild and 4 percent rated as moderate or severe (NSCH, 2012a). The percentage of learning disabilities by severity and race/ethnicity is displayed in Figure 16-1. The percentage of learning disabilities by severity and poverty level is displayed in Figure 16-2. With the exception of an apparent increase in moderate to severe LD in the black non-Hispanic group, there are no race/ethnicity differences. In contrast, there is a clear poverty-related gradient for LD.

Prevalence Based on the Early Childhood Longitudinal Studies

The ECLS consists of three cohorts—the birth cohort (ECLS-B), the kindergarten class 1998–1999 (ECLS-K), and the kindergarten class

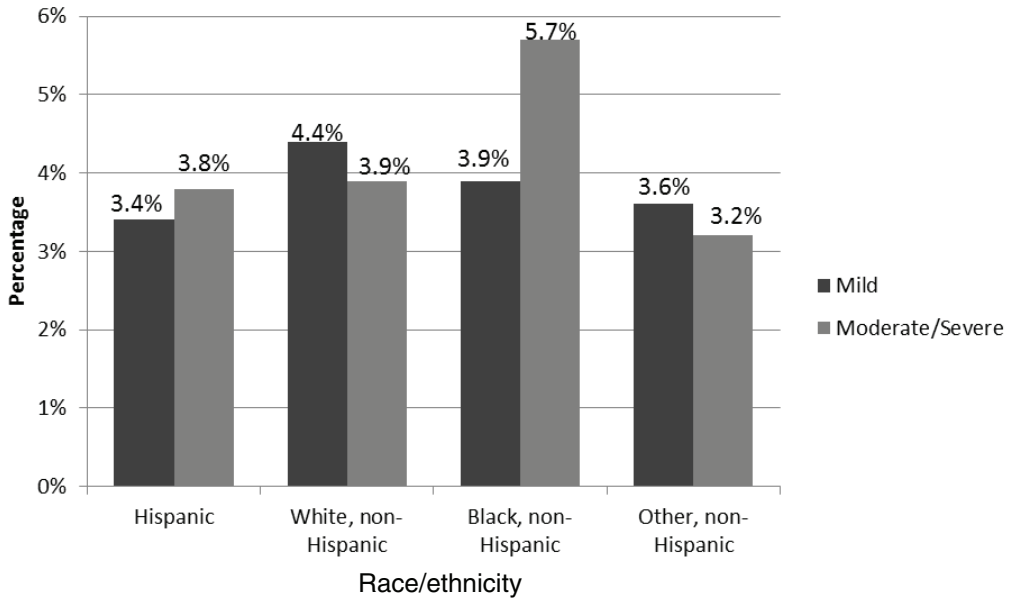

FIGURE 16-1 Percentage of children with learning disabilities by severity and race/ethnicity.
SOURCE: NSCH, 2012b.

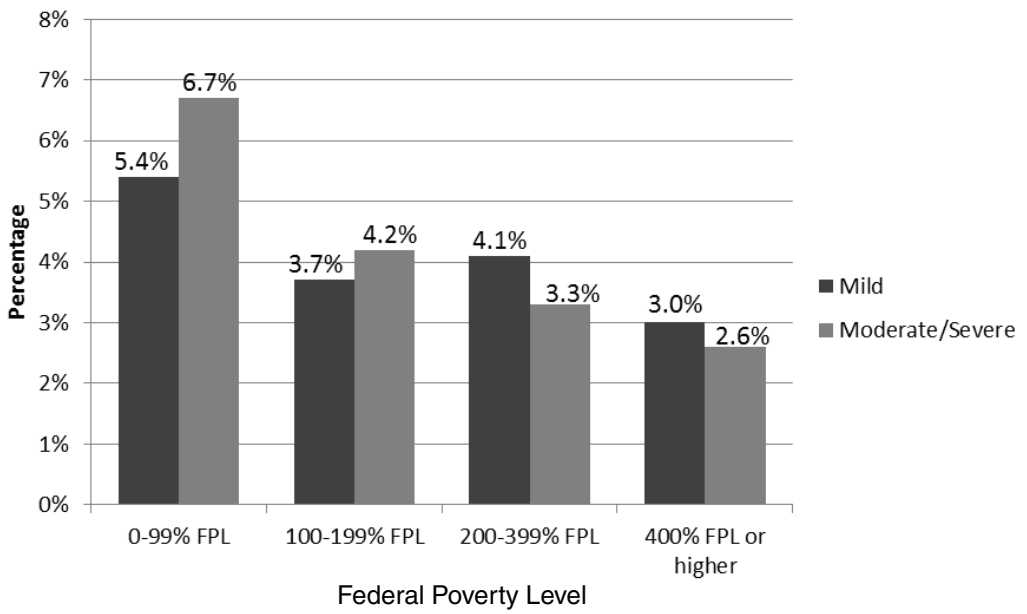

FIGURE 16-2 Percentage of children with learning disabilities by the federal poverty level (FPL).
SOURCE: NSCH, 2012c.

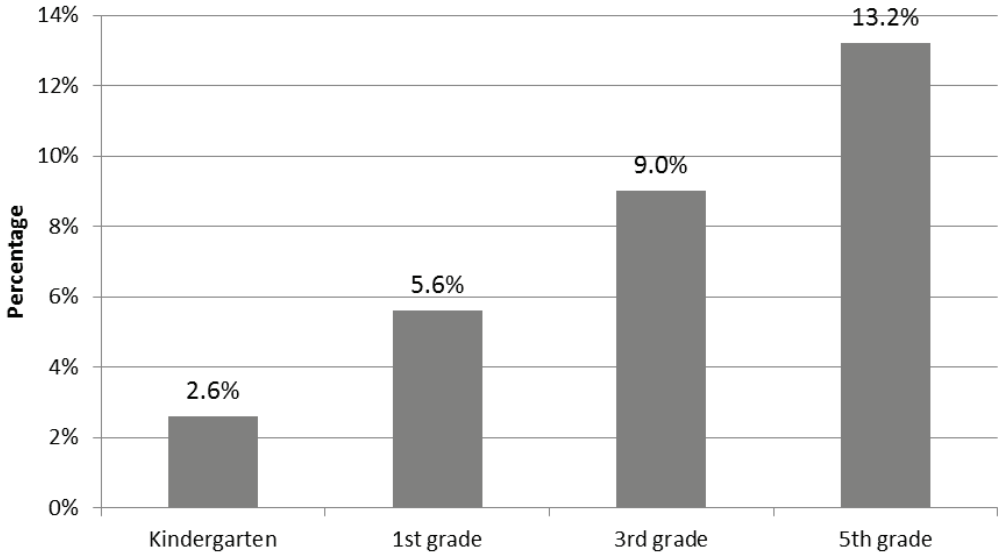

FIGURE 16-3 Ever diagnosed with learning disability: ECLS-K, 1998–2004.
SOURCE: Dhuey and Lipscomb, 2009.

2010–2011 (ECLS-K:2011)—that are used to examine child development, school readiness, and early school experiences (Dhuey and Lipscomb, 2009; Livermore et al., 2011). All three studies have large sample sizes (ECLS-B: 14,000 children; ECLS-K: 21,387; ECLS-K:2011: data collection ongoing) and use several sources of data, including child assessments, interviews, and records (Dhuey and Lipscomb, 2009; Livermore et al., 2011). Results from the ECLS-K indicate that the prevalence of ever being diagnosed with a learning disability increased across the age spectrum from 2.6 percent (kindergarten) to 13.2 percent (5th grade) (see Figure 16-3).

Prevalence Trends

The committee also sought to identify two data sets that would provide the most accurate information on trends in the rates of learning disabilities over recent years. For trend estimates, the committee focused on the IDEA data and the NHIS (Cortiella and Horowitz, 2014; Dhuey and Lipscomb, 2009).

Since 1975, IDEA has provided public access to state-supplied administrative records about children and youths with disabilities up to the age of 21. The data available from IDEA include information on the number and distribution of students served under this law and on the services utilized. Trend estimates for learning disabilities have been measured from 1976 to 2012. As shown in Figure 16-4, from 2004 to 2012, the percentage of

school children identified as having learning disabilities, reported through the IDEA system, decreased steadily from 5.8 percent in 2003–2004 to 4.7 percent in 2011–2012.

The NHIS is the principal source of information on the health of the civilian noninstitutionalized population of the United States. It produces statistical information on the prevalence, distribution, and effects of illness and disability in the United States and on the services rendered because of such conditions. This nationally representative survey has been conducted annually since 1957 and samples approximately 35,000 households containing 87,500 individuals each month (Halfon et al., 2012). From each family in the NHIS, one sample adult and one sample child (if any children are present) are randomly selected, and information on each is collected. Since 1997 the question used in the NHIS for ascertaining LD has been, "Has a representative from the school or a health professional ever told you that [survey child] has a learning disability?" Over the period of interest, from 2004 to 2013, the percent fluctuated between 6.9 and 8.2 percent, with no clear evidence of an increasing or decreasing trend. More detailed information on the NHIS estimated prevalence of LD can be seen in Table 16-1.

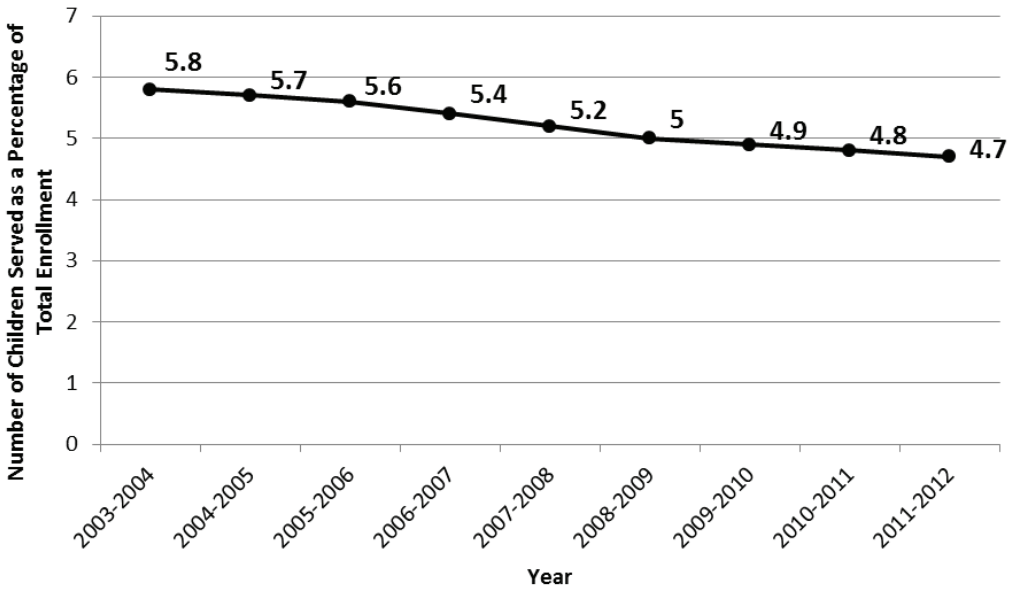

FIGURE 16-4 Children with LD, ages 3–21 served under IDEA, as a percentage of all school children, 2003–2012.
SOURCE: NCES, n.d.

TABLE 16-1 Percentage of Children, Ages 3–17, Reported to Have Ever Been Diagnosed by a School or a Health Professional as Having a Learning Disability

	1997	1998	1999	2000	2001	2002	2003
Total	7.8	7.5	7.2	7.9	7.7	8.1	7.5
Gender							
Male	10.1	9.5	9.8	9.9	9.7	10.1	9.2
Female	5.3	5.4	4.5	5.7	5.5	6.0	5.6
Race/Hispanic origin							
Non-Hispanic white	8.5	7.5	7.6	8.3	7.8	8.5	8.0
Non-Hispanic black	7.6	9.7	7.7	9.2	9.0	10.7	7.6
Hispanic	5.7	6.1	5.5	6.1	6.5	5.8	6.1
Non-Hispanic other	4.1	4.1	5.1	4.2	5.3	3.2	4.8
Age group							
Ages 3–4	1.8	2.7	1.1	2.3	1.5	1.0	2.0
Ages 5–11	7.2	6.6	6.9	7.4	7.4	8.0	7.1
Ages 12–17	10.5	10.2	9.6	10.3	10.0	10.5	9.6
Poverty status							
At or above poverty	—	6.9	6.8	8.0	7.3	7.5	7.6
Below poverty	—	11.4	11.9	10.7	12.6	14.1	9.7

NOTE: Reproduced with permission.
SOURCE: Child Trends Databank, 2014.

With the exception of a recent increase in the percent of all 3- to 4-year-olds reported to have LD, there are no clear gender, race/ethnicity, age, or economic status trends during this 17-year period.

TRENDS IN THE RATES OF LEARNING DISABILITY AMONG SSI AND MEDICAID POPULATIONS

This section of the report presents data on trends in the rates of LD in the SSI program for children from 2004 to 2014 and in Medicaid from 2001 to 2010.

SSI

Within the SSI program for children with mental disorders, LD is the basis for a relatively small but still substantial number of allowances, determinations, and recipients for SSI benefits.

Table 16-2 provides the SSI administrative data on LD among children. Column 1 shows a decreasing number of child allowances made on the basis of LD. Column 2 shows little variation in the total number of child

2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
8.0	6.9	7.8	7.5	8.1	8.2	7.9	7.5	8.0	7.5
9.5	8.7	9.6	9.6	10.0	10.6	9.3	9.2	10.0	9.0
6.4	5.1	5.9	5.3	6.1	5.7	6.4	5.7	6.0	5.9
8.5	7.0	8.6	8.0	9.1	8.7	8.1	8.1	8.7	7.5
9.6	8.4	7.9	7.7	9.1	9.6	10.3	8.5	8.2	9.5
5.6	7.0	6.3	6.7	5.8	7.1	6.5	6.3	7.0	7.2
4.8	2.5	2.7	2.6	4.3	3.9	4.2	4.5	5.2	3.2
2.5	1.5	2.1	2.1	2.3	2.8	3.2	2.6	2.4	3.2
7.4	6.5	7.2	6.7	8.8	7.6	8.0	7.0	8.1	7.8
10.5	9.2	10.2	10.2	9.4	10.8	9.3	9.8	9.7	9.3
7.9	6.5	7.6	7.4	7.9	7.7	7.1	6.8	7.4	6.4
11.3	11.0	10.7	9.3	12.4	11.4	12.3	9.8	11.8	11.9

recipients who received SSI benefits on the basis of LD, particularly if 2004 data are excluded. Column 3 shows the estimated total number of children in households with incomes under 200 percent of the federal poverty level (FPL) for each year. To control for the changes in the magnitude of child poverty, as displayed in column 3, columns 4 and 5 show the rates of allowances and recipients as a percentage of the number of children in households under 200 percent FPL. Column 4 shows the percentage of children in households under 200 percent FPL who were allowed benefits for LD, meaning they were found to be disabled due to a diagnosis of LD. Column 5 shows the percentage of children in households under 200 percent FPL who were recipients of SSI payments for LD in December of each year. Figure 16-5 plots the percentages from columns 4 and 5 along with the 10-year average of the percentages of allowances and recipients for LD as a visual reference point.

As shown in Figure 16-5, over the 10-year period from 2004 to 2013 the proportion of children under 200 percent FPL who were child SSI LD recipients increased from 2004 through 2007, decreased through 2011, then increased slightly through 2013. No overall trend is noted. Over the same time period, the rate of child SSI LD allowances gradually and

TABLE 16-2 SSI Child Initial Allowances and Recipient Numbers for LD

	1	2	3	4	5
Year	# of Child SSI Allowances for LD	# of Child SSI Recipients for LD	# of Children in Households Under 200% FPL	% of Children Under 200% FPL Allowed SSI Benefits for LD	% of Children Under 200% FPL Who Are Recipients of SSI Benefits for LD
2004	6,940	33,833	28,753,000	0.024%	0.118%
2005	6,720	37,118	28,539,000	0.023%	0.130%
2006	5,811	38,934	28,757,000	0.020%	0.135%
2007	5,230	39,597	28,999,000	0.018%	0.137%
2008	5,211	39,619	30,064,000	0.017%	0.132%
2009	5,428	39,868	31,505,000	0.017%	0.127%
2010	5,681	40,278	32,254,000	0.018%	0.125%
2011	5,590	40,533	32,678,000	0.017%	0.124%
2012	5,061	40,924	32,269,000	0.016%	0.127%
2013	4,513	40,461	31,364,000	0.014%	0.129%

NOTE: The Current Population Survey table creator was used to generate numbers of children below 200 percent of the federal poverty level. Parameters used to generate the numbers include get count of: persons in poverty universe (everyone except unrelated individuals under 15); years: 2004 to 2013; Census 2010 weights; row variable: age; column variable: income-to-poverty ratio; and customized formatting: income-to-poverty ratio percent cutoff of 200 percent.
SOURCES: U.S. Census Bureau, 2015; unpublished data set provided by the SSA.

continuously decreased. The rate of child LD allowances among children in households under 200 percent FPL decreased by 40.4 percent, from 0.024 percent in 2004 to 0.014 percent in 2013. Despite these declining annual allowance rates, the total number of recipients each year increased throughout this period, from 0.118 percent in 2004 to 0.129 percent in 2013, an increase of 9.6 percent, although if the 2004 number were excluded, the 9-year change would be downward.

Medicaid

Table 16-3 shows the percentage of children who were diagnosed with LD in two different groups of Medicaid enrollees for each year from 2001 to 2010. Column 1 shows the percentage of all Medicaid enrollees who had a diagnosis of LD, by year. Column 2 shows the percentage of LD diagnoses among the smaller subpopulation of Medicaid enrollees who

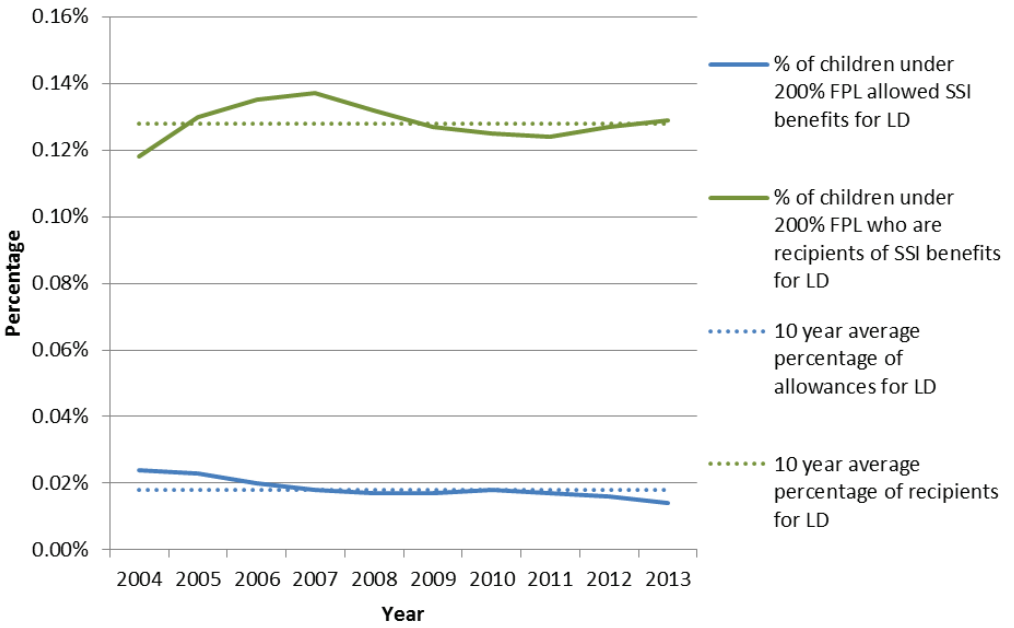

FIGURE 16-5 Percentages of SSI child initial allowances and recipients for LD under 200 percent FPL.
NOTE: The Current Population Survey table creator was used to generate numbers of children below 200 percent of the federal poverty level. Parameters used to generate the numbers include get count of: persons in poverty universe (everyone except unrelated individuals under 15); years: 2004 to 2013; Census 2010 weights; row variable: age; column variable: income-to-poverty ratio; and customized formatting: income-to-poverty ratio percent cutoff of 200 percent.
SOURCES: U.S. Census Bureau, 2015; unpublished data set provided by the SSA.

were eligible to be enrolled in Medicaid on the basis of their eligibility to receive SSI benefits.

The rate of LD diagnoses among all child Medicaid enrollees stayed essentially unchanged between 2001 and 2010 (see Figure 16-6). However, during the same period the proportion of child SSI-eligible Medicaid enrollees with a diagnosis of LD increased from 5.6 to 6.8 percent (an increase of 21.4 percent), with most of the increase occurring between 2008 and 2010.

For the 6-year period of overlap between the Medicaid and SSI administrative data sets, from 2004 to 2010, the rate of LD diagnoses among all Medicaid-enrolled children increased by 20 percent, while the rate of LD diagnoses among SSI-eligible Medicaid-enrolled children increased by 15.25 percent. There was a 9.6 percent increase in the rate of SSI recipients for LD among children in households under 200 percent FPL.

TABLE 16-3 Percentage of Child Medicaid Enrollees and SSI Medicaid Enrollees Diagnosed with LD

	1	2
Year	% of All Child Medicaid Enrollees with LD Diagnosis	% of Child SSI Medicaid Enrollee Subpopulation with LD Diagnosis
2001	1.20%	5.60%
2002	1.10%	5.70%
2003	1.10%	5.80%
2004	1.00%	5.90%
2005	1.00%	5.90%
2006	1.10%	6.00%
2007	1.10%	5.70%
2008	1.10%	5.80%
2009	1.10%	6.00%
2010	1.20%	6.80%

SOURCE: MAX data.

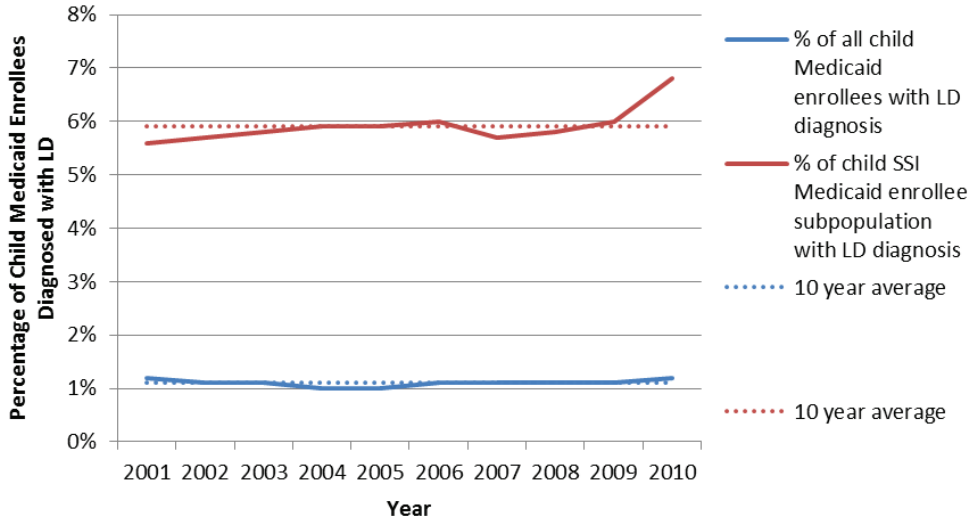

FIGURE 16-6 Percentage of child Medicaid enrollees and SSI Medicaid enrollees diagnosed with LD.
SOURCE: MAX data.

DISCUSSION

The trends in the estimated prevalence of LD among children vary depending on the population studied and on the ways that cases of LD are identified. Overall, the trends in the SSI program are generally consistent with trends generated from surveys of the general population, special education service use, or diagnoses among children in the Medicaid population.

The estimates of prevalence from the population surveys suggest no clear trend, either increasing or decreasing, from 2004 to 2013. The NHIS results showed no clear trend, with the prevalence of LD fluctuating between 6.9 and 8.2 percent, with no increase or decrease between 2004 and 2013, of the percentage of children of ages 3–17 reported to have ever been diagnosed by a school or health professional as having a learning disability. IDEA special education service utilization data showed that the rates of special education use for LD decreased from 5.8 percent in 2004 to 4.7 percent in 2011–2012, a decrease of 18.96 percent. The results of studies that show difference by race and ethnicity must be cautiously interpreted, since there is evidence of diagnostic and test bias for children with LD, even after taking into account the effects of socioeconomic status (Coutinho et al., 2002; Jencks and Phillips, 1998).

The SSI data from 2004 to 2012 indicate that a gradually decreasing percentage of children under 200 percent FPL are being allowed SSI disability benefits for LD. Over the same time period, the percentage of children under 200 percent FPL who were recipients of SSI benefits for LD fluctuated, showing an increase from 2004 to 2007, a decrease from 2007 to 2011, and then another increase from 2011 to 2013; over the 10-year period the total increase was 0.011 percent.

The trends in the rate of LD diagnoses among all child Medicaid enrollees from 2001 to 2010 remained flat. The trends in the rate of LD diagnoses among children enrolled in Medicaid based on SSI eligibility also remained flat from 2004 to 2009; however, a marked increase in the rates of diagnoses occurred in 2010. It is not clear why this increase was observed.

In 2012, there were approximately 32 million children under age 18 living at or below 200 percent of the federal poverty level. Of these, approximately 21 million were of school age (ages 6–17 years). Recent U.S. prevalence data suggest that approximately 4 percent of the child population were diagnosed with a moderate or severe learning disorder (NSCH, 2012a). This suggests that there are approximately 840,000 school-aged children below 200 percent FPL with a severe learning disability, an estimate that is likely to be quite conservative. By contrast, in 2012, 40,924 children received SSI benefits with a diagnosis of learning disability, or approximately 5 percent, which was well below the estimated eligible number. Figure 16-7 illustrates these relationships.

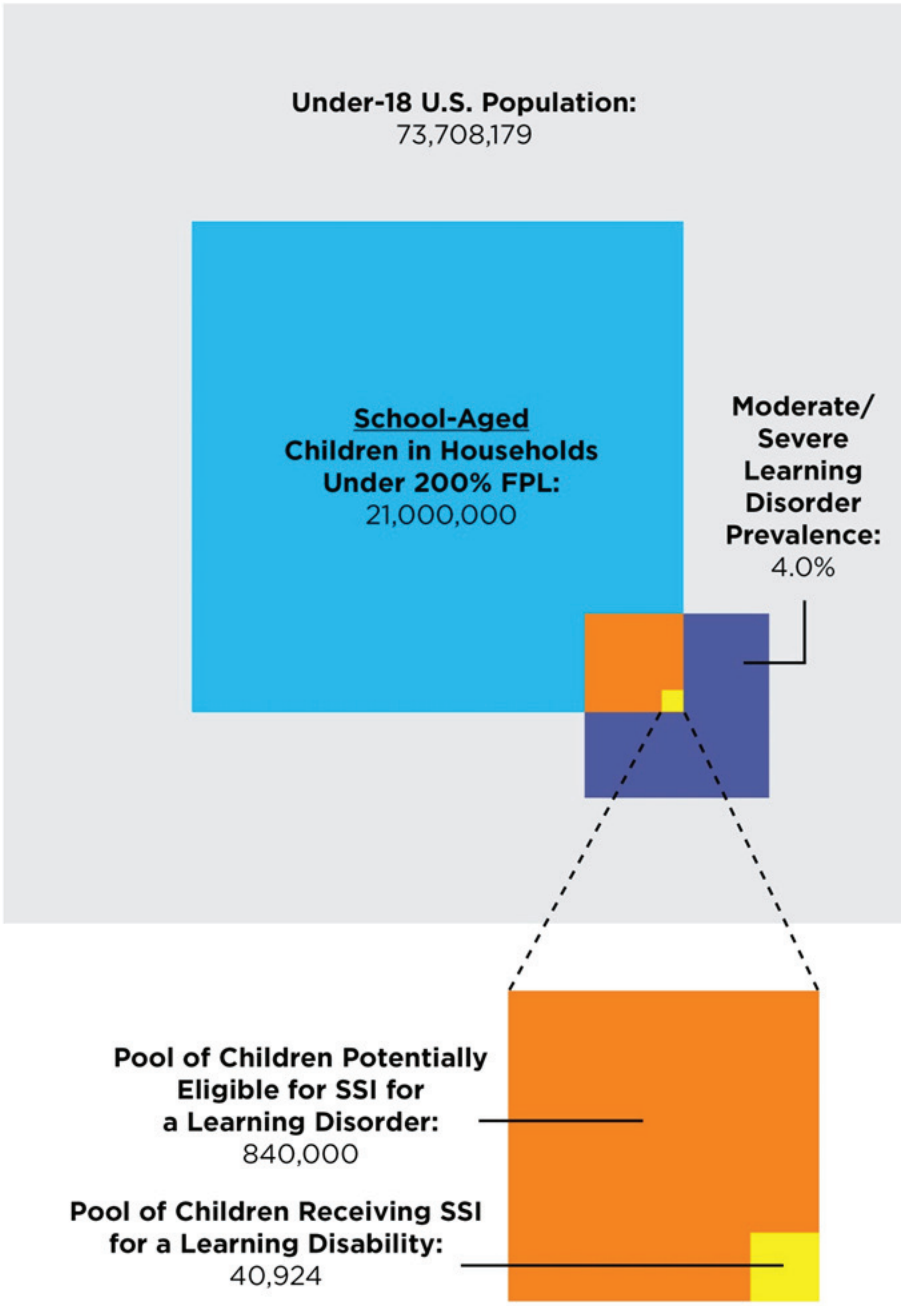

FIGURE 16-7 Children potentially eligible for SSI for LD versus children receiving SSI for LD in 2013, according to the NSCH.
NOTE: The Current Population Survey table creator was used to generate numbers of children below 200 percent of the federal poverty level. Parameters used to generate the numbers include get count of: persons in poverty universe (everyone except unrelated individuals under 15); years: 2004 to 2013; Census 2010 weights; row variable: age; column variable: income-to-poverty ratio; and customized formatting: income-to-poverty ratio percent cutoff of 200 percent.
SOURCES: U.S. Census Bureau, 2014, 2015; NSCH, 2012a; unpublished data set provided by the SSA.

FINDINGS

- Prevalence estimates for LD in the general population range between 5 and 9 percent.
- Prevalence in the general population is stable, but from 2003 to 2012 the number of children receiving special education services based on an LD diagnosis decreased.
- Within the SSI program, trends in both the number of LD allowances and the rate of LD allowances in children in low-income households is decreasing. From 2004 to 2013, the number of the SSI recipients for LD was stable.
- Among children enrolled in Medicaid on the basis of SSI eligibility, the rate of children with an LD diagnosis appears to be increasing. Among all children enrolled in Medicaid, there does not appear to be an increase in the rates of LD diagnoses.

CONCLUSIONS

- Rough estimates of the number of children in low-income households with moderate to severe ID suggest that less than 24 percent of children who are likely eligible for SSI benefits due to ID are recipients of these benefits.
- There is no evidence that the trends observed in the proportion of children receiving SSI benefits for LD are inconsistent with the prevalence trends observed in the general or Medicaid populations.

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EXHIBIT 89

Quick Statistics About Voice, Speech, Language

Voice, Speech, Language, and Swallowing

- Nearly 1 in 12 (7.7 percent) U.S. children ages 3-17 has had a disorder related to voice, speech, language, or swallowing in the past 12 months.[1]
- Among children who have a voice, speech, language, or swallowing disorder, 34 percent of those ages 3-10 have multiple communication or swallowing disorders, while 25.4 percent of those ages 11-17 have multiple disorders.[1]
- Boys ages 3-17 are more likely than girls to have a voice, speech, language, or swallowing disorder (9.6 percent compared to 5.7 percent).[1]
- The prevalence of voice, speech, language, or swallowing disorders is highest among children ages 3-6 (11.0 percent), compared to children ages 7-10 (9.3 percent), and children ages 11-17 (4.9 percent).[1]
- Nearly one in 10, or 9.6 percent, of black children (ages 3-17) has a voice, speech, language, or swallowing disorder, compared to 7.8 percent of white children and 6.9 percent of Hispanic children.[1]
- More than half (55.2 percent) of U.S. children ages 3-17 with a voice, speech, language, or swallowing disorder received intervention services in the past year.[1] White children (ages 3-17) with a voice, speech, language, or swallowing disorder are more likely to have received intervention services in the past 12 months, compared to Hispanic and black children, at 60.1 percent, 47.3 percent, and 45.8 percent respectively.[1]
- Boys (ages 3-17) with a voice, speech, language, or swallowing disorder are more likely than girls to receive intervention services, at 59.4 percent and 47.8 percent, respectively.[1]
- Among children ages 3-17 who have a voice, speech, language, or swallowing disorder, those

with speech or language problems, 67.6 percent and 66.8 percent respectively, are more likely to receive intervention services, compared to those who have a voice disorder (22.8 percent) or swallowing problems (12.7 percent).[1]

Voice

- An estimated 17.9 million U.S. adults ages 18 or older, or 7.6%, report having had a problem with their voice in the past 12 months.[3,4] Approximately 9.4 million (4.0%) adults report having a problem using their voice that lasted one week or longer during the last 12 months.[2]
- 1.4 percent of U.S. children have a voice disorder that lasted for a week or longer during the past 12 months.[1]
- Spasmodic dysphonia, a voice disorder caused by involuntary movements of one or more muscles of the larynx (voice box), can affect anyone. The first signs of this disorder are found most often in people ages 30-50. More women than men appear to be affected.[5]

Speech

- 5 percent of U.S. children ages 3-17 have a speech disorder that lasted for a week or longer during the past 12 months.[1]
- The prevalence of speech sound disorders (namely, articulation disorders or phonological disorders) in young children is 8 to 9 percent. By the first grade, roughly 5 percent of children have noticeable speech disorders, including stuttering, speech sound disorders, and dysarthria; the majority of these speech disorders have no known cause.[6,7]
- More than three million Americans (about one percent) stutter. Stuttering can affect individuals of all ages, but occurs most frequently in young children between the ages of 2 and 6. Boys are two to three times more likely than girls to stutter. Although most children who stutter outgrow the condition while young, as many as one in four will continue to stutter for the rest of their lives, a condition known as persistent developmental stuttering.[8,9]

Language

- 3.3 percent of U.S. children ages 3-17 have a language disorder that lasted for a week or longer during the past 12 months.[1]
- Research suggests that the first 6 months of life are the most crucial to a child's development of language skills. For a person to become fully competent in any language, exposure must begin as early as possible, preferably before school age.[10,11]
- Anyone can acquire aphasia (a loss of the ability to use or understand language), but most people who have aphasia are in their middle to late years. Men and women are equally affected. Nearly 180,000 Americans acquire the disorder each year.[12] About 1 million persons in the U.S. currently have aphasia.[12]

Swallowing

- 0.9 percent of U.S. children ages 3-17 have a swallowing disorder that lasted for a week or longer during the past 12 months.[1]

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EXHIBIT 90

Epilepsy

Overview

Epilepsy is a central nervous system (neurological) disorder in which brain activity becomes abnormal, causing seizures or periods of unusual behavior, sensations, and sometimes loss of awareness.

Anyone can develop epilepsy. Epilepsy affects both males and females of all races, ethnic backgrounds and ages.

Seizure symptoms can vary widely. Some people with epilepsy simply stare blankly for a few seconds during a seizure, while others repeatedly twitch their arms or legs. Having a single seizure doesn't mean you have epilepsy. At least two unprovoked seizures are generally required for an

epilepsy diagnosis.

Treatment with medications or sometimes surgery can control seizures for the majority of people with epilepsy. Some people require lifelong treatment to control seizures, but for others, the seizures eventually go away. Some children with epilepsy may outgrow the condition with age.

Epilepsy care at Mayo Clinic

Symptoms

Because epilepsy is caused by abnormal activity in the brain, seizures can affect any process your brain coordinates. Seizure signs and symptoms may include:

- Temporary confusion
- A staring spell
- Uncontrollable jerking movements of the arms and legs
- Loss of consciousness or awareness
- Psychic symptoms such as fear, anxiety or deja vu

Symptoms vary depending on the type of seizure. In most cases, a person with epilepsy will tend to have the same type of seizure each time, so the symptoms will be similar from episode to episode.

Doctors generally classify seizures as either focal or generalized, based on how the abnormal brain activity begins.

Focal seizures

When seizures appear to result from abnormal activity in just one area of your brain, they're called focal (partial) seizures. These seizures fall into two categories:

- **Focal seizures without loss of consciousness.** Once called simple partial seizures, these seizures don't cause a loss of consciousness. They may alter emotions or change the way things look, smell, feel, taste or sound. They may also result in involuntary jerking of a body part, such as an arm or leg, and spontaneous sensory symptoms such as tingling, dizziness and flashing lights.
- **Focal seizures with impaired awareness.** Once called complex partial seizures, these seizures involve a change or loss of consciousness or awareness. During a complex partial seizure, you may stare into space and not respond normally to your environment or perform repetitive movements, such as hand rubbing, chewing, swallowing or walking in circles.

Symptoms of focal seizures may be confused with other neurological disorders, such as migraine, narcolepsy or mental illness. A thorough examination and testing are needed to distinguish epilepsy from other disorders.

Generalized seizures

Seizures that appear to involve all areas of the brain are called generalized seizures. Six types of generalized seizures exist.

- **Absence seizures.** Absence seizures, previously known as petit mal seizures, often occur in children and are characterized by staring into space or subtle body movements such as eye blinking or lip smacking. These seizures may occur in clusters and cause a brief loss of awareness.
- **Tonic seizures.** Tonic seizures cause stiffening of your muscles. These seizures usually affect muscles in your back, arms and legs and may cause you to fall to the ground.
- **Atonic seizures.** Atonic seizures, also known as drop seizures, cause a loss of muscle control, which may cause you to suddenly

collapse or fall down.

- **Clonic seizures.** Clonic seizures are associated with repeated or rhythmic, jerking muscle movements. These seizures usually affect the neck, face and arms.
- **Myoclonic seizures.** Myoclonic seizures usually appear as sudden brief jerks or twitches of your arms and legs.
- **Tonic-clonic seizures.** Tonic-clonic seizures, previously known as grand mal seizures, are the most dramatic type of epileptic seizure and can cause an abrupt loss of consciousness, body stiffening and shaking, and sometimes loss of bladder control or biting your tongue.

When to see a doctor

Seek immediate medical help if any of the following occurs:

- The seizure lasts more than five minutes.
- Breathing or consciousness doesn't return after the seizure stops.
- A second seizure follows immediately.
- You have a high fever.
- You're experiencing heat exhaustion.
- You're pregnant.
- You have diabetes.
- You've injured yourself during the seizure.

If you experience a seizure for the first time, seek medical advice.

Request an Appointment at Mayo Clinic

Causes

Epilepsy has no identifiable cause in about half the people with the condition. In the other half, the condition may be traced to various factors,

including:

- **Genetic influence.** Some types of epilepsy, which are categorized by the type of seizure you experience or the part of the brain that is affected, run in families. In these cases, it's likely that there's a genetic influence.

  Researchers have linked some types of epilepsy to specific genes, but for most people, genes are only part of the cause of epilepsy. Certain genes may make a person more sensitive to environmental conditions that trigger seizures.

- **Head trauma.** Head trauma as a result of a car accident or other traumatic injury can cause epilepsy.

- **Brain conditions.** Brain conditions that cause damage to the brain, such as brain tumors or strokes, can cause epilepsy. Stroke is a leading cause of epilepsy in adults older than age 35.

- **Infectious diseases.** Infectious diseases, such as meningitis, AIDS and viral encephalitis, can cause epilepsy.

- **Prenatal injury.** Before birth, babies are sensitive to brain damage that could be caused by several factors, such as an infection in the mother, poor nutrition or oxygen deficiencies. This brain damage can result in epilepsy or cerebral palsy.

- **Developmental disorders.** Epilepsy can sometimes be associated with developmental disorders, such as autism and neurofibromatosis.

Risk factors

Certain factors may increase your risk of epilepsy:

- **Age.** The onset of epilepsy is most common in children and older adults, but the condition can occur at any age.

- **Family history.** If you have a family history of epilepsy, you may be at an increased risk of developing a seizure disorder.

- **Head injuries.** Head injuries are responsible for some cases of epilepsy. You can reduce your risk by wearing a seat belt while riding in a car and by wearing a helmet while bicycling, skiing, riding a

motorcycle or engaging in other activities with a high risk of head injury.

- **Stroke and other vascular diseases.** Stroke and other blood vessel (vascular) diseases can lead to brain damage that may trigger epilepsy. You can take a number of steps to reduce your risk of these diseases, including limiting your intake of alcohol and avoiding cigarettes, eating a healthy diet, and exercising regularly.
- **Dementia.** Dementia can increase the risk of epilepsy in older adults.
- **Brain infections.** Infections such as meningitis, which causes inflammation in your brain or spinal cord, can increase your risk.
- **Seizures in childhood.** High fevers in childhood can sometimes be associated with seizures. Children who have seizures due to high fevers generally won't develop epilepsy. The risk of epilepsy increases if a child has a long seizure, another nervous system condition or a family history of epilepsy.

Complications

Having a seizure at certain times can lead to circumstances that are dangerous to yourself or others.

- **Falling.** If you fall during a seizure, you can injure your head or break a bone.
- **Drowning.** If you have epilepsy, you're 15 to 19 times more likely to drown while swimming or bathing than the rest of the population because of the possibility of having a seizure while in the water.
- **Car accidents.** A seizure that causes either loss of awareness or control can be dangerous if you're driving a car or operating other equipment.

  Many states have driver's license restrictions related to a driver's ability to control seizures and impose a minimum amount of time that a driver be seizure-free, ranging from months to years, before being allowed to drive.
- **Pregnancy complications.** Seizures during pregnancy pose dangers to both mother and baby, and certain anti-epileptic

medications increase the risk of birth defects. If you have epilepsy and you're considering becoming pregnant, talk to your doctor as you plan your pregnancy.

Most women with epilepsy can become pregnant and have healthy babies. You'll need to be carefully monitored throughout pregnancy, and medications may need to be adjusted. It's very important that you work with your doctor to plan your pregnancy.

- **Emotional health issues.** People with epilepsy are more likely to have psychological problems, especially depression, anxiety and suicidal thoughts and behaviors. Problems may be a result of difficulties dealing with the condition itself as well as medication side effects.

Other life-threatening complications of epilepsy are uncommon, but may happen, such as:

- **Status epilepticus.** This condition occurs if you're in a state of continuous seizure activity lasting more than five minutes or if you have frequent recurrent seizures without regaining full consciousness in between them. People with status epilepticus have an increased risk of permanent brain damage and death.
- **Sudden unexpected death in epilepsy (SUDEP).** People with epilepsy also have a small risk of sudden unexpected death. The cause is unknown, but some research shows it may occur due to heart or respiratory conditions.

  People with frequent tonic-clonic seizures or people whose seizures aren't controlled by medications may be at higher risk of SUDEP. Overall, about 1 percent of people with epilepsy die of SUDEP.

By Mayo Clinic Staff

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EXHIBIT 91

Epilepsy

Epilepsy Data and Statistics

Epilepsy Prevalence in the United States

In 2015, 1.2% of the US population had active epilepsy (95% CI* = 1.1-1.4). This is about 3.4 million people with epilepsy nationwide: **3 million adults** and **470,000 children**. Find the prevalence estimates for your state in the data table below. Learn more about epilepsy and public health in your state by visiting the Resources for States at the bottom of the page.

What Is Active Epilepsy?

An adult aged 18 or older has *active epilepsy* if they report they have a history of doctor-diagnosed epilepsy or seizure disorder and

- Are currently taking medication to control it or
- Had one or more seizures in the past year (or both) (from the National Health Interview Survey, 2015).

A child aged 17 years or younger has *active epilepsy* if their parent or guardian reports:

- That a doctor or health care provider has ever told them that their child had epilepsy or seizure disorder, and
- Their child currently has epilepsy or seizure disorder (from the National Survey of Children's Health, 2011-2012).

To learn more about the methods used to calculate epilepsy prevalence, please read the full study.

Active Epilepsy Prevalence, by State

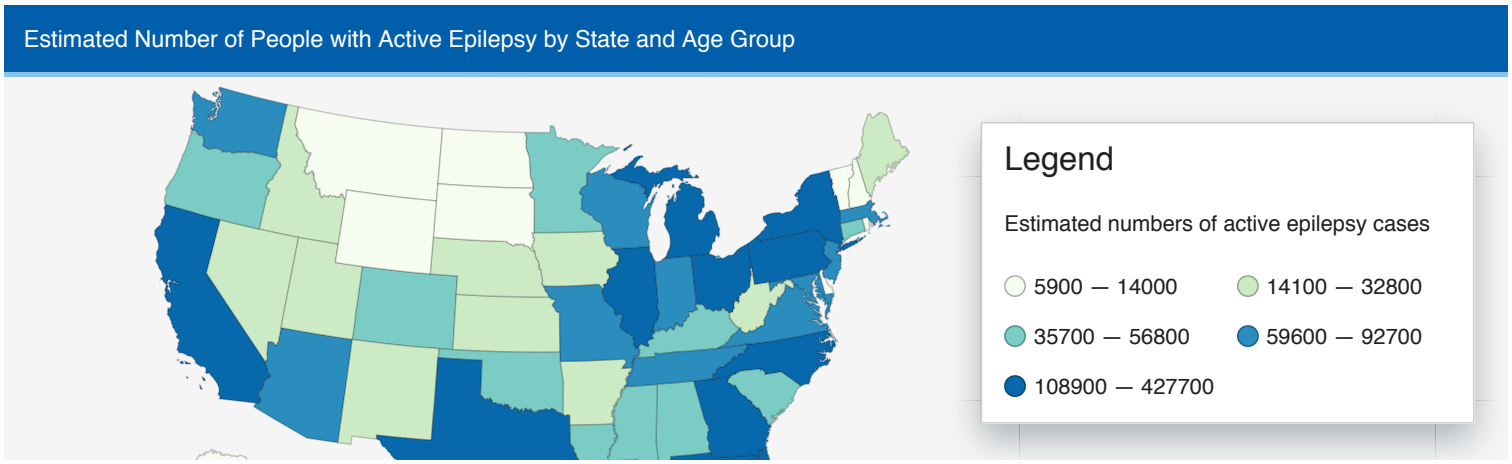


Exhibit 91

Data Table

Location	No. of cases (…	95% CI (all ages)	No. of cases (a…	95% CI (ages …	No. of cases (a…	95% CI (ages …
Alaska	7200	(6,100-8,300)	1,100	(800-1,400)	6,100	(5,000-7,200)
Alabama	54100	(46,400-61,900)	7,500	(5,900-9,200)	46,600	(39,000-54,200)
Arkansas	32800	(28,000-37,600)	4,900	(3,700-6,100)	28,000	(23,300-32,600)
Arizona	77000	(66,400-87,500)	11,200	(8,900-13,600)	65,700	(55,400-76,000)
California	427700	(372,600-482,…	59,800	(49,000-70,600)	367,900	(313,800-422,0…
Colorado	56800	(48,300-65,300)	7,800	(6,000-9,600)	49,000	(40,700-57,300)
Connecticut	35900	(30,400-41,400)	4,500	(3,400-5,700)	31,400	(26,000-36,800)
Delaware	9700	(8,200-11,100)	1,300	(900-1,600)	8,400	(7,000-9,900)
Florida	223900	(194,100-253,…	27,300	(21,900-32,800)	196,600	(167,200-225,9…
Georgia	110200	(94,900-125,500)	16,700	(13,200-20,100)	93,500	(78,600-108,500)
Hawaii	14000	(11,900-16,100)	2,000	(1,500-2,400)	12,000	(10,000-14,100)
Iowa	31400	(26,800-36,100)	4,400	(3,400-5,400)	27,000	(22,500-31,600)
Idaho	16800	(14,200-19,300)	2,600	(2,000-3,200)	14,200	(11,700-16,600)
Illinois	136600	(117,900-155,4…	18,600	(14,900-22,400)	118,000	(99,700-136,400)
Indiana	69500	(59,600-79,400)	10,600	(8,300-13,000)	58,900	(49,200-68,500)
Kansas	29900	(25,500-34,300)	4,400	(3,400-5,400)	25,500	(21,200-29,900)
Kentucky	49500	(42,000-57,000)	6,800	(4,900-8,700)	42,700	(35,500-50,000)
Louisiana	54900	(46,600-63,200)	7,900	(6,200-9,700)	47,000	(38,900-55,100)
Massachusetts	71600	(60,900-82,300)	8,400	(6,500-10,300)	63,200	(52,600-73,700)
Maryland	59900	(50,700-69,100)	7,900	(6,200-9,700)	52,000	(42,900-61,000)
Maine	14100	(11,900-16,300)	1,700	(1,200-2,200)	12,400	(10,300-14,600)
Michigan	108900	(93,300-124,500)	13,600	(10,800-16,400)	95,300	(79,900-110,600)
Minnesota	53700	(45,700-61,700)	7,400	(5,900-9,000)	46,300	(38,400-54,100)
Missouri	61200	(52,400-70,000)	8,300	(6,500-10,100)	52,900	(44,200-61,600)
Mississippi	35700	(30,600-40,700)	5,100	(3,900-6,300)	30,600	(25,700-35,500)
Montana	10800	(9,100-12,600)	1,400	(1,000-1,800)	9,400	(7,700-11,100)
North Carolina	110100	(94,700-125,500)	15,200	(11,800-18,500)	94,900	(79,900-110,000)
North Dakota	7300	(6,200-8,500)	1,000	(700-1,200)	6,400	(5,300-7,500)
Nebraska	19600	(16,600-22,500)	2,800	(2,200-3,500)	16,700	(13,800-19,600)
New Hampshire	13100	(11,100-15,200)	1,500	(1,100-1,900)	11,600	(9,600-13,700)
New Jersey	92700	(79,100-106,200)	12,000	(9,500-14,500)	80,600	(67,300-93,900)
New Mexico	23200	(19,800-26,500)	3,400	(2,600-4,200)	19,800	(16,400-23,100)
Nevada	31600	(26,800-36,400)	4,400	(3,300-5,400)	27,200	(22,500-31,900)
New York	215200	(186,300-244	26,600	(21,600-31,500)	188,600	(160,200-217,1

New York	215200	(186,300-244,…	20,000	(21,000-31,300)	188,000	(160,200-217,1…
Ohio	126400	(109,300-143,…	16,900	(13,600-20,300)	109,400	(92,700-126,200)
Oklahoma	41100	(34,900-47,300)	6,400	(5,000-7,900)	34,700	(28,700-40,700)
Oregon	42900	(36,300-49,400)	5,400	(4,100-6,800)	37,400	(31,000-43,900)
Pennsylvania	133000	(114,600-151,4…	16,900	(13,500-20,200)	116,100	(98,000-134,200)
Rhode Island	11100	(9,300-12,900)	1,300	(900-1,700)	9,800	(8,100-11,500)
South Carolina	53400	(45,500-61,300)	7,100	(5,500-8,700)	46,300	(38,500-54,000)
South Dakota	8900	(7,400-10,400)	1,300	(900-1,600)	7,600	(6,200-9,100)
Tennessee	73900	(62,900-84,800)	10,000	(7,800-12,300)	63,800	(53,100-74,600)
Texas	292900	(255,400-330,…	47,200	38,500-56,000)	245,600	(209,200-282,0…
Utah	29300	(24,900-33,600)	5,300	(4,100-6,500)	24,000	(19,800-28,200)
Virginia	84800	(72,600-97,000)	11,000	(8,800-13,200)	73,800	(61,800-85,800)
Vermont	6300	(5,300-7,300)	700	(500-900)	5,600	(4,700-6,600)
Washington	74600	(64,000-85,200)	10,200	(8,100-12,300)	64,400	(54,000-74,800)
Wisconsin	59600	(50,800-68,300)	7,900	(6,300-9,500)	51,700	(43,100-60,300)
West Virginia	21500	(18,100-25,000)	2,500	(1,900-3,100)	19,000	(15,600-22,500)
Wyoming	5900	(5,000-6,800)	800	(600-1,000)	5,100	(4,200-6,000)

*CI = Confidence Interval. CI describes the level of uncertainty of an estimate and specifies the range in which the true value is likely to fall. These reports use a 95% level of significance, which means that 95% of the time, the true value falls within these boundaries.

Source: Zack MM, Kobau R. National and state estimates of the numbers of adults and children with active epilepsy — United States, 2015. *MMWR*. 2017;66:821–825. DOI: 10.15585/mmwr.mm6631a1. html

Resources for States

Find out more about epilepsy and public health in your state.

- Epilepsy Foundation State Affiliates
- CDC Chronic Disease State Snapshots
- Association of State and Territorial Health Officials
- Behavioral Risk Factor Surveillance System Coordinators
- Healthy People 2020 State and Territory Coordinators

More Information about Epilepsy

More information about epilepsy from the CDC Epilepsy Program.

- Publications
- Research
- About Epilepsy
- CDC Addresses Epilepsy
- Communications Center

Page last reviewed: January 25, 2019

EXHIBIT 92

CDC Newsroom

More Americans have epilepsy than ever before

First estimates available for every state show disorder is widespread.

Press Release

Embargoed Until: Thursday, August 10, 2017, 1:00 p.m. ET

Contact: Media Relations
(404) 639-3286

The number of U.S. adults and children with epilepsy is increasing, with at least 3.4 million people living with the disorder, according to data released today in CDC's Morbidity and Mortality Weekly Report. It's the first time epilepsy estimates have been available for every state.

The data show the disorder is widespread. In 2015, about 3 million U.S. adults and 470,000 children had active epilepsy (under treatment or with recent seizures). The number of adults with active epilepsy rose from 2.3 million in 2010 to 3 million in 2015. The number of children with the condition increased from 450,000 in 2007 to 470,000 in 2015. These increases are likely due to population growth.

"Millions of Americans are impacted by epilepsy, and unfortunately, this study shows cases are on the rise," said CDC Director Brenda Fitzgerald, M.D. "Proper diagnosis is key to finding an effective treatment – and at CDC we are committed to researching, testing, and sharing strategies that will improve the lives of people with epilepsy."

Epilepsy is a disorder of the brain that causes seizures. Different conditions can cause epilepsy, such as stroke, brain tumor, head injury, central nervous system infections, or genetic risks. Although epilepsy is widely recognized by the public, few people understand it, even among those who know someone with the disorder.

Key findings from analysis of epilepsy rates

The CDC study provides national and state-specific estimates of epilepsy prevalence based on the 2015 National Health Interview Survey, and the National Survey of Children's Health, and the 2014 Current Population Survey.

- Overall, 1.2 percent of the U.S. population (3.4 million people) reported active epilepsy in 2015.
- The number of cases of active epilepsy among adults ranged from 5,100 in Wyoming to 367,900 in California.
- The number of epilepsy cases among children ranged from 800 in Wyoming to 59,800 in California.
- Eleven states had more than an estimated 92,000 people with epilepsy.

- Data from 2010-2015 indicate increases in the number of persons with active epilepsy, probably because of population growth.

CDC researchers and others have previously reported that many adults with epilepsy face challenges including work limitations, difficulty finding transportation, and difficulty affording medical care. Students with epilepsy are more likely to fall behind in school and to need special education services. Children with epilepsy are more likely to live in low-income households.

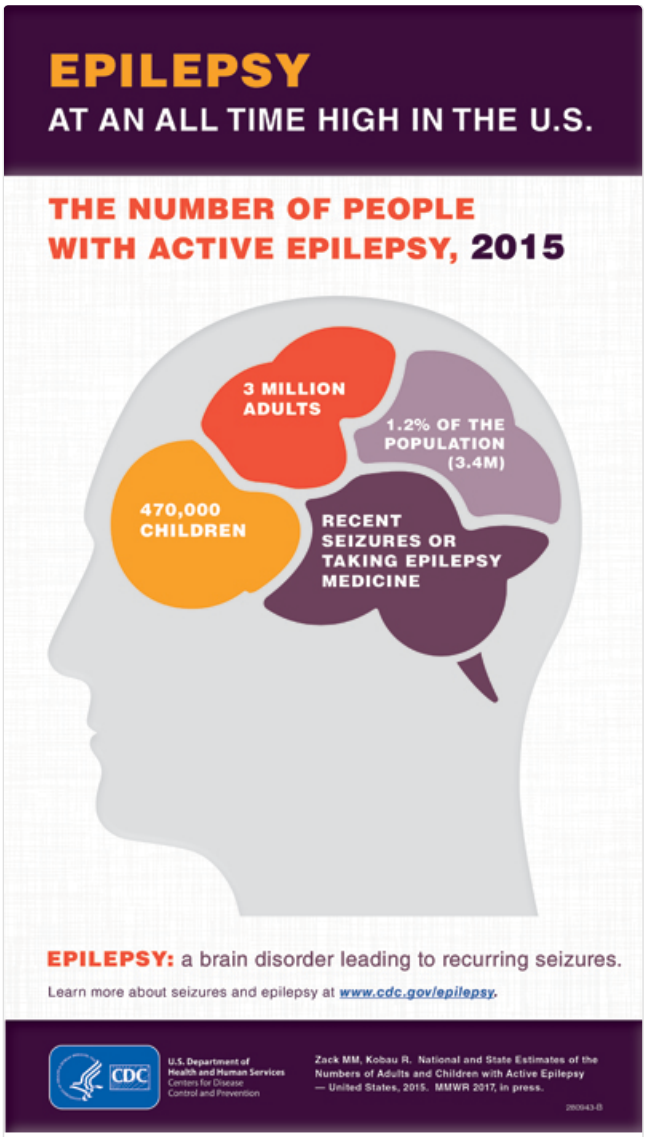
“Epilepsy is common, complex to live with, and costly. It can lead to early death if not appropriately treated,” said Rosemarie Kobau, M.P.H, head of CDC’s Epilepsy Program. “Everyone should know how to recognize a seizure and how to give appropriate first aid.”

Recognizing seizures

There are at least 30 different types of seizures. Sometimes it is hard to tell that a person is having a seizure. People having some types of seizures may seem confused or look like they are staring at something that isn’t there. Other seizures can cause people to fall, shake, and become unaware of what’s going on around them.

First aid for seizures involves keeping the person safe until the seizure stops on its own and knowing when to call 911 for emergency assistance.

People should share concerns about their seizure symptoms with their doctors. A person with epilepsy who has uncontrolled seizures may want to see a neurologist specifically trained to treat epilepsy. Health care providers should learn more about how to classify seizures and treat epilepsy appropriately.



More Americans have epilepsy than ever before
Epilepsy At a Glance
Different types of seizures
First aid for seizures

CDC’s Partnership efforts to address epilepsy

CDC’s Epilepsy Program collects data to monitor epilepsy trends, mortality, costs, and impact on families. CDC also collaborates with partners such as the Epilepsy Foundation, the American Epilepsy Society, and other researchers to:

- Keep children and adults with epilepsy safe in their communities by conducting seizure recognition and first aid training programs for school nurses, school staff, law enforcement, first responders, child care providers, and older adult caregivers.
- Reach rural and underserved populations with proven epilepsy self-management programs that can reduce health care costs and improve quality of life.

For more information about epilepsy and CDC's Epilepsy Program, visit www.cdc.gov/epilepsy.

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Page last reviewed: August 10, 2017 (archived document)
Content source: Centers for Disease Control and Prevention

EXHIBIT 93

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Vaccine Safety

Childhood Vaccines and Febrile Seizures

What is a febrile seizure?

Sometimes, fevers can cause a child to experience spasms or jerky movements called seizures. Seizures caused by fever are called "febrile seizures." They are most common with fevers of 102°F (38.9°C) or higher, but they can also happen at lower body temperatures or when a fever is going down. Most febrile seizures last for less than one or two minutes.

Febrile seizures can be frightening, but nearly all children who have a febrile seizure recover quickly. Febrile seizures do not cause any permanent harm and do not have any lasting effects.

Febrile seizures can happen with any condition that causes a fever.

Fevers can be caused by common childhood illnesses like colds, the flu, an ear infection, or roseola. Vaccines can sometimes cause fevers, but febrile seizures are uncommon after vaccination.

Infants and young children are most at risk for febrile seizures.

Up to 5% of young children will have a febrile seizure at some time in their life. Febrile seizures happen in children between the ages of 6 months and 5 years, with most occurring between 14–18 months of age. About 1 out of every 3 children who have a febrile seizure will have at least one more during childhood. **There is a small increased risk for febrile seizures after MMR and MMRV vaccines.**

Studies have shown a small increased risk for febrile seizures during the 5 to 12 days after a child has received their first vaccination with the measles, mumps, rubella (MMR) vaccine. The risk is slightly higher with the measles, mumps, rubella, varicella (MMRV) combination vaccine, but the risk is still small. Studies have not shown an increased risk for febrile seizures after the separate varicella (chickenpox) vaccine.

There is a small increased risk for febrile seizures when inactivated influenza vaccine (flu shot) is given at the same doctor visit as either the PCV13 (pneumococcal) vaccine or the DTaP vaccine.

A CDC study of children aged 6 months to 2 years has shown a small increased risk for febrile seizures during the 24 hours after a child receives the inactivated influenza vaccine (flu shot) at the same time as the pneumococcal 13-valent conjugate (PCV13) vaccine or the diphtheria, tetanus, acellular pertussis (DTaP) vaccine. The flu shot was not associated with an increased risk of febrile seizures when it was given on a different day from the other two vaccines. Studies have not shown an increased risk for febrile seizures after the DTaP vaccine, except when it is given at the same time as the flu shot. **There may be a small increase in the risk of febrile seizure when PCV13 (pneumococcal) vaccine is given by itself.**

The risk of febrile seizure with any combination of these vaccines is small (at most 30 febrile seizures in 100,000 children vaccinated) and CDC's Advisory Committee on Immunization Practices (ACIP) continues to encourage the vaccination of children according to the vaccination schedule, which allows for the flu, pneumococcal and DTaP vaccinations to be given during the same doctor's visit.

Vaccines can also help prevent febrile seizures.

Vaccinating children at the recommended age may prevent some febrile seizures by protecting children against measles, mumps, rubella, chickenpox, influenza, pneumococcal infections and other diseases that can cause fever and febrile seizures.

CDC and FDA closely monitor the safety of all vaccines.

CDC and the Food and Drug Administration (FDA) are committed to ensuring that vaccines provided to the public are safe and effective. Once vaccines are licensed in the United States, CDC and FDA monitor the safety of these vaccines through several systems. If any vaccine is found to cause health problems, the vaccine may be withdrawn and no longer given to the public.

For more information, see Questions and Answers on Febrile Seizures Following Childhood Vaccinations, Including Influenza Vaccination.

Related Links

Immunizations for Infants and Toddlers

National Institutes of Health – Febrile Seizures Fact Sheet

Febrile Seizures Following Childhood Vaccinations

MMRV and Febrile Seizures

Page last reviewed: January 29, 2020

Content source: Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Healthcare Quality Promotion (DHQP)

EXHIBIT 94

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Vaccine Safety

Measles, Mumps, Rubella (MMR) Vaccine

Safety Information

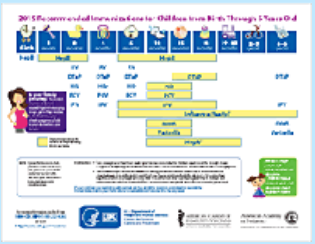
Measles, Mumps, and Rubella Diseases and How to Protect Against Them

Measles causes fever, rash, cough, runny nose, and red, watery eyes. Complications can include ear infection, diarrhea, pneumonia, brain damage, and death.

Mumps causes fever, headache, muscle aches, tiredness, loss of appetite, and swollen salivary glands. Complications can include swelling of the testicles or ovaries, deafness, inflammation of the brain and/or tissue covering the brain and spinal cord (encephalitis/meningitis) and, rarely, death.

Rubella, causes fever, sore throat, rash, headache, and red, itchy eyes. If a woman gets rubella while she is pregnant, she could have a miscarriage or her baby could be born with serious birth defects.

You can protect against these diseases with safe, effective vaccination.



See CDC's Immunization Schedule to view MMR vaccine recommendations.

MMR Vaccine Side Effects

The MMR vaccine is very safe, and it is effective at preventing measles, mumps, and rubella. Vaccines, like any medicine, can have side effects. Most people who get MMR vaccine do not have any serious problems with it. Getting MMR vaccine is much safer than getting measles, mumps or rubella.

Common Side Effects of MMR Vaccine

- Sore arm from the shot
- Fever
- Mild rash
- Temporary pain and stiffness in the joints, mostly in teenage or adult women who did not already have immunity to the rubella component of the vaccine

MMR vaccine has been linked with a very small risk of febrile seizures (seizures or jerking caused by fever). Febrile seizures following MMR are rare and are not associated with any long-term effects. Because the risk of febrile seizures increases as infants get older, it is recommended that they get vaccinated as soon as recommended.

Some people may experience swelling in the cheeks or neck. MMR vaccine rarely causes a temporary low platelet count, which can cause a bleeding disorder that usually goes away without treatment and is not life threatening.

Extremely rarely, a person may have a serious allergic reaction to MMR vaccine. Anyone who has ever had a life-threatening allergic reaction to the antibiotic neomycin, or any other component of MMR vaccine, should not get the vaccine.

Available MMR Vaccine

There is one MMR vaccine approved for use in the United States.
M-M-R II [PDF – 11 pages] The Food and Drug Administration (FDA) approved this vaccine in 1971 for use in people 12 months of age and older.

The measles, mumps, rubella, and varicella (MMRV) vaccine also protects against these diseases.

How CDC Monitors MMR Vaccine Safety

CDC and FDA continuously monitor the safety of vaccines after they are approved. If a problem is found with a vaccine, CDC and FDA will inform health officials, health care providers, and the public.

CDC uses three systems to monitor vaccine safety:

- The Vaccine Adverse Event Reporting System (VAERS): an early warning system that helps CDC and FDA monitor problems following vaccination. Anyone can report possible vaccine side effects to VAERS.
- The Vaccine Safety Datalink (VSD): a collaboration between CDC and nine health care organizations which allows ongoing monitoring and proactive searches of vaccine-related data.
- The Clinical Immunization Safety Assessment (CISA) Project: a partnership between CDC and several medical centers that conducts clinical research on vaccine-associated health risks.

A Closer Look at the Safety Data

- Two recent studies (Rowhani-Rahbar et al, 2013 ; Klein et al, 2010) indicate that for every 10,000 children who get their first MMR and varicella vaccines as separate shots when they are 12-23 months old, about four will have a febrile seizure during the 7-10 days following vaccination. Children of the same age who get the combined measles, mumps, rubella and varicella (MMRV) vaccine as their first vaccine against these diseases are twice as likely to have a febrile seizure during the same time period.
- Studies have shown that for children younger than 7 years old, there is a very small increased risk of febrile seizures approximately 6 to 14 days after MMR vaccination; this happens in about 1 in 3,000 to 4,000 children.
- Joint pain is associated with the rubella portion of MMR vaccine among people who do not have immunity to rubella. Joint pain and temporary arthritis happen more often after MMR vaccination in adults than in children. Women also experience this reaction more often than men. Joint pain or stiffness occurs in up to 1 in 4 of females past puberty who were not previously immune to rubella; their symptoms generally begin 1 to 3 weeks after vaccination, are usually mild and last about 2 days. These symptoms rarely come back.
- Immune thrombocytopenic purpura (ITP) is a disorder that decreases the body's ability to stop bleeding. It can happen after both natural measles infection as well as after getting the MMR vaccine. However, it is usually not life threating. Treatment may include blood transfusion and medications. The risk of ITP has been shown to be increased in the six weeks following an MMR vaccination, with one study estimating 1 case per 40,000 vaccinated children.
- Measles inclusion body encephalitis, or severe brain swelling caused by the measles virus, is a complication of getting infected with the wild-type measles virus. While rare, this disorder almost always happens in patients with weakened immune systems. The illness usually develops within 1 year after initial measles infection and has a high death rate. There have been three published reports of this complication happening to vaccinated people. In these cases, encephalitis developed between 4 and 9 months after MMR vaccination. In one case, the measles vaccine strain was identified as the cause.
- Some parents might worry that the vaccine causes autism. Signs of autism typically appear around the same time that children are recommended to receive the MMR vaccine. Vaccine safety experts, including experts at CDC and the American Academy of Pediatrics (AAP), agree that MMR vaccine is not responsible for increases in the number of children with autism. Read more about vaccines and autism.

More Resources

- MMR Vaccine Information Statement
- MMR Vaccine: Who Should Not Get Vaccinated
- Two Options for Protecting Your Child Against Measles, Mumps, Rubella, and Varicella
- The MMR Decision Aid from the Australia National Centre for Immunisation Research & Surveillance
- Q&As About the Options for Protecting Your Child Against Measles, Mumps, Rubella, and Varicella
- Fact Sheet for Healthcare Providers: MMR & Varicella Vaccines or MMRV Vaccine – Discussing Options with Parents
- Q&As About Vaccination Options for Preventing Measles, Mumps, Rubella, and Varicella: Questions and Answers for Healthcare Providers
- CDC Studies on Vaccines and Autism [PDF – 2 pages]

Featured resource: **Understanding MMR Vaccine Safety** [PDF – 2 pages]

Related Scientific Articles

2011 – Present

Jain A, Marshall J, Buikema A, Bancroft T, Newschaffer CJ. Autism occurrence by MMR vaccine status among US children with older siblings with and without autism , *JAMA* 2015 Apr 21:313(15):1534-40.

Rowhani-Rahbar A, Fireman B, Lewis E, Nordin J, Naleway A, et al. Effect of age on the risk of Fever and seizures following immunization with measles-containing vaccines in children . *JAMA Pediatr*. 2013 Dec;167(12):1111-7.

2001-2010

1990-2000

Prior to 1990

Related Links

Multiple Vaccines and the Immune System

Childhood Vaccines and Febrile Seizures

Immunization Action Coalition: MMR vaccine does not cause autism

Frequently Asked Questions about Multiple Vaccines

Page last reviewed: June 8, 2020, 12:00 AM

Content source: Centers for Disease Control and Prevention, National Center for Emerging and Zoonotic Infectious Diseases (NCEZID), Division of Healthcare Quality Promotion (DHQP)

EXHIBIT 95

Genetics Home Reference | Your Guide to Understanding Genetic Conditions

Tourette syndrome

Tourette syndrome is a complex disorder characterized by repetitive, sudden, and involuntary movements or noises called tics. Tics usually appear in childhood, and their severity varies over time. In most cases, tics become milder and less frequent in late adolescence and adulthood.

Tourette syndrome involves both motor tics, which are uncontrolled body movements, and vocal or phonic tics, which are outbursts of sound. Some motor tics are simple and involve only one muscle group. Simple motor tics, such as rapid eye blinking, shoulder shrugging, or nose twitching, are usually the first signs of Tourette syndrome. Motor tics also can be complex (involving multiple muscle groups), such as jumping, kicking, hopping, or spinning.

Vocal tics, which generally appear later than motor tics, also can be simple or complex. Simple vocal tics include grunting, sniffing, and throat-clearing. More complex vocalizations include repeating the words of others (echolalia) or repeating one's own words (palilalia). The involuntary use of inappropriate or obscene language (coprolalia) is possible, but uncommon, among people with Tourette syndrome.

In addition to frequent tics, people with Tourette syndrome are at risk for associated problems including attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), anxiety, depression, and problems with sleep.

Frequency

Although the exact incidence of Tourette syndrome is uncertain, it is estimated to affect 1 to 10 in 1,000 children. This disorder occurs in populations and ethnic groups worldwide, and it is more common in males than in females.

Causes

A variety of genetic and environmental factors likely play a role in causing Tourette syndrome. Most of these factors are unknown, and researchers are studying risk factors before and after birth that may contribute to this complex disorder. Scientists believe that tics may result from changes in brain chemicals (neurotransmitters) that are responsible for producing and controlling voluntary movements.

Mutations involving the *SLITRK1* gene have been identified in a small number of people with Tourette syndrome. This gene provides instructions for making a protein that is active in the brain. The SLITRK1 protein probably plays a role in the development of nerve cells, including the growth of specialized extensions (axons and dendrites) that allow each nerve cell to communicate with nearby cells. It is unclear how mutations in the *SLITRK1* gene can lead to this disorder.

Most people with Tourette syndrome do not have a mutation in the *SLITRK1* gene. Because mutations have been reported in so few people with this condition, the association of the *SLITRK1* gene with this disorder has not been confirmed. Researchers suspect that changes in other genes, which have not been identified, are also associated with Tourette syndrome.

Inheritance Pattern

The inheritance pattern of Tourette syndrome is unclear. Although the features of this condition can cluster in families, many genetic and environmental factors are likely to be involved. Among family members of an affected person, it is difficult to predict who else may be at risk of developing the condition.

Tourette syndrome was previously thought to have an autosomal dominant pattern of inheritance, which suggests that one mutated copy of a gene in each cell would be sufficient to cause the condition. Several decades of research have shown that this is not the case. Almost all cases of Tourette syndrome probably result from a variety of genetic and environmental factors, not changes in a single gene.

Other Names for This Condition

- Chronic Motor and Vocal Tic Disorder
- Gilles de la Tourette Syndrome
- Gilles de la Tourette's syndrome
- GTS
- TD
- Tourette Disorder
- Tourette's Disease
- TS

Diagnosis & Management

Genetic Testing Information

- What is genetic testing?
  /primer/testing/genetictesting
- Genetic Testing Registry: Tourette Syndrome
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C0040517/

Research Studies from ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22Tourette+syndrome%22

Other Diagnosis and Management Resources

- MedlinePlus Encyclopedia: Gilles de la Tourette syndrome
  https://medlineplus.gov/ency/article/000733.htm

Additional Information & Resources

Health Information from MedlinePlus

- Encyclopedia: Gilles de la Tourette syndrome
  https://medlineplus.gov/ency/article/000733.htm
- Health Topic: Tourette Syndrome
  https://medlineplus.gov/tourettesyndrome.html

Genetic and Rare Diseases Information Center

- Tourette syndrome
  https://rarediseases.info.nih.gov/diseases/7783/tourette-syndrome

Additional NIH Resources

- National Institute of Neurological Disorders and Stroke: Tourette Syndrome Fact Sheet
  https://www.ninds.nih.gov/Disorders/All-Disorders/Tourette-Syndrome-Information-Page

Educational Resources

- Boston Children's Hospital
  http://www.childrenshospital.org/conditions-and-treatments/conditions/t/tourettes-syndrome
- Cedars-Sinai Medical Center
  https://www.cedars-sinai.edu/Patients/Health-Conditions/Tourette-Syndrome.aspx
- Cincinnati Children's Hospital Medical Center
  https://www.cincinnatichildrens.org/health/t/tics-ts-meds
- Great Ormond Street Hospital for Children (UK)
  https://www.gosh.nhs.uk/conditions-and-treatments/conditions-we-treat/tourette-syndrome
- KidsHealth from the Nemours Foundation
  https://kidshealth.org/en/parents/tourette.html
- MalaCards: gilles de la tourette syndrome
  https://www.malacards.org/card/gilles_de_la_tourette_syndrome
- Merck Manual Consumer Version
  https://www.merckmanuals.com/home/children-s-health-issues/neurologic-disorders-in-children/tourette-syndrome-and-other-tic-disorders-in-children-and-adolescents

- Orphanet: NON RARE IN EUROPE: Tourette syndrome
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=856
- University of Virginia Health System
  https://uvahealth.com/services/neurology/tourette-syndrome

Patient Support and Advocacy Resources

- Tourette Syndrome Association
  https://tourette.org/
- Tourette Syndrome Foundation of Canada
  https://tourette.ca/

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28Tourette+Syndrome%5BMAJR%5D%29+AND+%28Tourette+syndrome%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

- GILLES DE LA TOURETTE SYNDROME
  http://omim.org/entry/137580

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Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/condition/tourette-syndrome

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Department of Health & Human Services

EXHIBIT 96

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Tourette Syndrome (TS)

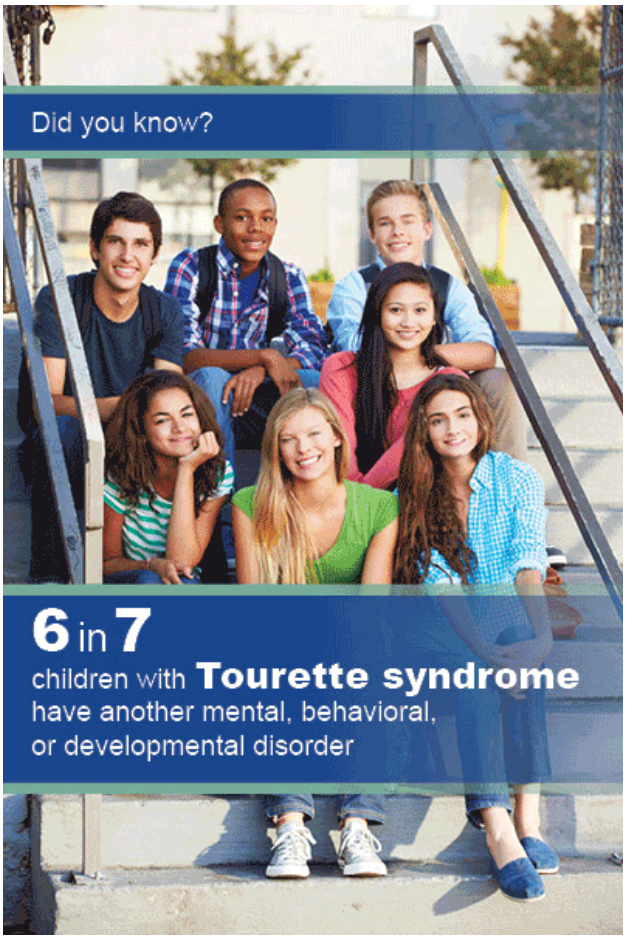
Data & Statistics on Tourette Syndrome

* The data on this page are from the study, "A National Profile of Tourette Syndrome, 2011-2012." unless otherwise noted. [Read article]1 [Read article on findings for 2007-08 data]2

How many children have Tourette Syndrome?

We do not know exactly how many people have Tourette Syndrome (TS).

- Studies that included children with diagnosed and undiagnosed TS have estimated that 1 of every 162 children (0.6%) have TS.
- A CDC study using parent report found that 1 of every 360 (0.3%) children 6 – 17 years of age in the US have received a diagnosis of TS; this is about 138,000 children.
- This suggests that about half of children with TS are not diagnosed.
- Among children diagnosed with TS,
  - 37% have been reported as having moderate or severe forms of the condition.
  - Boys are three to five times more likely to have TS than girls. People from all racial and ethnic groups can have TS. Non-Hispanic white children are twice as likely to have a TS diagnosis as Hispanic and non-Hispanic black children.
  - Children 12 – 17 years of age are twice as likely to have TS as children 6 – 11 years of age.



How many children with TS have another disorder?

- Among children diagnosed with TS, 86% also have been diagnosed with at least one additional mental, behavioral, or developmental disorder, such as:
  - 63% had ADHD.
  - 26% had behavioral problems, such as oppositional defiant disorder (ODD) or conduct disorder (CD).
  - 49% had anxiety problems.
  - 25% had depression.

What parents say about Tourette and development

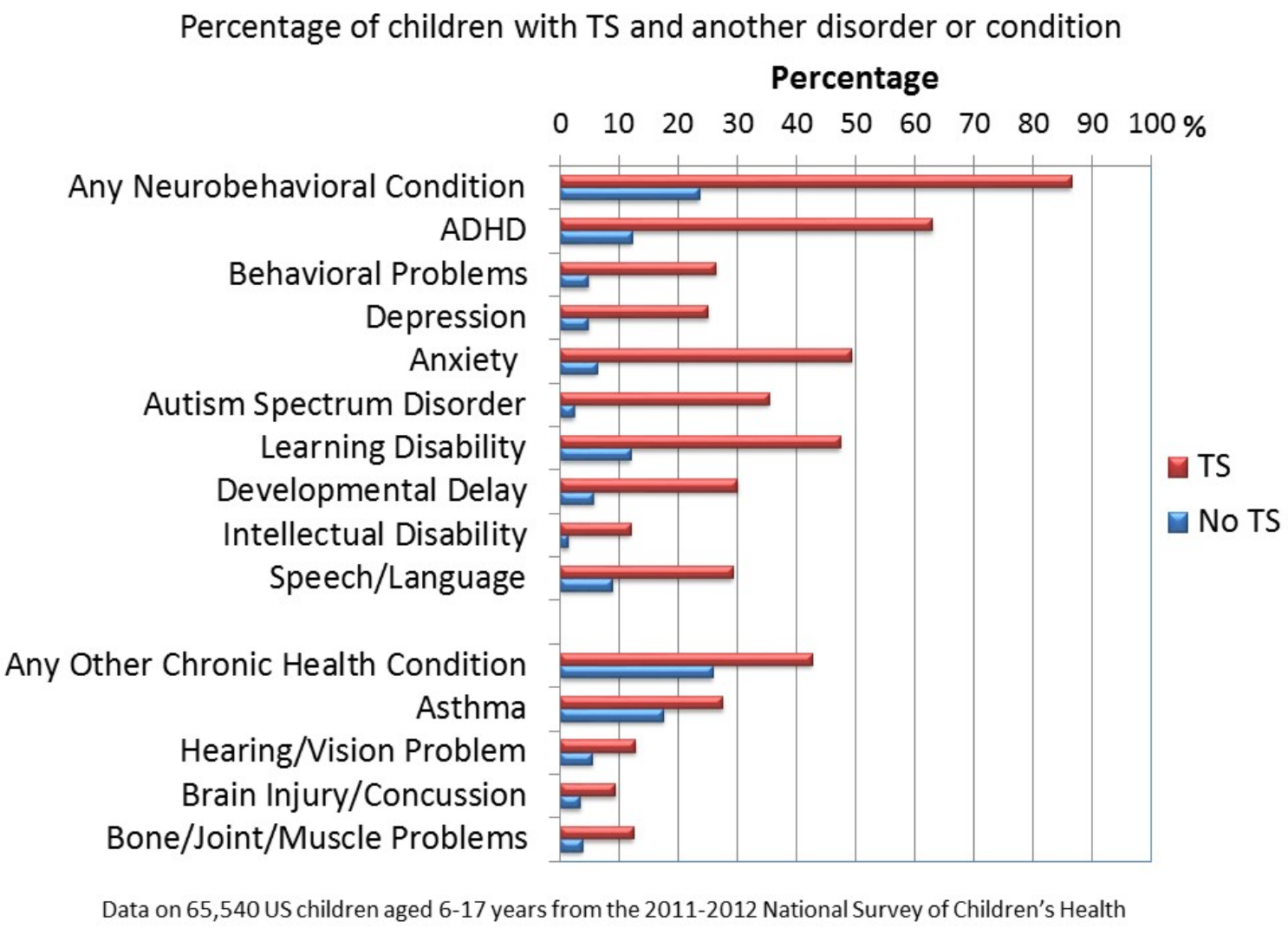
A recent survey of parents of children with Tourette syndrome found[1]

- Parents typically first noticed tics in children at about 6 years of age on average (in early elementary school).
- The average time from initially noticing tics to receiving a diagnosis of Tourette syndrome was about 2 years.
- The average age when Tourette symptoms were most severe was 9 years of age.
- Most parents reported their child's tics were noticeable to strangers.
- How much tics interfere with daily functioning was linked to how severe the symptoms were.
- Almost 70% of parents reported that major changes, like starting a new school, moving into a new class, or being tired made their child's tics worse.
- About half of the parents reported that exercise or quiet hobbies made tics better.

Read more

had autism spectrum disorder.

  - 47% had learning disabilities.
  - 29% had speech or language problems.
  - 30% had developmental delays.
  - 12% had intellectual disabilities.
- More than one-third of people with TS also have obsessive-compulsive disorder.[3,4]
- 42.6% have at least one co-occuring chronic health condition.



View Larger

New Study

Children with Tourette syndrome are more likely to struggle with social competence, particularly when they have moderate to severe Tourette syndrome and when they are diagnosed with other mental, emotional, or behavioral disorders.

Read more

Life Course of TS

In most cases, tics decrease during adolescence and early adulthood, and sometimes disappear entirely; however, many experience tics into adulthood and, in some cases, tics can become worse in adulthood.[4, 5]

- One study that followed youth with TS over time found that at 18 years of age, almost half (47%) of the youth had been tic-free the week before they were interviewed, just over 10% had minimal tics, over a quarter (28%) had mild symptoms, and 11% had moderate to severe tics.[2,3]

Public Health Impact of TS

CDC is working to understand TS and to improve the health and wellbeing of people with TS. Learn about what public health can do to **bridge the gaps in knowledge** to help individuals with Tourette Syndrome.

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Page last reviewed: June 12, 2020
Content source: National Center on Birth Defects and Developmental Disabilities,, Centers for Disease Control and Prevention

EXHIBIT 97

Tourette Syndrome (TS)

Risk Factors and Causes for Tourette Syndrome

Scientists are studying the causes of and risk factors for Tourette Syndrome (TS) in an effort to understand it better, and to find better ways to manage TS and to reduce the chances of a person having TS. The causes of TS and other tic disorders are not well understood.

Although the risk factors for and causes of TS are unknown, current research shows that *genes* play an important role:[1,2]

- Genetic studies have indicated that TS is inherited as a dominant gene, with about a 50% chance of parents passing the gene on to their children.
- Boys with the gene(s) are three to four times more likely than girls to display symptoms of TS.
- TS can be triggered by abnormal metabolism (breakdown) of a chemical in the brain called dopamine.

Some research has shown that TS is a genetically complex disorder that likely occurs as a result of the effects of multiple genes interacting with other factors in the environment. Scientists are studying other possible causes and environmental risk factors that might contribute to TS. Some studies have shown that the following factors might be associated with TS, but additional research is needed to better understand these associations:[2, 3]

- Smoking during pregnancy.
- Pregnancy complications.
- Low birthweight.
- Infection. Researchers have found mixed results about whether certain children are more likely to develop tics following infections.[2,4]

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3. Ting-Kuang C, Jing H, Pringsheim T. Prenatal risk factors for Tourette Syndrome: a systematic review. BMC Pregnancy & Childbirth. 2014; 14(1): 1-27.
4. Orlovska, S, Vestergaard, CH, Bech, BH, Nordentoft, M, Vestergaard, M, & Benros, ME. Association of streptococcal throat infection with mental disorders: Testing key aspects of the PANDAS hypothesis in a nationwide study. JAMA Psychiatry. 2017; 74(7): 740-746.

Page last reviewed: May 13, 2020

EXHIBIT 98

COVID-19 is an emerging, rapidly evolving situation.

Get the latest public health information from CDC: https://www.coronavirus.gov
Get the latest research information from NIH: https://www.nih.gov/coronavirus

The National Institute of Mental Health: www.nimh.nih.gov

Mental Illness

Mental illnesses are common in the United States. Nearly one in five U.S. adults live with a mental illness (46.6 million in 2017). Mental illnesses include many different conditions that vary in degree of severity, ranging from mild to moderate to severe. Two broad categories can be used to describe these conditions: Any Mental Illness (AMI) and Serious Mental Illness (SMI). AMI encompasses all recognized mental illnesses. SMI is a smaller and more severe subset of AMI. Additional information on mental illnesses can be found on the NIMH Health Topics Pages (www.nimh.nih.gov//health/topics/index.shtml).

Definitions

The data presented here are from the 2017 National Survey on Drug Use and Health (NSDUH) by the Substance Abuse and Mental Health Services Administration (SAMHSA). For inclusion in NSDUH prevalence estimates, mental illnesses include those that are diagnosable currently or within the past year; of sufficient duration to meet diagnostic criteria specified within the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV); and, exclude developmental and substance use disorders.

Any Mental Illness

Any mental illness (AMI) is defined as a mental, behavioral, or emotional disorder. AMI can vary in impact, ranging from no impairment to mild, moderate, and even severe impairment (e.g., individuals with serious mental illness as defined below).

Serious Mental Illness

Serious mental illness (SMI) is defined as a mental, behavioral, or emotional disorder resulting in serious functional impairment, which substantially interferes with or limits one or more major life activities. The burden of mental illnesses is particularly concentrated among those who experience disability due to SMI.

Prevalence of Any Mental Illness (AMI)

Figure 1 shows the past year prevalence of AMI among U.S. adults.

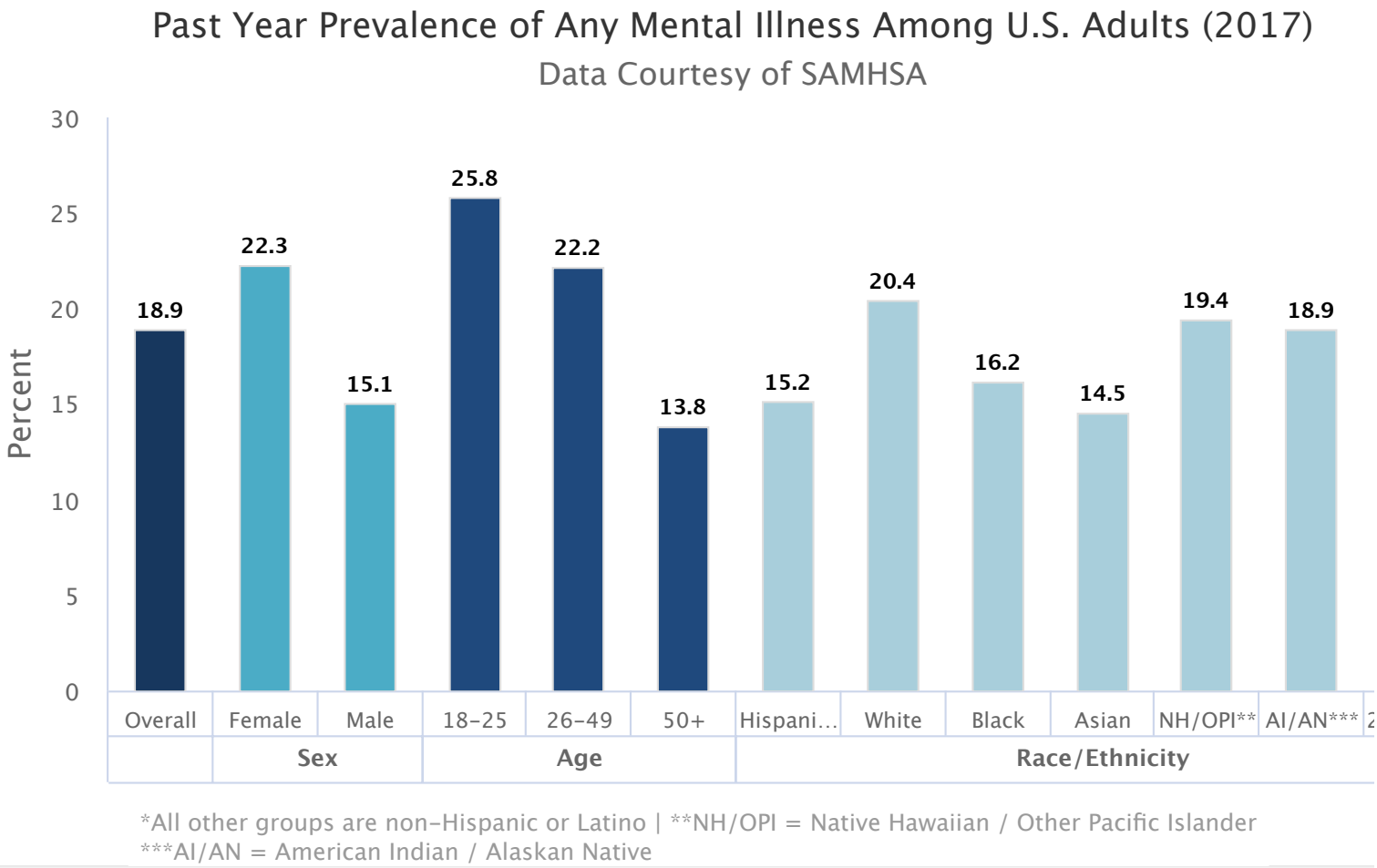
In 2017, there were an estimated 46.6 million adults aged 18 or older in the United States with AMI. This number represented 18.9% of all U.S. adults.

The prevalence of AMI was higher among women (22.3%) than men (15.1%).

Young adults aged 18-25 years had the highest prevalence of AMI (25.8%) compared to adults aged 26-49 years (22.2%) and aged 50 and older (13.8%).

The prevalence of AMI was highest among the adults reporting two or more races (28.6%), followed by White adults (20.4%). The prevalence of AMI was lowest among Asian adults (14.5%).

Figure 1



Mental Health Services — AMI

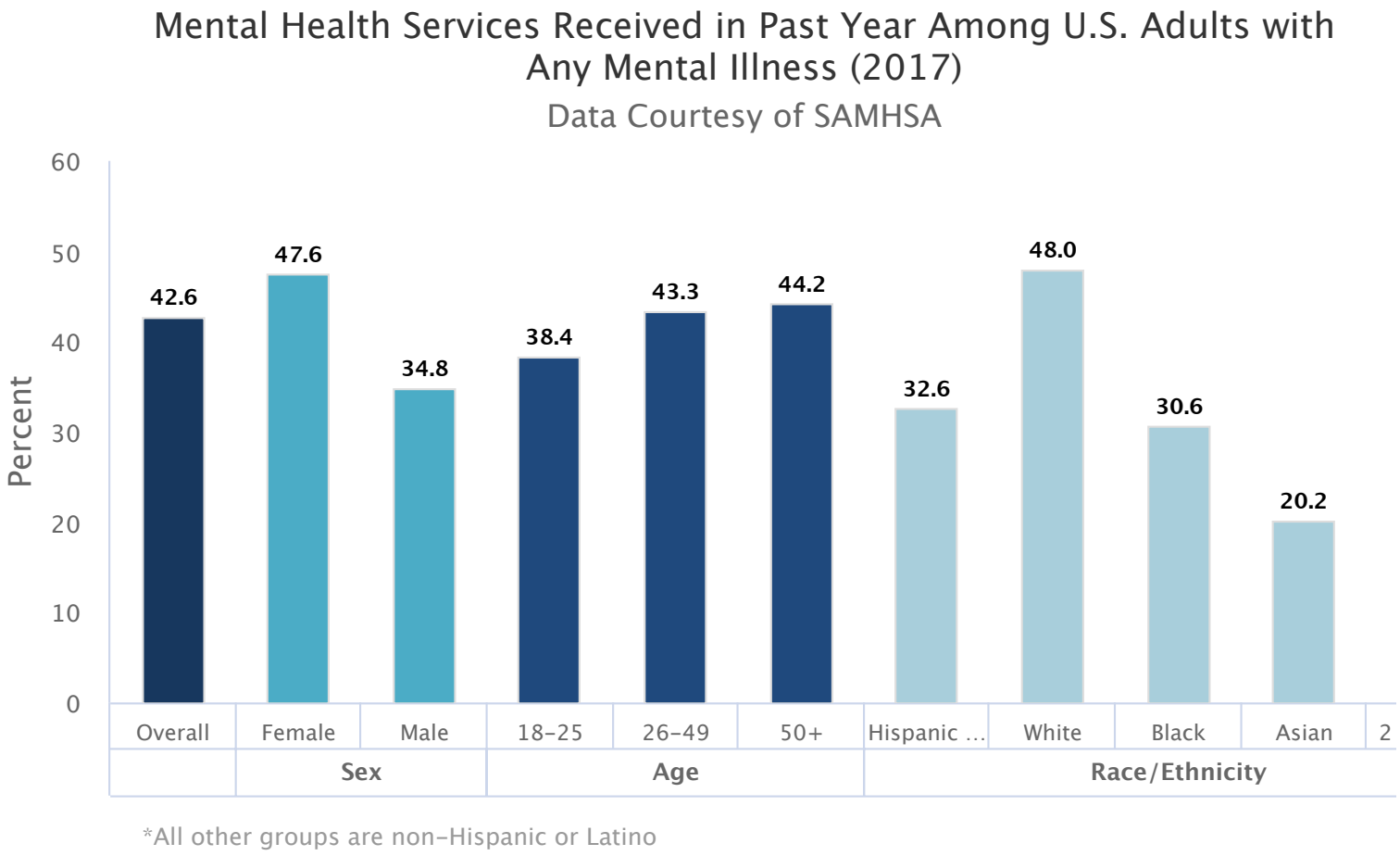
Figure 2 presents data on mental health services received within the past year by U.S. adults aged 18 or older with any mental illness (AMI). NSDUH defines mental health services as having received inpatient treatment/counseling or outpatient treatment/counseling, or having used prescription medication for problems with emotions, nerves, or mental health.

In 2017, among the 46.6 million adults with AMI, 19.8 million (42.6%) received mental health services in the past year.

More women with AMI (47.6%) received mental health services than men with AMI (34.8%).

The percentage of young adults aged 18-25 years with AMI who received mental health services (38.4%) was lower than adults with AMI aged 26-49 years (43.3%) and aged 50 and older (44.2%).

Figure 2



Prevalence of Serious Mental Illness (SMI)

Figure 3 shows the past year prevalence of SMI among U.S. adults.

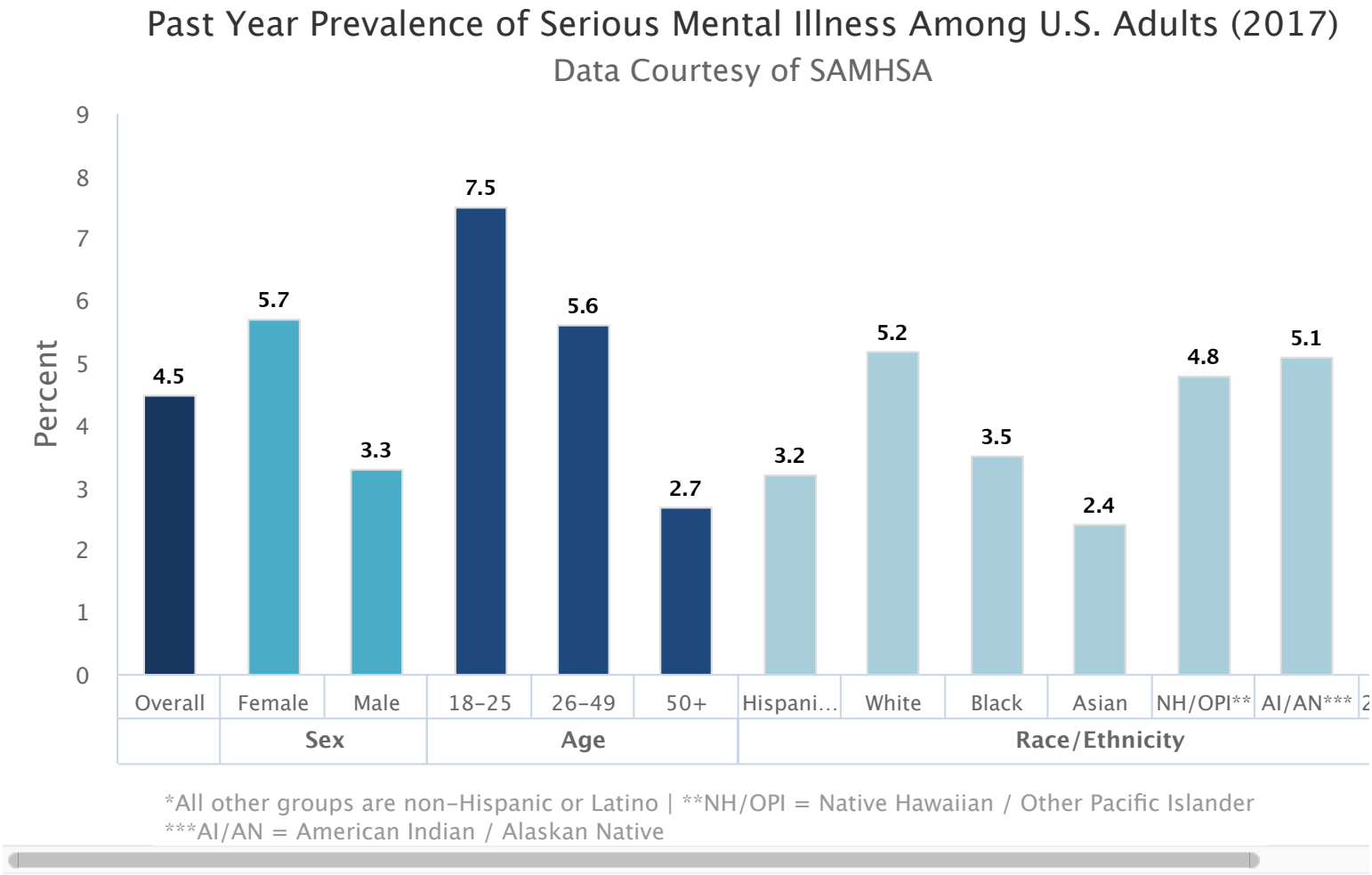
In 2017, there were an estimated 11.2 million adults aged 18 or older in the United States with SMI. This number represented 4.5% of all U.S. adults.

The prevalence of SMI was higher among women (5.7%) than men (3.3%).

Young adults aged 18-25 years had the highest prevalence of SMI (7.5%) compared to adults aged 26-49 years (5.6%) and aged 50 and older (2.7%).

The prevalence of SMI was highest among the adults reporting two or more races (8.1%), followed by White adults (5.2%). The prevalence of SMI was lowest among Asian adults (2.4%).

Figure 3



Mental Health Services — SMI

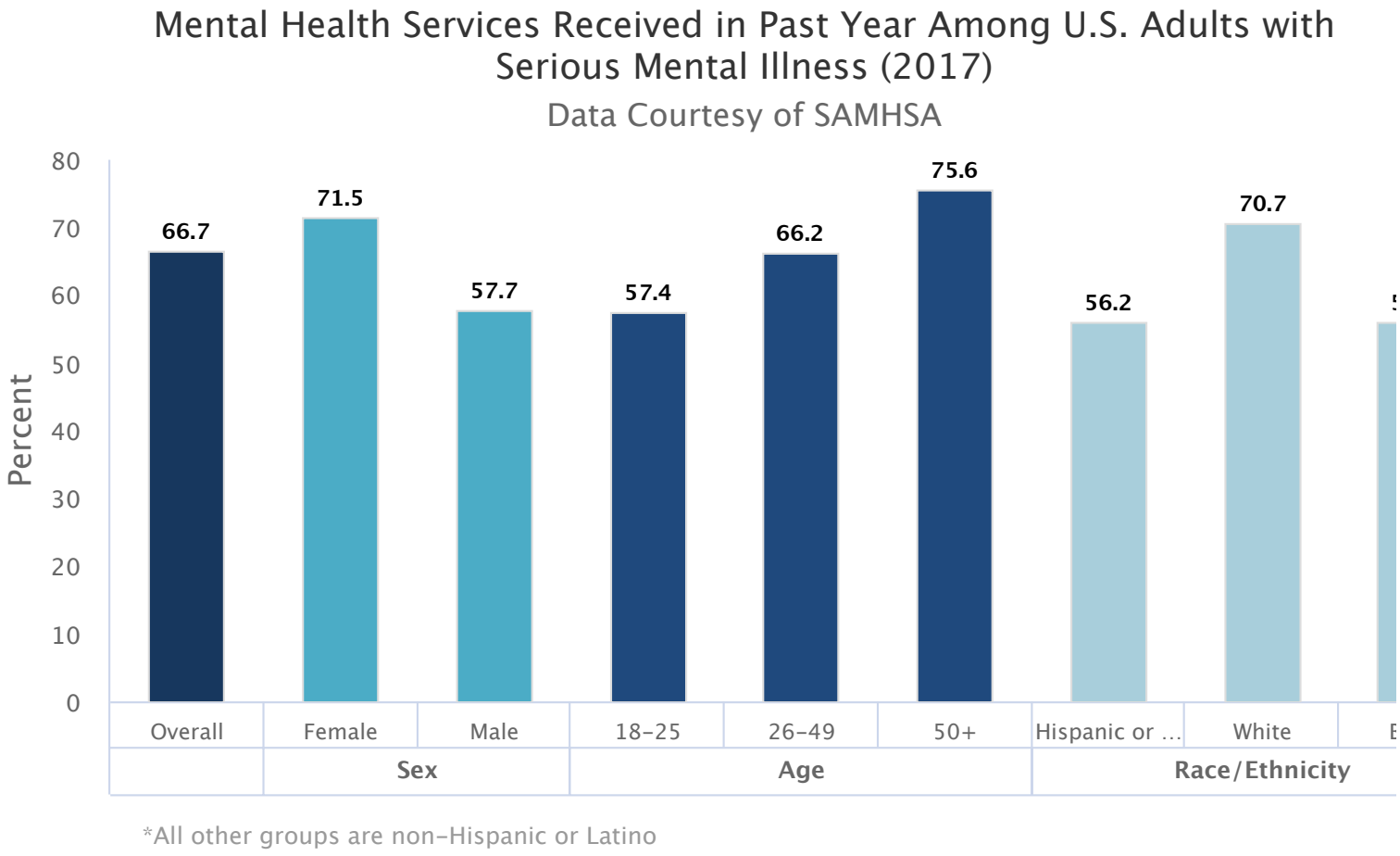
Figure 4 presents data on mental health services received within the past year by U.S. adults 18 or older with serious mental illness (SMI). The NSDUH defines mental health services as having received inpatient treatment/counseling or outpatient treatment/counseling or having used prescription medication for problems with emotions, nerves, or mental health.

In 2017, among the 11.2 million adults with SMI, 7.5 million (66.7%) received mental health treatment in the past year.

More women with SMI (71.5%) received mental health treatment than men with SMI (57.7%).

The percentage of young adults aged 18-25 years with SMI who received mental health treatment (57.4%) was lower than adults with SMI aged 26-49 years (66.2%) and aged 50 and older (75.6%).

Figure 4



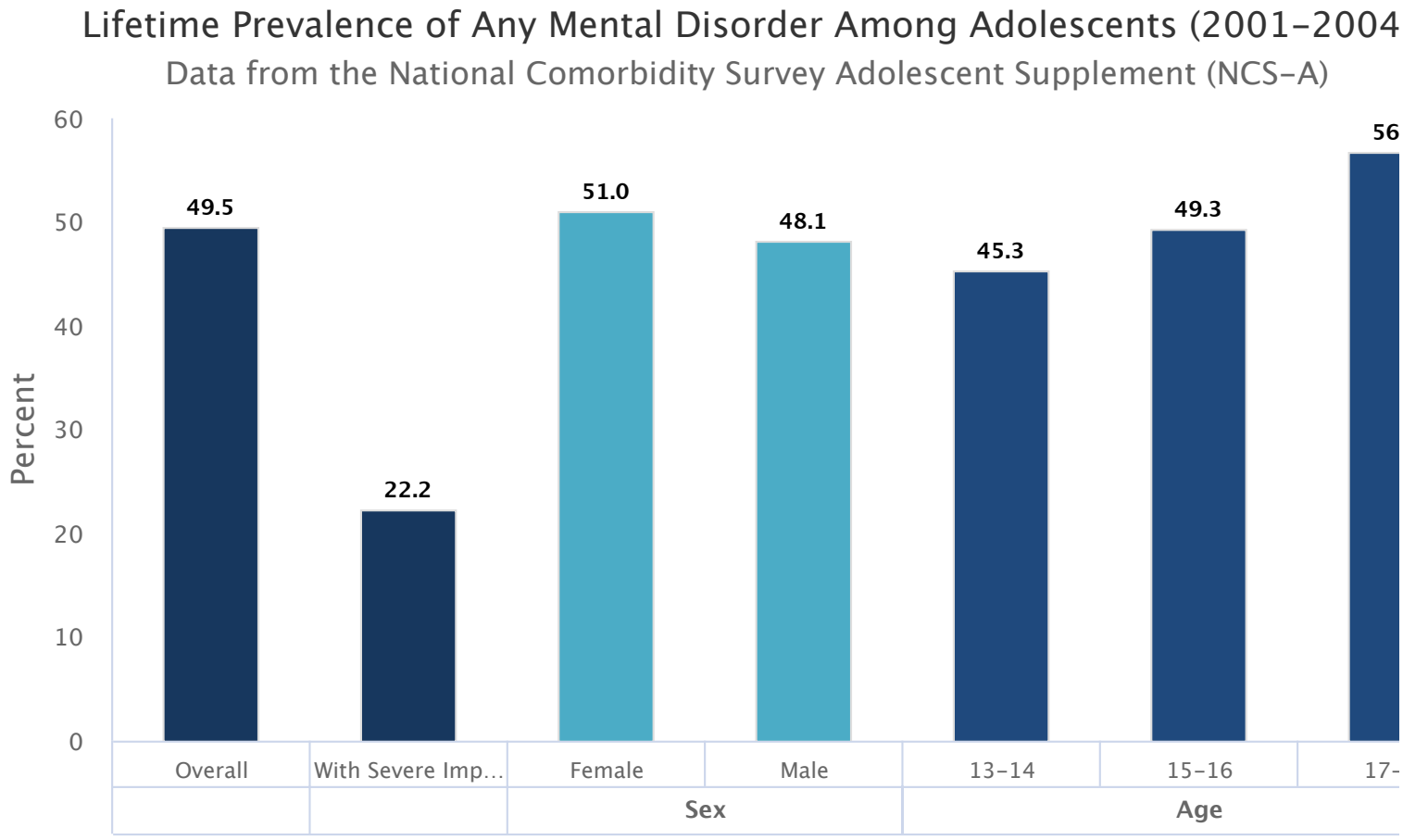
Prevalence of Any Mental Disorder Among Adolescents

Based on diagnostic interview data from National Comorbidity Survey Adolescent Supplement (NCS-A), Figure 5 shows lifetime prevalence of any mental disorder among U.S. adolescents aged 13-18.[1]

An estimated 49.5% of adolescents had any mental disorder.

Of adolescents with any mental disorder, an estimated 22.2% had severe impairment. DSM-IV based criteria were used to determine impairment level.

Figure 5



Data Sources

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Statistical Methods and Measurement Caveats

National Survey on Drug Use and Health (NSDUH)

Diagnostic Assessment:

The NSDUH AMI and SMI estimates were generated from a prediction model created from clinical interview data collected on a subset of adult NSDUH respondents who completed an adapted (past12 month) version of the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (Research Version, Non-patient Edition) (SCID-I/NP; First, Spitzer, Gibbon, & Williams, 2002), and was differentiated by level of functional impairment based on the Global Assessment of Functioning Scale (GAF; Endicott, Spitzer, Fleiss, & Cohen, 1976).
The assessment included diagnostic modules assessing: mood, anxiety, eating, impulse control, substance use, adjustment disorders, and a psychotic symptoms screen.
The assessment did not contain diagnostic modules assessing: adult attention deficit hyperactivity disorder (ADHD), autism spectrum disorders, schizophrenia or other psychotic disorders (although the assessment included a psychotic symptom screen).
People who only have disorders that are not included in these diagnostic modules may not be adequately detected. However, there are known patterns of high comorbidities among mental disorders; these patterns increase the likelihood that people who meet AMI and/or SMI criteria were detected by the study, as they may also have one or more of the disorders assessed in the SCID-I/NP.

Population:

The entirety of NSDUH respondents for the AMI and SMI estimates were the civilian, non-institutionalized population aged 18 years old or older residing within the United States.
The survey covered residents of households (persons living in houses/townhouses, apartments, condominiums; civilians living in housing on military bases, etc.) and persons in non-institutional group quarters (e.g., shelters, rooming/boarding houses, college dormitories, migratory workers' camps, and halfway houses).
The survey did not cover persons who, for the entire year, had no fixed address (e.g., homeless and/or transient persons not in shelters); were on active military duty; or who resided in institutional group quarters (e.g., correctional facilities, nursing homes, mental institutions, long-term hospitals).
Some people in these excluded categories had AMI and/or SMI, but were not accounted for in the NSDUH AMI and/or SMI estimates.

Survey Non-response:

In 2017, 32.9% of the selected NSDUH sample did not complete the interview.
Reasons for non-response to interviewing include: refusal to participate (23.11%); respondent unavailable or never at home (5.0%); and other reasons such as physical/mental incompetence or language barriers (4.8%).
People with mental illness may disproportionately fall into these non-response categories. While NSDUH weighting includes non-response adjustments to reduce bias, these adjustments may not fully account for differential non-response by mental illness status.

Please see the 2017 National Survey on Drug Use and Health Methodological Summary and Definitions report for further information on how these data were collected and calculated.

National Comorbidity Survey Adolescent Supplement (NCS-A)

Diagnostic Assessment and Population:

The NCS-A was carried out under a cooperative agreement sponsored by NIMH to meet a request from Congress to provide national data on the prevalence and correlates of mental disorders among U.S. youth. The NCS-A was a nationally representative, face-to-face survey of 10,123 adolescents aged 13 to 18 years in the continental United States. The survey was based on a dual-frame design that included 904 adolescent residents of the households that participated in the adult U.S. National Comorbidity Survey Replication and 9,244 adolescent students selected from a nationally representative sample of 320 schools. The survey was fielded between February 2001 and January 2004. DSM-IV mental disorders were assessed using a modified version of the fully structured World Health Organization Composite International Diagnostic Interview.

Survey Non-response:

The overall adolescent non-response rate was 24.4%. This is made up of non-response rates of 14.1% in the household sample, 18.2% in the un-blinded school sample, and 77.7% in the blinded school sample. Non-response was largely due to refusal (21.3%), which in the household and un-blinded school samples came largely from parents rather than adolescents (72.3% and 81.0%, respectively). The refusals in the blinded school sample, in comparison, came almost entirely (98.1%) from parents failing to return the signed consent postcard.
For more information, see PMID: 19507169 and the NIMH NCS-A study page (www.nimh.nih.gov//archive/news/2010/national-survey-confirms-that-youth-are-disproportionately-affected-by-mental-disorders.shtml).

Last Updated: February 2019

STATISTICS HOME (www.nimh.nih.gov//health/statistics/index.shtml)

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Top

EXHIBIT 99

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Children's Mental Health

Children's Mental Disorders

Mental disorders among children are described as serious changes in the way children typically learn, behave, or handle their emotions, which cause distress and problems getting through the day.

Healthcare professionals use the guidelines in The American Psychiatric Association's Diagnostic and Statistical Manual, Fifth edition (DSM-5)[1], to help diagnose mental health disorders in children.

Click on these links to learn more about these disorders, including symptoms, treatment, and what can be done to prevent them:

- Anxiety
- Depression
- Oppositional Defiant Disorder (ODD)
- Conduct Disorder (CD)
- Attention-Deficit/Hyperactivity Disorder (ADHD)
- Tourette Syndrome
- Obsessive-Compulsive Disorder (OCD)
- Post-traumatic Stress Disorder (PTSD)

Other conditions and concerns that affect children's learning, behavior, and emotions include learning and developmental disabilities, autism, and risk factors like substance use and self-harm. Read more about related conditions.

Reference

1. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th edition. Arlington, VA., American Psychiatric Association, 2013

Page last reviewed: March 30, 2020
Content source: National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention

EXHIBIT 100

2016 Child Mind Institute Children's Mental Health Report

Mental health disorders are the most common health issues faced by our nation's school-aged children. One in five children suffers from a mental health or learning disorder, and 80% of chronic mental disorders begin in childhood. There is an urgent need to identify the signs of these conditions early in life if children are to get the care and support they need to thrive.[1]

Children struggling with mental health and learning disorders are at risk for poor outcomes in school and in life, and outdated approaches to discipline are only making matters worse. Instead of putting kids further at risk, schools should be identifying and supporting at-risk children. A widely deployed, integrated system of evidence-supported, school-based mental health and preventive services is needed. If we want to help our children and our schools, we cannot wait.

This report examines:

- Negative effects (suspension, dropout) of mental health disorders in school
- Early intervention and prevention programs
- School-wide behavior plans and targeted interventions

Schools present an important opportunity for recognizing early signs of mental health problems in children. K-12 enrollment in the United States is around 55 million,[2] providing our best chance to reach the 17.1 million young people who will be affected by mental health disorders before the age of 18.[3] Working together, parents, educators and professionals can ensure that all children reap the benefits of education and receive the support they deserve.

Introduction

Just as success in school has profound effects in many parts of life, identifying and providing mental health interventions for children in school can have benefits far beyond the classroom. School communities give teachers and administrators important opportunities to share information and work with parents and families. With their concentrations of children and trained caregivers, schools are an ideal place to leverage evidence-based mental health knowledge and make a transformative impact on the mental health landscape of this country.

There is tremendous variability in how schools identify and manage mental health problems in children. Many schools don't have adequate training or resources to recognize and appropriately help children adjust to emotional and behavioral problems. There are an alarming number of incidents in which children with behavioral issues are reprimanded, suspended or expelled from school. Disciplinary infractions in school often land children in trouble with the law because of zero-tolerance policies — the so-called school-to-prison pipeline that pulls troubled or needy students inexorably towards jail. At the same time, youth with anxiety disorders and depression go unrecognized. Dropout rates are as high as 40% among those enrolled in special education programs because of learning, attention or emotional problems.

Schools are by no means ignoring these issues. The results of the only nationally representative sample of adolescents in the United States revealed that schools can and do provide services for youth with attention and behavior problems that are more obvious to teachers and are more common in youth with learning problems. Federal mandates for evaluation and treatment of children with specific learning difficulties have also facilitated care for these children. In fact, young people with access to mental health services in school-based health centers are **10 times more likely to seek care for mental health or substance abuse** than those who do not.[4] But we do not yet have true parity between mental and physical health care, nor do robust mental health services in schools currently exist.

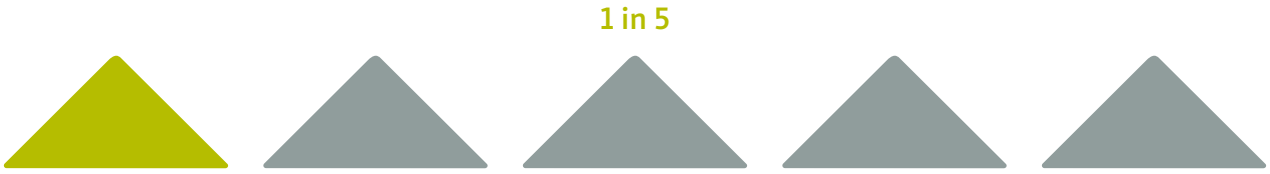
Today, optimal models of care pair school-wide behavior and discipline systems with services using community partners for targeted help. In this report, we provide examples of interventions and approaches that are working to help children with specific disorders and to improve the mental health of all children in the school environment. These programs can work for children today and spur innovation that will help more children tomorrow through the sensible integration of universal approaches with individualized, focused attention from professionals partnering with educators in the school environment.

N.B. Because this report does not generally cover clinical approaches to mental health care, interventions and outcomes are described using the common school-based language of symptoms and behaviors, not diagnoses.

Child Mental Health Disorders Are Common

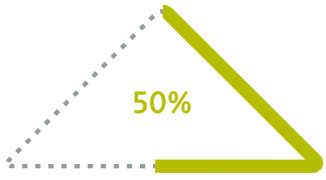
The prevalence of mental health disorders among young people in this country approximates that of adults, and their impact may be even greater in youth because these disorders strike during critical periods of educational, emotional and social development.

17.1 million young people have or have had a diagnosable psychiatric disorder.[5] Put another way, one out of every five children in the US meets criteria for a major mental disorder.

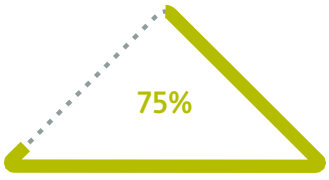


20% of US children have a mental health disorder

Fifty percent of mental health disorders begin before age 14 and 75% before age 24, affecting the learning and school experience for all children.



50% of disorders begin before age 14



75% of disorders begin before age 24

These are disorders of childhood and adolescence that, if untreated, will have a marked effect on students' ability to learn and function in the school environment. For instance:

- 75% of social phobia manifests by age 15
- 75% of separation anxiety disorder manifests by age 10
- 75% of oppositional defiant disorder manifests by age 14
- 75% of ADHD manifests by age 8[6]

Anxiety disorders such as social phobia can make students twice as likely to drop out or fail a grade;[7] ADHD, mood and anxiety symptoms and disruptive behavior at age 6 predict math and reading achievement at age 17;[8] and combinations of mental health disorders (including substance abuse) are predictors for low levels of lifetime educational attainment.[9]

Mental Health Impacts in Schools

Children with mental health and learning disorders face frequent discipline and school failure, which can lead to problems later in life. These trajectories can be corrected, but only with recognition and intervention.

Emotional and behavioral problems can lead to office discipline referrals, school avoidance, suspension and being left back. Mental health and learning disorders can also lead students to drop out of school entirely. The consequences of these school-related discipline problems down the road are serious: underemployment and unemployment, prison, and reduced quality of life.

Problems start early.

- Expulsions in prekindergarten are almost twice as common — **89% higher** — when classrooms don't have regular access to a psychiatrist or psychologist.[10] Only 23% of pre-K programs nationwide have on-site psychiatrists/psychologists or scheduled visits.
- Being at risk for mental health problems **in first grade** leads to a 5% drop in academic performance in **just two years**.[11]

Students in special education are at high risk.

- **More than 77,000 children** in special education receive **suspensions or expulsions for more than 10 cumulative days** in a year—including children with autism, anxiety and learning disorders.[12]
- Those suspended or expelled for more than 10 days include 5.7% of children with emotional disturbance and 2.6% of students with "other health impairments" (OHI), like ADHD.
- In one study of special education students, the suspension/expulsion rate for students with emotional disturbances was 64%.[13]

Despite the stereotype that all special education takes place in separate or "special" classrooms, students served under the Individuals with Disabilities Education Act (IDEA) are very much a part of "mainstream" education because of inclusionary policies that "push in" instead of "pull out." Ninety-five percent of students served under IDEA attend regular schools, and 61.1% of them spend more than 80% of their time in "mainstream" or general classrooms.[14]

95% of special education students attend regular schools

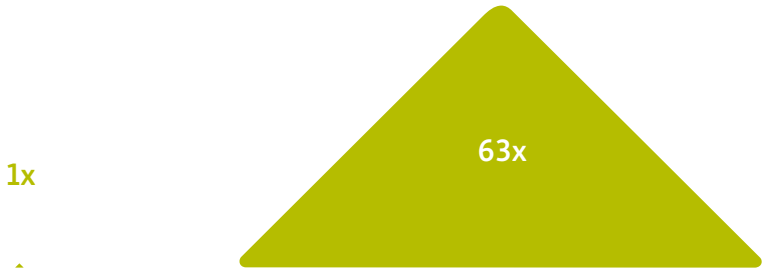
61.1% of them spend more than 80% of their time in mainstream classrooms

Mental health and learning disorders are tied to higher dropout rates. The dropout rate for all students is 7%; for students served under IDEA it is 21.1%; for the subset of students served under IDEA with emotional disturbance, the dropout rate climbs to 38.7%.

Total dropout rate | Dropout rate for special education students | Dropout rate for special education students with emotional disturbance

27,985 children aged 14–21 with autism, emotional disturbance or other health impairments including ADHD drop out each year. And 45,846 students with specific learning disorders drop out each year as well.[15]

Dropout leads to prison. High-school dropouts are 63 times more likely to be jailed than four-year college graduates.[16]



Compared to college graduates, high-school dropouts are 63 times more likely to be jailed

70.4% of youth involved in the juvenile justice system meet criteria for a psychiatric diagnosis,[17] and 68% of state prison inmates have not completed high school.[18]

70.4% of youth involved in the juvenile justice system have a mental illness

68% of state prison inmates have not completed high school

Dropout leads to poor quality of life.

- Persons without a high-school education **live 9.2 fewer years** than persons who graduate from high school.[19]

Higher prevalence of ADHD and LD exacerbates discipline problems.[20]

- States in **regions with above-average rates of ADHD and LD** (FL, District of Columbia) **suspend children at twice the national average.**
- States in **regions with below-average rates of ADHD and LD** (UT, WY, ID) **suspend children at half the national average.**[21]

Suspension and Zero Tolerance

All children face rising rates of suspension, especially minority children; the ill effects of harsh discipline are not limited to children with a mental health diagnosis. But the "zero tolerance" focus on mandatory punishment for certain behaviors targets children with impulse or emotion regulation control problems often caused by mental health disorders.

The use of out-of-school suspension nearly doubled, from 1.7 million in 1974 to 3.1 million in 2001.[22]

Annual suspensions in US public schools, 1974

Annual suspensions in US public schools, 2001

In the same period, enrollment in public elementary and secondary schools increased just 7.5%, from 44 million to 47.6 million.[23]

One study found that **95% of out-of-school suspensions were for nonviolent, minor disruptions** such as tardiness or disrespect.[24]

A Texas study of one million students over the course of six school years found the following:

- 54% experienced at least one in-school suspension over the study period.
- 31% experienced an out-of-school suspension.
- 3% were state-mandated suspensions and expulsions.
- **97% of suspensions were discretionary, in response to conduct codes.**

Compared to their typical peers, suspended students were two times as likely to repeat a grade, and three times more likely to be in contact with the juvenile justice system within a year.[25]

Students without suspensions

Suspended students are twice as likely to repeat a grade

Suspended students are three times more likely to be in contact with the law

These trends are compounded for minority children, particularly those with mental health and learning disorders. **More than 25% of boys of color served under IDEA receive an out-of-school suspension.**

- Black children make up **18% of preschool enrollment, but represent 48% of preschool children who have received more than one out-of- school suspension.**

Preschool enrollment of black children as percentage of total

Preschool suspension rate of black children as percentage of total

- Although black students represent **16% of student enrollment**, they represent 27% of students referred to law enforcement and **31% of students subjected to a school-related arrest.**[26]

School enrollment of black children as percentage of total

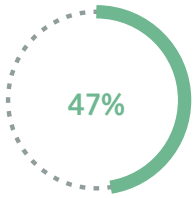
Law enforcement contact rate of black children as percentage of total

School-related arrest rate of black children as percentage of total

What Can We Do?

Given the prevalence of mental health issues in school, it makes sense to focus prevention and intervention efforts there. The emerging research on clinical mental health services in school is promising.

- Access to mental health services in school-based health centers leads to a **tenfold increase in treatment** for mental health or substance abuse.[27]
- **Expulsions in prekindergarten are reduced by more than 47%** when classrooms have regular access to a psychiatrist or psychologist.[28]



Reduction in preschool expulsions with access to mental health professional

However, a dedicated mental health presence in school-based health centers has not yet become a reality on a national scale. A critical shortage of mental health professionals like child and adolescent psychiatrists and clinical child psychologists translates to a knowledge gap in schools concerning how to best manage and mitigate mental health disorders. There are approximately 8,300 practicing child psychiatrists in the United States; the estimated number needed to satisfy demand is 12,600.[29, 30]

Number of child psychiatrists

Estimated demand

Today, schools rely on referrals, community partnerships and universal prevention programs to address the demonstrated need and decrease risk for poor outcomes.

In the following section we look at promising interventions at various levels that help children to stay in school and improve mental health, both generally and in terms of specific disorders and symptoms. In their own way, each of the following examples of school-based interventions can address one of the persistent problems and poor outcomes described in the previous section. **If educators, policymakers, parents and mental health professionals come together to advocate for sensible integration of these approaches, mental health promotion in school may provide a stunning return on investment.**

Prevention and Early Intervention

Intervening early in school helps prevent behavioral issues from developing into problems that lead to suspension, expulsion and dropping out. Enlisting parents and teachers can make these interventions more effective—and prevention approaches can be effective at various developmental stages, as indicated below.

Infancy and Early Childhood

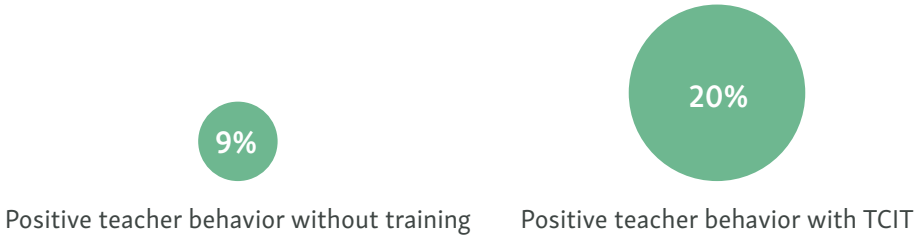
The Incredible Years is a widely disseminated program engaging teachers, parents and children to reduce disruptive behavior disorders, violence and delinquency. It has been used with general populations and adapted for children with early onset conduct problems and other risk factors, including socioeconomic status and other mental health disorders. The program is designed to train parents and teachers to help children from birth through school age.

Studies show robust positive effects of the intervention for decreasing disruptive behavior and increasing prosocial behavior. A meta-analysis of research studies reported a **15.5% improvement across domains of behavior**[31] for children whose families and school communities participated in the Incredible Years prevention program.

Childhood

Teacher-Child Interaction Training (TCIT) is a classroom intervention for children aged 3–7, based on an individualized treatment for disruptive behavior and family conflict called Parent-Child Interaction Therapy (PCIT).

One study showed that after teacher training and coaching, positive teacher behavior improved more than 100%, from 9% of interactions to 20% of interactions. Focused positive encouragement — "labeled praise" — increased fivefold.[32]



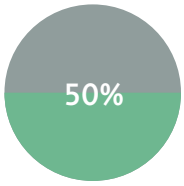
Another study showed significant improvement in ratings of resilience and behavioral control.[33]

One assumption behind TCIT is that by improving the classroom environment, teachers will have more time and attention for teaching and encouraging each child, and young students will experience more of the benefits of focused early education and fewer of the distractions and ill effects of problematic behavior and disruption.

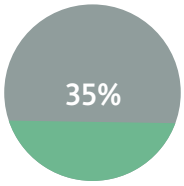
The Good Behavior Game (GBG) is a classroom-based behavioral management program shown to have long-lasting effects in preventing later poor outcomes. In a study, first and second graders in GBG classrooms were divided into teams that "compete" for rewards by adhering to teacher-defined rules for behavior. All teams can win by keeping the number of infractions down. The goal of the intervention is to encourage a positive learning environment and healthy social communication.[34]

GBG is effective in reducing problem behaviors in the classroom, and it also has significant effects many years later. A follow-up study of children in GBG classrooms when they reached the age of 19–21 found significantly lower rates of drug and alcohol use disorders, regular smoking, antisocial personality disorder, delinquency and incarceration for violent crimes and suicide thoughts.

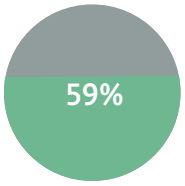
Young adult outcomes for children in the GBG group showed a 50% reduction in risk of drug abuse or dependence; a 35% risk reduction for alcohol abuse or dependence; a 59% decreased risk for regular smoking; and a 32% reduction in risk of developing antisocial personality disorder.[35]



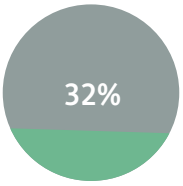
Risk reduction for drug abuse or dependence



Risk reduction for alcohol abuse or dependence



Risk reduction for regular smoking



Risk reduction for developing antisocial personality disorder

Middle Childhood and Early Adolescence

Daily Report Card (DRC) is another evidence-based behavior modification program developed for children with disruptive behavior disorders including ADHD. The DRC intervention works as a collaboration between school and home, and is constructed to address and reward progress related to problem behaviors identified in a child's individualized education plan (IEP). Each DRC intervention is unique to the child and to the relationship between child, teacher and parents.

One study showed that children aged 6–12 with ADHD participating in the DRC intervention were:

- Twice as likely to be rated as unimpaired at the end of the study when compared to the control group.[36]

Universal Programs and Screening

One of the most important components of early intervention for behavioral and emotional health concerns is early identification. School is the ideal place for this.

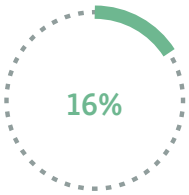
Chile has a widespread universal intervention plan for mental health in its schools, called Skills for Life. It begins in first grade with:

- Screening using instruments like the TOCA-R and a clinical scale called the Pediatric Symptom Checklist.
- Students identified at risk in first grade receive an intervention in second grade in the form of workshops administered by trained bachelor's-level psychologists.

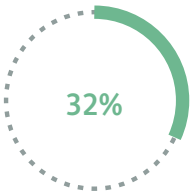
Skills for Life:

- Is in 20% of Chilean schools
- Has screened over 1 million students in 10 years
- Identifies as at-risk, and provides support to, 16.4% of first-grade students

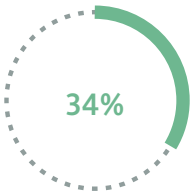
Students who complete the intervention workshops, compared with those who did not, are less likely to remain at risk, less likely to be held back after third grade and less likely to have poor attendance.[37]



Reduction in "at risk" scores on the TOCA-R



Decrease in children held back after third grade



Decrease in poor attendance in third grade

Why Screen?

Many mental health studies of schoolchildren rely on broader teacher reports of behavior and functioning. One of these scales, the Teacher Observation of Classroom Adaptation–Revised (TOCA-R), is used to assess interventions addressing:

- Aggressive and disruptive behaviors
- Concentration problems
- Prosocial behaviors
- Emotion regulation[38]

Studies have shown that TOCA-R scores may predict later poor outcomes like school dropout, unemployment and mental health disorders, **alerting professionals that early intervention may be warranted.** It must be noted that large-scale screening often results in "false positive" assessments of risk; effective programs must follow screening with more sensitive appraisals of an individual child.

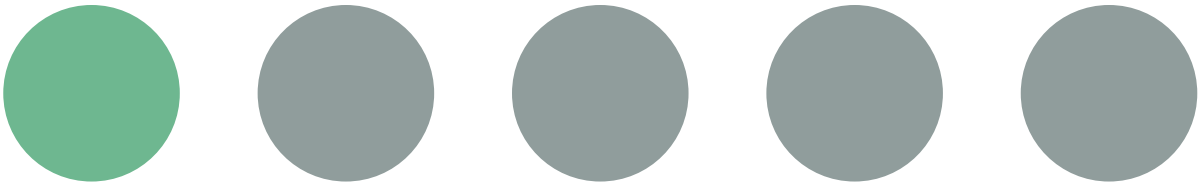
Social-Emotional Learning Approaches

In addition to prevention, screening and individual interventions, researchers are looking at the effects of entire curricula that reinforce good citizenship and behavior. Big-picture changes can be the ideal backdrop for individual improvement.

An emerging approach to encouraging positive mental health and behavior in young people is to adopt social and emotional learning (SEL) curricula in schools. A wide variety of models and interventions have been developed to explicitly teach these skills and decrease problems in emotional regulation and interpersonal interactions.

A meta-analysis of 213 studies including more than 270,000 students suggests that SEL programs and interventions have a broad positive effect. Students in SEL programs showed:[39]

- 22% improvement in SEL skills
- 10% increase in "positive social behaviors"
- 10% decrease in "emotional distress"
- 11% improvement in academic performance



More than 20% improvement in social and emotional skills

The **Promoting Alternative Thinking Strategies Curriculum (PATHS)** is administered by Head Start teachers over the course of nine months. Like other SEL interventions, it is based on explicit instruction in SEL curricula. Teachers rate children who have completed PATHS as:

- more cooperative
- more emotionally aware
- more interpersonally skilled[40]

The intervention shows:

- Significant increase in emotional vocabulary
- Reduction in false attribution of negative emotions

Like other universal interventions, it has not been shown to have a significant effect on more clinical symptoms like lack of inhibitory control or attention deficit.

Restorative Justice

To reduce the negative effects of disciplinary action, some programs work explicitly to bring down the number of suspensions and expulsions—and replace them with more constructive responses.

Restorative Discipline/Justice includes strategies to both *prevent* children from breaking the rules and *intervene* after an infraction has occurred. Some elements are focused on reducing the likelihood of student rule breaking (proactive circles where students and teachers talk about their feelings and expectations) and others on intervening afterwards (e.g., restorative conferences where the parties talk about what happened). In all cases the focus is on avoiding punishment for the sake of punishment.

In a district implementing restorative approaches over a period of six years, the suspension rate fell for students of all races and ethnicities. The reduction was 47% for all students; 41% for black students; 53% for Latino students; and 61% for white students.[41]

All students | Black students | Latino students | White students

Multi-Tiered Systems of Support

We already have programs in many schools that integrate concepts of SEL and restorative justice. These programs are showing positive results; the next step is to integrate them more fully with individualized interventions.

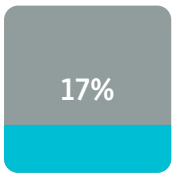
Positive behavioral interventions and supports (PBIS) is a large-scale behavioral intervention in widespread use in schools in the United States. It is intended to effect systemic change in school discipline and behavioral outcomes through training, reporting and constant feedback.

PBIS is an example of a "multi-tiered system of supports" (MTSS) or "response to intervention" (RTI) model. All students and classrooms receive a "universal intervention" aimed at improving academic success, discipline and school functioning through a set of positive behavioral expectations.[42]

At the second "tier," students identified as "at risk" receive more targeted interventions with the expectation that with support they will move back to tier one.

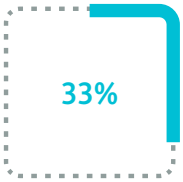
At the third tier, students with significant academic, behavioral or emotional problems receive individualized and evidence-based interventions designed with the aid of individualized evaluation.

PBIS is intended to provide support in mainstream settings to reduce the need for special education. The universal, "tier one" application of PBIS is called "School-wide PBIS," or SWPBIS, and is in place in approximately 17,000 US schools.[43]



PBIS is established in 17,000 US schools, or 17%

A four-year randomized controlled trial looked at 12,334 children in 37 schools. Children in PBIS schools were 33% less likely to receive an office discipline report (ODR),[44] and suspended 10% less often than children in comparison schools.[45]



Reduction in office discipline reports (33%)

The universal school-wide intervention has small but significant positive effects on:

- Disruptive behaviors
- Concentration problems
- Emotion regulation
- Prosocial behavior

Targeted Interventions

Interventions that address specific concerns in specific populations of children are vital to mental health efforts in schools. Community partnerships have proven invaluable to many programs.

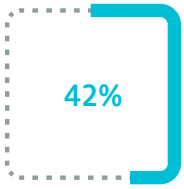
Aside from one-on-one mental health care from an office-based professional, clinicians have begun to develop school-based mental health interventions that leverage the environment to deliver care.

Below are two examples, one focused on aggression and the other on traumatic stress.

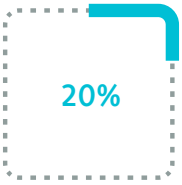
Second Step is an evidence-based prevention program for 4– to 14-year-olds that addresses impulsive and aggressive behavior, promotes anger management, and teaches problem-solving skills.

A study of 790 students showed that teacher and parent reports were not affected by the intervention—a common problem in school-based trials of behavioral approaches. But behavior observations by professional observers indicated significant decreases in physical aggression and increases in prosocial behavior.[46]

Analysis of the program in 3,616 middle school students showed a 42% decrease in physical aggression[47] and a 20% decrease of bullying in special education environments.[48]



Decrease in physical aggression with Second Step



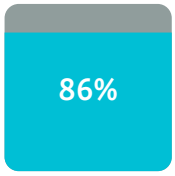
Decrease in bullying in special ed with Second Step

Cognitive Behavioral Intervention for Trauma in Schools (CBITS) is an evidence-based intervention for children with symptoms of post-traumatic stress disorder (PTSD). Children are identified by experienced school personnel and treated by a trained professional working with the school.

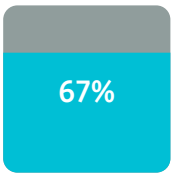
PTSD is a significant problem in young people, particularly in the poor urban environments CBITS was developed to serve.

- Lifetime PTSD in children 14–18: 5%[49]

CBITS is a novel group intervention that lasts for 12 sessions (10 group and 2 individual) and can be delivered by school-based mental health personnel. A study of 126 students with PTSD and depression symptoms showed that, compared to no intervention, 86% reported less severe PTSD symptoms and 67% reported less severe depression symptoms.[50]



Reduction in PTSD symptoms



Reduction in depression symptoms

Conclusions

Despite the best efforts of so many devoted educators, children who struggle with mental health and learning disorders still face an array of serious challenges and obstacles in school. Most schools today are ill equipped to evaluate and provide or refer for treatment, and we face major problems with the way we mete out discipline and promote the school-to-prison pipeline. Nevertheless, there is a silver lining for a nation that has a history of advocating for children who face barriers to learning and where there is a general consensus regarding the need to allocate more resources among the political and educational communities. The tools to improve the school environment for all children are being developed, and our task is to bring these promising, evidence-based approaches to more schools across the nation.

Mental health in school means many things — from social-emotional competency to an atmosphere of respect to supports for children with learning disorders, ADHD, PTSD and more. The landscape of "mental health in schools" is fractured, but these different areas of concern mirror all the things Americans want school to do for their children. In the words of Robert Balfanz, the education reformer and director of the Everybody Graduates Center, the ideal is "to be able to say to any child, in any part of the United States, 'Your schools will educate you, challenge you, care for you, support you, and graduate you ready to succeed in the world.'"

Schools have already made the effort to accommodate and encourage children facing different hurdles to learning and success: physical handicaps, for instance. The education reform movement in the United States has made great strides in transforming curricula and other aspects of the educational system. Social, emotional and behavioral health is the necessary next step for building better schools to nurture healthy brains and happy children. Now it is time for schools to make a change for children struggling with mental health disorders.

Schools must continue to innovate and integrate approaches to school-based mental health — bringing the systemic focus of programs like PBIS into closer alignment with intensive individualized interventions while encouraging developmental awareness through early screening and progress monitoring. Schools must become the prime driver behind improving the mental health of America's children. But to do this, evidence-based practices must be adopted at a large scale, and partnerships between educators and mental health professionals from the policy level on down to the individual child must be encouraged.

Imagine the differences our schools could make for children if they supported programs like these, and if they were equipped with the information they need to truly assess what is wrong and how to make it right. At last, we might have created a mental health safety net for all.

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EXHIBIT 101

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Children's Mental Health

Improving Children's Behavioral Health

Learn what CDC is doing about gaps in behavioral treatment for children.

It is estimated that as many as 1 out of 5 children experience a mental disorder in a given year, and an estimated $247 billion is spent each year on treatment and management of childhood mental disorders. Because of their impact on children, families, and communities, children's mental disorders are an important public health issue.

The Centers for Disease Control and Prevention (CDC) joins the Substance Abuse and Mental Health Services Administration (SAMHSA), along with other agencies, in learning more about strategies for integrating behavioral health with primary health care, child welfare, and education.

Childhood mental disorders

The term childhood mental disorder means all mental disorders that can be diagnosed and begin in childhood. Mental disorders among children are described as serious changes in the way children typically learn, behave, or handle their emotions. Some examples of childhood mental and behavioral disorders are:

- Attention-deficit/hyperactivity disorder (ADHD)
- Behavior disorders
- Anxiety and Depression
- Substance use disorders
- Tourette syndrome

Learn about CDC's research on children's mental health.

ADHD and behavioral health

CDC collaborates with partners to learn more about children's mental health, understand the causes of mental disorders, and find and promote effective prevention and intervention strategies. ADHD is one of the most common neurobehavioral disorders of childhood. Behavioral therapy is an important form of treatment for children with ADHD.

Experts recommend that preschool children (4-5 years of age) with ADHD should receive behavioral therapy as the first line of treatment. Once children reach school age (6-17 years of age), behavioral treatment is recommended in combination with medication. Parent training in behavior management is a good treatment option. Read about ADHD treatment.

Gaps in recommended treatment for ADHD

To find out what kind of treatments children are receiving for ADHD, CDC researchers looked at data from a national sample of children with special health care needs collected in 2009-10 and found that most children with ADHD received either medication treatment or behavioral therapy; however, many were not receiving treatment as outlined in the best practice guidelines released in 2011 by the American Academy of Pediatrics (AAP).

- Less than 1 in 3 children with ADHD received both medication treatment and behavioral therapy, which is now the preferred treatment approach for children ages 6 and older.
- Only half of preschoolers (4-5 years of age) with ADHD received behavioral therapy, which is now the recommended first-line treatment for this group.
- About half of preschoolers with ADHD were taking medication for ADHD, and about 1 in 4 were treated only with medication .

This information described clinical practice at the time that the guidelines were published.

It provided a greater understanding of the patterns and gaps in the treatment of ADHD and what more may need to be done to improve the quality of care for children with ADHD. Read more about this study.

Closing the gap

CDC works with partners to learn more about any gaps in effective treatment for ADHD. CDC is working to understand the barriers that families may face when seeking behavioral treatment, and those that healthcare professionals may encounter when providing behavioral treatments or referrals. Understanding these barriers for children with ADHD will also provide insight into the barriers to effective behavioral treatment for children with other mental disorders.

- Future research and policy evaluation can help us better understand what factors and strategies increase rates of use of behavior therapy.
- Parents should be aware that there are recommendations for behavioral treatment for children of specific ages, and that they should seek care from an experienced provider.
- Clinicians should be aware of effective behavioral treatments and resources in their community, so that they can refer children for behavior therapy as recommended by the American Academy of Pediatrics and the American Academy of Child and Adolescent Psychiatry.

Increasing rates of behavior therapy would increase the alignment of current and best practice, and improve the quality of care for children.

Tourette syndrome and behavioral health

Tourette syndrome is a childhood neurobehavioral disorder which causes people to have tics. Children with Tourette commonly have mental disorders that occur along with Tourette, including ADHD and obsessive-compulsive disorder. In the past, medication was the only real treatment option for children and adults with Tourette. Now there is a treatment option that does not use medication, called Comprehensive Behavioral Intervention for Tics, or CBIT. CDC has partnered with the Tourette Association of America to provide CBIT training for health professionals, and educational programs about CBIT for those who have Tourette and their families.

Mental health across the lifespan and across the globe

In addition to efforts focused on children, CDC also works on mental health issues among U.S adults, as well as among people in other countries. These activities focus on:

- health related quality of life,
- mental illness and chronic disease,
- violence prevention,
- disaster and environmental mental health,
- women's mental health before, during, and after pregnancy,
- mental health promotion and prevention of mental illness in the community.

Read more about CDC's work on mental health here.

Glossary

Behavioral health describes the connection between a person's behaviors and the health and well-being of the body and mind.

Mental disorders include emotional or psychiatric disorders (such as manic-depression, obsessive-compulsive disorder, and schizophrenia) or behavior disorders (such as ADHD and oppositional-defiant disorder).

Neurobehavioral means the way the brain affects emotion, behavior, and learning.

Tics are sudden twitches, movements, or sounds that people do repeatedly. People who have tics cannot stop their body from doing these things like blinking over and over again or making grunting sounds without meaning to.

More Information

- CDC Children's Mental Health
- CDC Mental Health
- CDC ADHD
- CDC Tourette Syndrome

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EXHIBIT 102

frontiers in Psychiatry

ORIGINAL RESEARCH
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Temporal Association of Certain Neuropsychiatric Disorders Following Vaccination of Children and Adolescents: A Pilot Case–Control Study

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Background: Although the association of the measles, mumps, and rubella vaccine with autism spectrum disorder has been convincingly disproven, the onset of certain brain-related autoimmune and inflammatory disorders has been found to be temporally associated with the antecedent administration of various vaccines. This study examines whether antecedent vaccinations are associated with increased incidence of obsessive–compulsive disorder (OCD), anorexia nervosa (AN), anxiety disorder, chronic tic disorder, attention deficit hyperactivity disorder, major depressive disorder, and bipolar disorder in a national sample of privately insured children.

Methods: Using claims data, we compared the prior year's occurrence of vaccinations in children and adolescents aged 6–15 years with the above neuropsychiatric disorders that were newly diagnosed between January 2002 and December 2007, as well as two control conditions, broken bones and open wounds. Subjects were matched with controls according to age, gender, geographical area, and seasonality. Conditional logistic regression models were used to determine the association of prior vaccinations with each condition.

Results: Subjects with newly diagnosed AN were more likely than controls to have had any vaccination in the previous 3 months [hazard ratio (HR) 1.80, 95% confidence interval 1.21–2.68]. Influenza vaccinations during the prior 3, 6, and 12 months were also associated with incident diagnoses of AN, OCD, and an anxiety disorder. Several other associations were also significant with HRs greater than 1.40 (hepatitis A with OCD and AN; hepatitis B with AN; and meningitis with AN and chronic tic disorder).

Conclusion: This pilot epidemiologic analysis implies that the onset of some neuropsychiatric disorders may be temporally related to prior vaccinations in a subset of individuals. These findings warrant further investigation, but do not prove a causal role of antecedent infections or vaccinations in the pathoetiology of these conditions. Given the modest magnitude of these findings in contrast to the clear public health benefits of

the timely administration of vaccines in preventing mortality and morbidity in childhood infectious diseases, we encourage families to maintain vaccination schedules according to CDC guidelines.

Keywords: anorexia nervosa, obsessive–compulsive disorder, anxiety disorder, tic disorder, vaccination, influenza, meningococcus

INTRODUCTION

There is a considerable body of scientific evidence indicating that the immune system plays a key role in normal brain development and in the pathobiology of several neuropsychiatric disorders (1). These include obsessive–compulsive disorder (OCD) (2, 3), anorexia nervosa (AN) (4), tic disorders (5), attention deficit hyperactivity disorder (ADHD) (6), major depressive disorder (7), and bipolar disorder (8). The precise role immune mechanisms play in these disorders remains to be determined.

In light of the role of the immune system in these central nervous system (CNS) conditions, the impact of vaccines on childhood-onset neuropsychiatric diseases had been considered and was mainly addressed with regards to the administration of the measles, mumps, and rubella (MMR) vaccine (and its various components) and the subsequent development of autism spectrum disorder (ASD). Although the controversy over MMR vaccination and ASD still exists for some members of the public, this association has been convincingly disproven (9, 10). On the other hand, the onset of a limited number of autoimmune and inflammatory disorders affecting the CNS has been found to be temporally associated with the antecedent administration of various vaccines (11). These disorders include idiopathic thrombocytopenic purpura, acute disseminated encephalomyelitis, and Guillain–Barré syndrome among others (12–16). More recently, data have emerged indicating an association between the administration of the H1N1 influenza vaccine containing the AS03 adjuvant and the subsequent new onset of narcolepsy in several northern European countries (17, 18). The immune mechanisms and host factors underlying these associations have not been identified or fully characterized, although preliminary data are beginning to emerge (18–23).

Given this growing body of evidence of immunological involvement in CNS conditions, and despite the controversy concerning the link between ASD and MMR and the clear public health importance of vaccinations, we hypothesized that some vaccines could have an impact in a subset of susceptible individuals and aimed to investigate whether there is a temporal association between the antecedent administration of vaccines and the onset of several neuropsychiatric disorders, including OCD, AN, tic disorder, anxiety disorder, ADHD, major depressive disorder, and bipolar disorder using a case–control population-based pediatric sample (children aged 6–15 years). To assess the specificity of any statistical associations, we also determined whether or not there were any temporal associations between antecedent vaccine administration and the occurrence of broken bones or open wounds.

MATERIALS AND METHODS

Data were obtained from the MarketScan® Commercial Claims and Encounters database, which is constructed and maintained by Truven Health Analytics. Data from 2002 to 2007 were used for the study. MarketScan consists of de-identified reimbursed health-care claims for employees, retirees, and their dependents of over 250 medium and large employers and health plans. Hence, individuals included in the database are covered under private insurance plans; no Medicaid or Medicare data are included. The database includes claims information describing the health-care experiences for approximately 56 million covered lives per year. The database is divided into subsections, including inpatient claims, outpatient claims, outpatient prescription drug claims, and enrollment information. Claims data in each of the subsections contain a unique patient identifier and information on patient age, gender, geographic location (including state and three-digit zip code), and type of health plan.

The inpatient and outpatient services subsections of the MarketScan database contain information on all services performed in an inpatient or outpatient setting. These data include information on dates of services, the diagnoses associated with the claim, and the procedures performed. The outpatient services subsection includes information for all services performed in a doctor's office, hospital outpatient clinic, emergency room, or other outpatient facility. Previous studies have used the MarketScan database to examine health-care service use and costs for children (24–29).

Study Population

The study sample consisted of children aged 6–15 with a diagnosis of one of the following conditions (ICD-9 codes in parentheses): OCD (300.3), AN (307.1), anxiety disorder (300.0–300.2), tic disorder (307.20 or 307.22), ADHD (314), major depression (296.2–296.3), and bipolar disorder (296.0–296.2, 296.4–296.8). To test the specificity of the models, we also included children with broken bones (800–829) and open wounds (870–897). To identify new cases, we further limited the sample in each diagnostic group to children who were continuously enrolled for at least 1 year prior to their first diagnosis for the condition (the index date). Next, a matched one-to-one control group was constructed for each diagnostic group consisting of children who did not have the condition of interest and were matched with their corresponding case on age, gender, date of the start of continuous enrollment, and three-digit zip code. Because vaccines tend to occur during certain times of year (such as before summer camps or the beginning of school), controls were also required to have an outpatient visit at which they did not receive a vaccine within 15 days of the date that the corresponding case was first diagnosed with the

condition, in an effort to control for seasonality. The date of this visit was the index date for children in the control group.

For each diagnostic group and their corresponding controls, individuals who were vaccinated in the 3, 6, or 12 months before the index date were identified. Exposure to vaccines was measured using CPT codes (list available from the authors upon request) and ICD-9 codes (V03–V06 or V07.2). Exposure to specific vaccines, including influenza, tetanus and diphtheria (TD), hepatitis A, hepatitis B, meningitis, and varicella, was tracked.

Statistical Analysis

The analyses were performed for each diagnostic group (and their controls) separately. Children with multiple conditions (e.g., ADHD and tic disorder) were included in each of the corresponding analytic groups. First, the proportion of children who were exposed to vaccines in the period before the index date was compared across the case and control groups. Next, bivariate conditional logistic regression models were estimated to determine the hazard ratios (HRs) and 95% confidence intervals (95% CIs) associated with the effect of vaccine exposure on having the condition of interest. Separate models were run for the 3-, 6-, and 12-month periods preceding the index date for each diagnostic group. The study was approved by the Penn State College of Medicine Institutional Review Board.

RESULTS

Characteristics of each of the diagnostic groups are presented in **Table 1**. Sample sizes ranged from 551 children diagnosed with AN to 85,151 children with a broken bone. The average age ranged from 9.5 ± 2.5 for children with tic disorder to 13.3 ± 1.7 for children with AN. Not surprisingly, the distribution of sex varied considerably across diagnostic groups, with higher percentages of females in the AN (86.6%) and major depression (56.3%) categories and higher proportions of males in the tic disorder (76.4%), ADHD (66.8%), open wound (62.2%), broken bone (58.4%), OCD (56.6%), and bipolar disorder (54.1%) categories.

Rates of receipt of vaccines in the 6 months before the first diagnosis of the disorder are also reported in **Table 1** and varied considerably across diagnostic groups. Receipt of any vaccine in the previous 6 months was highest for children with AN (21.4%), followed by OCD (15.9%) and tic disorder (15.8%), and was lowest for children with open wounds (10.3%). Rates of receipt of specific vaccines were fairly low, ranging from 0.5% for the hepatitis vaccine among children with tic disorder to 8.4% for the influenza vaccine among children with tic disorder. In general, vaccination rates were highest among children in the AN, OCD, and tic disorder groups and were lowest for children in the open wound or bipolar disorder groups.

Table 2 presents HRs from the bivariate associations of receipt of vaccine within the 3-, 6-, and 12-month periods preceding the index date for each diagnostic group compared to their matched controls. Children with OCD, AN, anxiety disorder, or ADHD were more likely to have had a vaccination in each of the preceding periods than their matched controls, and children with tic disorder were more likely to have had a vaccination in the

TABLE 1 | Characteristics of the sample.

Characteristic	Broken bone		Open wound		OCD		Anorexia nervosa		Anxiety disorder		Tic disorder		ADHD		Major depression		Bipolar disorder	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
N	85,151		73,290		3,222		551		23,462		2,547		46,640		13,295		5,892	
Age, mean ± SD	11.1 ± 2.7		10.6 ± 2.9		11.1 ± 2.6		13.3 ± 1.7		11.3 ± 2.8		9.5 ± 2.5		10.3 ± 2.8		12.9 ± 2.2		12.3 ± 2.6	
Gender																		
Male	49,689	58.4	45,562	62.2	1,825	56.6	74	13.4	11,357	48.4	1,945	76.4	31,170	66.8	5,811	43.7	3,185	54.1
Female	35,462	41.6	27,728	37.8	1,397	43.4	477	86.6	12,105	51.6	602	23.6	15,470	33.2	7,484	56.3	2,707	45.9
Receipt of vaccine[a]																		
Any vaccine	10,308	12.1	7,577	10.3	512	15.9	118	21.4	3,389	14.4	402	15.8	5,536	11.9	1,700	12.8	682	11.6
Influenza	3,550	4.2	2,783	3.8	246	7.6	42	7.6	1,418	6.0	214	8.4	2,366	5.1	548	4.1	247	4.2
TD	2,061	2.4	1,358	1.9	68	2.1	27	4.9	520	2.2	53	2.1	913	2.0	405	3.0	159	2.7
HepA	1,950	2.3	1,462	2.0	86	2.7	14	2.5	570	2.4	62	2.4	1,005	2.2	285	2.1	100	1.7
HepB	713	0.8	550	0.8	20	0.6	12	2.2	201	0.9	14	0.5	366	0.8	150	1.1	60	1.0
Meningitis	1,325	1.6	835	1.1	61	1.9	24	4.4	422	1.8	36	1.4	495	1.1	223	1.7	88	1.5
Varicella	1,002	1.2	750	1.0	52	1.6	8	1.5	323	1.4	44	1.7	577	1.2	93	0.7	42	0.7

[a]*Reciept of vaccine in the 6 months before first diagnosis of the disorder.*

OCD, obsessive–compulsive disorder; ADHD, attention deficit hyperactivity disorder; TD, tetanus and diphtheria; Hep, hepatitis.

TABLE 2 | Bivariate associations of receipt of vaccine with new diagnosis.[a]

Vaccine	Broken bone *N* = 85,151			Open wound *N* = 73,290			OCD *N* = 3,222			Anorexia nervosa *N* = 551			Anxiety disorder *N* = 23,462			Tic disorder *N* = 2,547			ADHD *N* = 46,640			Major depression *N* = 13,295			Bipolar disorder *N* = 5,892		
	Hazard ratio (HR)	95% CI		HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI	
Any vaccine																											
3 months	**1.04**	**1.00**	**1.08**	0.96	0.92	1.00	**1.23**	**1.02**	**1.49**	**1.80**	**1.21**	**2.68**	**1.12**	**1.04**	**1.20**	1.11	0.90	1.38	**1.06**	**1.00**	**1.12**	**0.88**	**0.80**	**0.97**	0.87	0.75	1.01
6 months	**1.08**	**1.05**	**1.11**	0.97	0.94	1.01	**1.27**	**1.10**	**1.47**	**1.63**	**1.17**	**2.27**	**1.13**	**1.07**	**1.19**	**1.25**	**1.06**	**1.47**	**1.04**	**1.00**	**1.09**	**0.92**	**0.86**	**0.99**	**0.82**	**0.73**	**0.91**
12 months	**1.07**	**1.04**	**1.09**	**0.97**	**0.94**	**1.00**	**1.23**	**1.09**	**1.38**	**1.47**	**1.12**	**1.93**	**1.14**	**1.09**	**1.19**	**1.19**	**1.04**	**1.36**	**1.08**	**1.05**	**1.12**	**0.89**	**0.84**	**0.95**	**0.87**	**0.79**	**0.95**
Influenza																											
3 months	1.03	0.96	1.11	0.93	0.86	1.01	**1.36**	**1.02**	**1.82**	**2.20**	**1.10**	**4.38**	**1.23**	**1.10**	**1.38**	1.24	0.91	1.67	0.98	0.91	1.07	**0.81**	**0.68**	**0.96**	**0.71**	**0.55**	**0.92**
6 months	**1.07**	**1.02**	**1.13**	0.96	0.91	1.02	**1.48**	**1.21**	**1.83**	**1.83**	**1.07**	**3.15**	**1.24**	**1.14**	**1.35**	**1.27**	**1.02**	**1.58**	0.97	0.91	1.02	0.89	0.79	1.00	**0.84**	**0.70**	**1.00**
12 months	**1.06**	**1.02**	**1.09**	0.97	0.93	1.01	**1.35**	**1.16**	**1.59**	1.52	0.99	2.34	**1.27**	**1.19**	**1.35**	**1.28**	**1.08**	**1.50**	1.04	0.99	1.09	0.93	0.84	1.02	0.87	0.76	1.00
TD																											
3 months	1.02	0.94	1.11	0.92	0.83	1.02	1.15	0.72	1.84	1.70	0.78	3.71	0.95	0.80	1.13	0.86	0.47	1.60	1.04	0.91	1.19	0.95	0.78	1.16	0.83	0.62	1.12
6 months	1.07	1.00	1.14	0.94	0.87	1.01	1.07	0.75	1.51	1.77	0.90	3.49	0.91	0.80	1.03	1.24	0.82	1.88	1.03	0.93	1.13	0.96	0.83	1.10	0.82	0.66	1.02
12 months	**1.07**	**1.02**	**1.12**	**0.93**	**0.88**	**0.98**	0.99	0.77	1.26	**1.63**	**1.05**	**2.52**	0.98	0.90	1.07	0.93	0.67	1.30	1.04	0.97	1.11	0.90	0.82	1.00	**0.80**	**0.68**	**0.93**
HepA																											
3 months	1.02	0.94	1.12	0.97	0.88	1.07	1.47	0.92	2.33	1.60	0.52	4.89	1.00	0.85	1.18	1.13	0.70	1.83	1.03	0.92	1.17	0.86	0.68	1.08	1.03	0.73	1.47
6 months	1.05	0.98	1.12	0.99	0.92	1.07	**1.43**	**1.02**	**2.01**	1.09	0.48	2.51	1.08	0.95	1.22	1.35	0.92	1.98	1.05	0.96	1.15	0.95	0.81	1.13	0.79	0.60	1.03
12 months	**1.08**	**1.02**	**1.13**	0.99	0.93	1.05	**1.40**	**1.07**	**1.82**	1.73	0.89	3.37	1.00	0.91	1.10	1.17	0.88	1.56	**1.09**	**1.02**	**1.18**	0.97	0.86	1.11	0.81	0.66	1.00
HepB																											
3 months	1.08	0.93	1.25	1.05	0.89	1.24	0.71	0.32	1.61	3.00	0.61	14.86	1.01	0.76	1.34	1.40	0.44	4.41	1.13	0.91	1.39	1.05	0.77	1.43	0.97	0.61	1.56
6 months	1.02	0.92	1.13	1.02	0.91	1.15	0.80	0.45	1.44	1.71	0.68	4.35	1.01	0.83	1.23	1.17	0.54	2.52	1.07	0.92	1.24	0.89	0.71	1.11	0.91	0.64	1.29
12 months	1.03	0.95	1.11	1.00	0.91	1.09	0.93	0.60	1.44	1.55	0.72	3.30	1.01	0.89	1.16	1.19	0.61	2.31	1.06	0.95	1.18	1.00	0.85	1.18	1.07	0.83	1.38
Meningitis																											
3 months	1.05	0.95	1.17	1.04	0.92	1.19	1.10	0.67	1.80	1.71	0.68	4.35	1.06	0.88	1.27	1.46	0.72	2.95	1.16	0.98	1.38	0.89	0.70	1.13	0.87	0.57	1.33
6 months	1.08	1.00	1.17	1.02	0.92	1.12	1.15	0.78	1.71	1.75	0.86	3.56	1.12	0.97	1.29	**1.94**	**1.08**	**3.46**	1.08	0.95	1.23	0.88	0.73	1.05	0.82	0.61	1.11
12 months	1.06	0.99	1.14	1.02	0.94	1.10	1.34	0.96	1.87	1.42	0.79	2.56	**1.14**	**1.01**	**1.29**	**1.73**	**1.07**	**2.80**	1.06	0.95	1.18	**0.81**	**0.70**	**0.94**	0.85	0.67	1.09
Varicella																											
3 months	**0.88**	**0.79**	**0.99**	0.90	0.79	1.03	1.33	0.79	2.26	1.00	0.20	4.96	1.06	0.85	1.31	0.73	0.42	1.27	1.06	0.90	1.24	0.85	0.58	1.24	1.08	0.63	1.87
6 months	0.97	0.88	1.06	0.96	0.87	1.07	1.38	0.89	2.15	2.66	0.71	10.04	1.17	0.99	1.38	0.91	0.59	1.40	1.09	0.97	1.23	0.85	0.64	1.14	0.79	0.52	1.21
12 months	1.00	0.93	1.08	0.93	0.85	1.01	1.36	0.92	1.99	1.29	0.48	3.45	1.11	0.97	1.28	0.97	0.67	1.40	1.06	0.95	1.17	0.84	0.66	1.06	0.74	0.53	1.05

[a]*Cases and controls matched on date (±15 days, see text) of the start of continuous enrollment, year of birth, gender, and three-digit zip code. N's represent cases only. Results in bold are statistically significant at $p < 0.05$. OCD, obsessive–compulsive disorder; ADHD, attention deficit hyperactivity disorder; TD, tetanus and diphtheria; Hep, hepatitis.*

preceding 6- and 12-month periods than their matched controls. HRs associated with receipt of any vaccine were highest for children with AN, ranging from 1.47 (95% CI 1.12–1.93) for the 12-month preceding period to 1.80 (95% CI 1.21–2.68) for the 3-month preceding period, followed by OCD, which ranged from 1.23 for both the 12-month (95% CI 1.12–1.93) and 3-month (95% CI 1.02–1.49) preceding periods to 1.27 (95% CI 1.10–1.47) for the 6-month preceding period. However, children with broken bones were also more likely to have had a vaccination in the preceding period, although the HRs were smaller, ranging from 1.04 (95% CI 1.00–1.08) for the 3-month preceding period to 1.08 (95% CI 1.05–1.11) for the 6-month preceding period. The other control condition, open wounds, showed no increased incidence following vaccinations. In addition, children with major depression were *less* likely to have had a vaccination in all 3 preceding periods, and children with bipolar disorder were also *less* likely to have had a vaccination in the 6- or 12-month preceding periods.

There were fewer statistically significant results when looking at the effects of the individual vaccines. Children with OCD were more likely to have received the influenza vaccine in each of the preceding periods, or the hepatitis A vaccine in the previous 6 or 12 months. Children with AN were also more likely to have received the influenza vaccine in the preceding 3 or 6 months, or the TD vaccine in the previous 12 months. Children with anxiety disorder were more likely to have received the influenza vaccine in the previous 12 months. Children with tic disorder were more likely to have received an influenza or a meningococcal vaccine in the previous 6 or 12 months. However, children with broken bones were also slightly more likely to have received the influenza vaccine during the previous 3-, 6-, and 12-month intervals. In contrast, children with major depression were *less* likely to have received the influenza vaccine in the previous 3 months or the meningitis vaccine in the previous 12 months. Similarly, children with bipolar disorder were also *less* likely to have received the influenza vaccine in the previous 3 or 6 months. Antecedent vaccination with any vaccine and with the TD vaccine during the previous 12 months was very modestly associated with a *decreased* incidence of open wounds (**Table 2**).

DISCUSSION

The principal findings of this study are as follows: (i) children with OCD, AN, anxiety disorder, and tic disorder were more likely to have received influenza vaccine during the preceding 1-year period (for OCD in the preceding 3-, 6-, and 12-month periods; for AN in the preceding 3- and 6-month periods; for anxiety disorder in the preceding 6- and 12-month periods; for tic disorder in the preceding 6- and 12-month periods) and (ii) HRs associated with receipt of any vaccine were highest for children with AN, ranging from 1.47 for the 12-month preceding period to 1.80 for the 3-month preceding period, followed by OCD, which ranged from 1.23 for both the 12- and 3-month preceding periods to 1.27 for the 6-month preceding period. However, if we apply a high standard [so that the upper limit of the of the 95% CI of the HR observed for the association between the administration of any vaccine and the subsequent occurrence of a broken bone (1.11) falls below the lower limit of the 95% CI observed for any of the HRs for any of the neuropsychiatric disorders], only the findings for AN pass this stringent threshold (**Table 2**). Applying a similar high standard for the individual vaccines, the only associations that pass this threshold concern the influenza vaccine given in the preceding 6- and 12-month periods for OCD and anxiety disorders.

Our findings showing that children with AN, OCD, or a tic disorder were more likely to have received the influenza vaccine in the preceding periods were noteworthy given the findings of increased incidence of narcolepsy in Finland, Sweden, Ireland, Norway, England, and France after vaccination with AS03-adjuvanted H1N1 vaccine (17, 18). Studies also show a threefold increase in the incidence of narcolepsy after following the 2009 H1N1 pandemic in China (30). Although the strong association between HLA class II and narcolepsy suggests that narcolepsy may be an autoimmune disorder, the exact mechanism leading to immune-related narcolepsy is not completely understood and other host factors are likely to play an important role (31, 32). Investigators have made use of *in silico* techniques to begin to identify potential causal pathways and the relevant host factors (19). More recently, Ahmed et al. (23) have shown that the H1N1 influenza vaccine containing the AS03 adjuvant triggers antibodies that bind to hypocretin receptor 2a. Additional work is needed to replicate and extend these findings.

It is also of note that the observed association between the antecedent administration of the influenza vaccine and the new onset of AN and OCD may suggest that aberrant immune functioning may be a common pathogenetic pathway for OCD and AN. The high comorbidity rates between OCD and AN, common cortico-striatal abnormalities in neuroimaging studies, and anti-putamen antibodies both in OCD and AN cases are some of the shared features of these two disorders worth considering (33–35). In addition, the increased risk for autoimmune disorders (such as type 1 diabetes mellitus, Crohn's disease, and celiac disease) in eating disorders (36) and the documented comorbidity of OCD and autoimmune diseases (such as systemic lupus erythematosus, thyroid dysfunction, and multiple sclerosis) (35) indicate the possible shared host factors and the role of immune-mediated mechanisms in the development of AN and OCD. We also note the findings of Zastrow and colleagues that vaccination to prevent H1N1 influenza is recommendable even in extremely underweight AN patients (37).

Limitations of this study include that we were unable to control for the fact that providers may designate ICD-9 insurance billing codes for vaccines generally without specifying the particular vaccine. Additionally, we were unable to match claims by providers in order to control for the diagnostic predilections of individual physicians and account for the possibility that some physicians might be more (or less) likely to diagnose one or more neuropsychiatric disorders and/or recommend specific vaccinations. The results of this study are further qualified by the limitations of the administrative retrospective data used in this study, rather than from systematically obtained clinical data, especially around diagnostic classification. This is a shortcoming inherent in studies that rely on secondary analyses to secure large sample sizes. Furthermore, early vaccines are grouped together in the first 15 months of infancy, some of them given

simultaneously at one visit and received by most of the infants. This leads to a limitation in analyzing the possibility of the temporal association between individual vaccines and the onset of neuropsychiatric disorders. We deliberately chose our sample from children aged 6–15 years in order to overcome this limitation. Another limitation concerns changes in vaccine guidelines during the time interval used in this analysis. For example, the American Academy of Pediatrics first recommended the use of the conjugate meningococcal vaccine in August 2005 and the varicella booster in April 2007. As a consequence, the size of the cohorts who received these vaccines is smaller in comparison to other vaccines. Another issue concerns the fact that the influenza vaccination is an annual vaccination using a vaccine specific for a given year to protect against the highly variable influenza virus. As a consequence, it is also the most frequently administered vaccine that indeed may well have disproportionately "driven" the "any vaccine" findings (**Table 1**). Given its variability and prevalence, in future studies, it will be important to look year-by-year. Perhaps the largest limitation and potential threat to the study's validity has to do with the fundamental impossibility of detecting a causal relationship within the context of such a case–control study. Indeed, this provides no more than a relative perspective of the potential risk, as opposed to the absolute risk (the real proportion of individuals who had a vaccination and then developed one or more of the investigated conditions) that might be expected to be reasonably small.

Moving forward, our findings require replication in a larger population-based sample, possibly including assessments of various potentially important host factors, e.g., the individual's genomic and epigenomic background, the individual's microbiome, their history of antecedent psychosocial stress, infections, as well as other potentially simultaneously administered vaccinations, the differences in vaccine types, and the route of administration (e.g., intramuscular or intranasal administration of influenza vaccine) as different routes of administration may lead to a difference in immune responses in the host.

It will also be critically important to determine whether or not newly acquired infectious diseases against which the children were vaccinated may themselves lead to an increased incidence to one or more of these neuropsychiatric disorders. In fact, it would not be surprising if the diseases *per se* represent a stronger risk factor than vaccinations. The documented increase in the incidence of narcolepsy following the 2009 H1N1 pandemic in China provides a clear example (30). Our earlier epidemiological study documenting a temporally related modest increase in the incidence of OCD, tic disorders, and ADHD following a prior streptococcal infection provides another example (25). Future epidemiologic investigations are needed to address this important question.

The present study has the potential to extend our knowledge about the role of the immune system in some pediatric-onset neuropsychiatric disorders. However, our findings do not demonstrate a causal role of vaccination in the pathoetiology of any of these conditions. This is especially important given the clear public health benefits of the timely administration of vaccines in preventing mortality and morbidity (38). Vaccines are among the most successful and cost-effective preventive public health interventions (39). Vaccination has led to eradication of smallpox, and we are close to the eradication of poliomyelitis across the world. Since most of the vaccine-preventable diseases are contagious from person to person, the increase in numbers of vaccinated individuals will decrease the chance of a disease to spread. Proper vaccination not only protects our generation but also protects future generations against epidemics of diseases. It should always be kept in mind that vaccines are crucial for eradicating infectious diseases and preventing the higher rates of morbidity and mortality due to infections. However, care should be taken to ensure that children scheduled to receive vaccinations are in good health and that recommended precautions are taken at the time a vaccine is to be administered.

Clinical Significance

These findings provide preliminary epidemiologic evidence that the onset of some pediatric-onset neuropsychiatric disorders, including AN, OCD, anxiety disorders, and tic disorders, may be temporally related to prior vaccinations. Each of these conditions is etiologically heterogeneous, and host factors likely play an important role in a small subset of vulnerable individuals. However, these findings, even if replicated in future studies, do not prove a causal role of vaccination in the pathoetiology of any of these conditions. Indeed, antecedent infections may also increase the risk of developing one or more of these disorders in vulnerable individuals. Finally, given the modest magnitude of these findings and the clear public health benefits of the timely administration of vaccines in preventing mortality and morbidity in childhood, we encourage families to maintain the currently recommended vaccination schedules while taking all necessary precautions as documented by the Centers for Disease Control and Prevention (http://www.cdc.gov/vaccines/recs/vac-admin/contraindications.htm).

AUTHOR NOTES

Data were obtained from the MarketScan® Commercial Claims and Encounters database, which is constructed and maintained by Truven Health Analytics.

AUTHOR CONTRIBUTIONS

DL, RK, BR, and JL designed the study and wrote the protocol. SG commented on the protocol. DL undertook the statistical analysis. BR, DL, and JL wrote the first draft of the manuscript. All the authors commented on the manuscript. All the authors contributed to and have approved the final manuscript.

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EXHIBIT 103

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Within-subject associations between inflammation and features of depression: Using the flu vaccine as a mild inflammatory stimulus

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Abstract

Background—Inflammation plays a role in mood and behavior that may be relevant to identifying risk factors and treatment for depression and other stress-related illnesses. The purpose of this study was to examine whether fluctuations in inflammation following a mild immune stimulus were associated with changes in daily reported features of depression for up to a week in a healthy sample of young adults.

Methods—Forty one undergraduate students completed daily diaries of mood, feelings of social disconnection, sleep, and physical symptoms for one week before and after receiving the seasonal influenza vaccine. Circulating plasma interleukin-6 (IL-6) was measured via blood samples taken immediately before and one day after vaccination.

Results—There was a significant increase in circulating IL-6 from pre- to post-intervention ($p = .008$), and there was significant variability in the magnitude of IL-6 change. Greater increases in IL-6 were associated with greater mood disturbance on post-vaccine days, specifically depressed mood and cognitive symptoms.

Conclusions—Minor increases in inflammation were associated with corresponding increases in features of depression, and these associations occurred in the absence of any physical symptoms. The influenza vaccine could be used to probe causal relationships with a high degree of ecological validity, even in high-risk and vulnerable populations, to better understand the role of inflammation in the pathogenesis of depression.

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Keywords

inflammation; interleukin-6; IL-6; depression; mood; influenza vaccine; sickness behavior

Introduction

The innate immune system is the body's first response to injury and pathogen exposure, and its effectiveness depends upon the mobilization of inflammatory cytokines (Iwasaki and Medzhitov, 2015). Inflammatory processes can lead to sickness behavior, or the short-term loss of appetite, sleepiness, withdrawal from normal social activities, fever, aching joints, and fatigue (Dantzer, 2001; Dantzer and Kelley, 2007). Prolonged inflammation has been implicated in the development of stress-related psychiatric disorders (Raison et al., 2006), including the pathophysiology of depression (Dantzer et al., 2008; Irwin, 2002; Slavich and Irwin, 2014).

Experimental paradigms that induce inflammation have provided the strongest evidence that inflammation can elicit features of depression. In animal models, inducing inflammation can cause changes in locomotor activity, social behavior, cognition, and anhedonic behaviors (Aubert, 1999; Kubera et al., 2011; Wohleb et al., 2015; Yirmiya and Goshen, 2011). Likewise, causal inferences can be drawn from experimental models in humans (Capuron et al., 2002; Eisenberger et al., 2010b; Wichers et al., 2007). The two primary models for inducing inflammation in healthy individuals are endotoxin administration and typhoid vaccination. Endotoxin injection causes a marked increase in peripheral markers of inflammation (Martich et al., 1993), as well as depressed mood, cognitive disturbance, and increased feelings of social disconnection (Eisenberger et al., 2010b; Moieni et al., 2015; Reichenberg et al., 2001). On average, the endotoxin paradigm leads to an 100 pg/mL increase in IL-6 (Eisenberger et al., 2009), which resolves within 6-hours of administration (Eisenberger et al., 2009; Martich et al., 1993). This paradigm enables measurement of robust inflammatory effects on short-term cognitive and behavioral outcomes. However, the elevations in circulating inflammatory markers induced using endotoxin are far greater than those observed among depressed individuals (Andrei et al., 2007; Häfner et al., 2011; Howren et al., 2009), or levels elicited by stress (Steptoe et al., 2007), one of the key predictors of depression.

The typhoid vaccine has also been used to interrogate the causal role inflammation plays in the neural and behavioral underpinnings of depression, and induces approximately 1.0 pg/mL increases in IL-6 at 3 hours post-injection (Brydon et al., 2008; Harrison et al., 2009b). Individuals who exhibit the largest inflammatory response to typhoid vaccination demonstrate degradations in mood, increases in fatigue and confusion, and slowed reactions times on cognitive tasks (Brydon et al., 2008; Harrison et al., 2009a; Strike et al., 2004).

It is important to note that studies using both endotoxin and the typhoid vaccine have focused on the within-subject associations between the magnitude of inflammatory responses and changes in mood or activity with neural substrates involved in emotion regulation and reward-processing (Brydon et al., 2008; Eisenberger et al., 2009; Harrison et al., 2009a, 2009b; Wright et al., 2005). Yet, studies using the typhoid vaccine and endotoxin

have limited their inquiry to the hours immediately following vaccine exposure. Whether fluctuations in inflammation exert sustained effects on mood and behavior that go beyond the laboratory remains unanswered. In the present study, we examined the association between a mild inflammatory stimulus and multiple domains of sickness behavior and features of depression including mood, sleep, feelings of social disconnection, and physical symptoms for up to a week, using daily diaries to assess sickness behavior and features of depression in the context of participants' typical day-to-day experiences.

The influenza vaccine results in a mild inflammatory response. Increases in IL-6 following the influenza vaccine can be seen as early as 60 minutes following vaccination (Edwards et al., 2006a). A significant increase in IL-6 following the influenza vaccine is consistently observed 1- (Carty et al., 2006; Christian et al., 2011; Tsai et al., 2005), and 2-days post-vaccination (Christian et al., 2011). This inflammatory response may resolve as early as 3-days post-vaccination (Tsai et al., 2005), and is no longer observed 7 days following vaccination (Christian et al., 2011; Tsai et al., 2005). In fact, one study provides evidence that the inflammatory response to the influenza vaccine resolved within 3 days (Tsai et al., 2005). Thus, use of the influenza vaccine as an inflammatory stimulus enables measurement of daily change in subjective mood and behavior over longer periods of time, and the gradual increase in circulating inflammatory markers over days may be a more useful model for clarifying the role of inflammation in the pathogenesis of depression (See Slavich and Irwin, 2014 for review). Yet, among the published studies of inflammatory responses to influenza vaccine, no studies have examined changes in mood and behavior as a function of the inflammatory response.

The purpose of this study was to examine the association between inflammatory responses to influenza vaccination and daily reports of mood, sleep, social disconnection, and physical symptoms in a healthy, young adult sample. Consistent with the approach used in the endotoxin and typhoid studies, we focused on individual differences in IL-6 responses to vaccination (Brydon et al., 2008; Eisenberger et al., 2009; Slavich et al., 2010). Given the time course and expected magnitude of the inflammatory response to influenza vaccination, we used daily diaries to capture subtle variations in correlates of depression for 1 week before and after the vaccine. We hypothesized that greater increases in IL-6 from immediately before to 1-day post-vaccine would be associated with increases in depressed mood, cognitive symptoms, tension, fatigue, and social disconnection. We also hypothesized that greater increases in IL-6 would be associated with decreases in subjective sleep quality and positive affect.

Method

Participants

Recruitment procedures included posting flyers on the university campus during the Fall quarter in 2015 and 2016. Participants completed a phone interview to determine study eligibility. Inclusion criteria for the study were undergraduate students (ages 18–22) who had not yet received the influenza vaccine that year. Participants were excluded if they were allergic to eggs, were currently using any medications (e.g., steroids, antidepressants) or substances (e.g., tobacco products) known to affect the immune system, or had any influenza

or upper respiratory symptoms, current depression, anxiety, any major medical condition (e.g., diabetes, asthma). Forty six individuals were enrolled in the study, 3 participants dropped from the study due to upper respiratory infection between study enrollment and vaccine administration, and 2 participants were dropped from analyses due to inability to complete the blood draw. Therefore all subsequent analyses represent complete data from 41 individuals. See Table 1 for characteristics of the study sample.

Procedures

Participants first came to the lab to complete informed consent, behavioral measures, and daily diary training. For the next 14 days, participants completed 3–5 minute, online daily diaries assessing sickness behavior and features of depression, including mood, energy, sleep, feelings of social disconnection, and physical symptoms. Participants received a link to this survey each evening at 8:00pm, and were instructed to complete each diary before bedtime. Participants who did not complete the daily diary by midnight each day received a reminder at 6:00am to complete the diary upon waking. Diaries completed after 9:00am the following day were considered invalid. We had an overall 97.0% completion rate of valid daily diaries across 41 participants, or 557 complete and valid diaries. The majority of participants (78.0%, $n = 32$) completed all 14 diaries; the fewest daily diaries any participant completed was 10 ($n = 3$).

Approximately 1 week following study enrollment, participants returned to the laboratory to provide a blood sample. Research staff then escorted participants to the campus health center where they received the influenza vaccine. The influenza vaccine varied depending on year of participation. The 2015/2016 vaccine was trivalent and included A/California/7/2009 (H1N1) pdm09-like virus, which had been in flu vaccines since 2009, A/Switzerland/9715293/2013 (H3N2)-like virus, and B/Phuket/3073/2013, which were both new in Fall 2015. The 2016/2017 influenza vaccine was also trivalent and consisted of A/California/7/2009 (H1N1) pdm09-like virus, A/Hong Kong/4801/2014 (H3N2)-like virus, and B/Brisbane/60/2008-like virus (B/Victoria lineage). The following day participants returned to the laboratory to provide a second blood sample and completed behavioral measures. The post-vaccine blood draw varied between 21 and 29 hours after the vaccination, Mean $_{\text{Vaccine Delay}}$ = 24:35, SD $_{\text{Vaccine Delay}}$ = 2:10. Participants continued to complete daily diaries for the remainder of the 14-day assessment period. This study was conducted in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). All study procedures were approved by the UCLA Institutional Review Board, and all participants provided informed consent. Participants were compensated up to $200 for their time, including up to $40 for each laboratory visit, and up to $30 for completing all 14 possible daily diaries.

Measures

Mood—Mood was measured via daily diary using the 15-item Profile of Mood States (POMS-15), which has been previously used in daily diary research (Cranford et al., 2006; Shrout et al., 2006). These items comprised 5 sub-domains: Depressed mood (sad, hopeless, discouraged), Vigor (vigorous, cheerful, lively), Tension (anxious, uneasy, on edge), Anger (angry, resentful, annoyed), Fatigue (fatigued, worn out, exhausted). Three additional items

were added to assess cognitive symptoms using items from the POMS-Confusion subscale (unable to concentrate, forgetful, confused) (McNair et al., 1981). Four additional items were included to assess positive affect (enthusiastic and interested (Watson et al., 1988; Watson and Clark, 1999), content and grateful (Fredrickson et al., 2003)). Participants were asked to indicate the degree to which they experienced each mood state that day and responded to each item according to a 5-point Likert scale from 1 = *not at all* to 5 = *extremely*. For multi-item diary scales, reliability coefficients ranging from 0 to 1 for between-person (R_{KF}) and day-to-day within-person change (R_C) were computed using methods described for daily diary scales (Cranford et al., 2006). For all POMS mood subscales, $R_{KF} > .96$. R_C for Depressed mood, Anxiety, Anger, Vigor, and Fatigue subscales were all between .65 – .87, and were comparable to prior work (Cranford et al., 2006). R_C for Confusion was .47.

Social disconnection—Social disconnection was measured via a 12-item scale reflecting the degree to which participants felt disconnected from other people that day. Participants responded according to a 5-point Likert scale from 1 = *not at all*, and 5 = *very much so*. These items were used in a previous study linking endotoxin-induced changes in inflammatory markers with subjective feelings of social disconnection (Eisenberger et al., 2010b; Moieni et al., 2015). Reliability for social disconnection, $R_{KF} = .97$, $R_C = .36$.

Sleep disturbance and sleep quantity—Subjective sleep quality was measured on the daily diary using one modified item from the Pittsburgh Sleep Quality Inventory (Buysse et al., 1989), similar to that used in previous diary studies (Kane et al., 2014). Participants rated their sleep quality for the previous night on a 4-point Likert scale from 1 = *very good* to 4 = *very bad*. Participants also indicated the time they went to bed each night and woke each morning for a measure of sleep quantity. Reliability coefficients R_{KF} and R_C cannot be computed for these single-item measures of sleep disturbance and sleep quantity, however the test-retest reliability for the measure of sleep disturbance across diary days was good, ICC = .76 (Cappelleri et al., 2009).

Physical symptoms—Participants reported physical symptoms they experienced in the past 24 hours including feeling sick, headache, chills, fever, muscle/joint aches or pains. For each symptom, participants could select *Absent*, *Mild*, *Moderate*, or *Severe* on a scale from 1 to 4. The chosen physical symptoms were taken from past studies using daily diaries to examine subjective symptoms following a viral challenge (Cohen et al., 2006). Reliability for physical symptoms was $R_{KF} = .95$, $R_C = .56$.

Inflammation—Interleukin-6 (IL-6) was used to assess within-subject change in inflammation following vaccination in order to optimize comparison of our results with existing literature. IL-6 is reliably elevated in depressed patients (Dowlati et al., 2010), and the majority of studies that have demonstrated an inflammatory response to the influenza vaccine have selected IL-6 as the inflammatory marker of interest (Carty et al., 2006; Christian et al., 2011; Edwards et al., 2006a; Segerstrom et al., 2012; Tsai et al., 2005). Furthermore, studies using typhoid vaccination and endotoxin have demonstrated an association between IL-6 and mood/behavior (Eisenberger et al., 2010a; Harrison et al.,

2009a; Wright et al., 2005). Blood samples for IL-6 were collected between 8:21am and 12:45pm ($Mean_{Blood\ Draw\ 1}$ = 9:59, $SD_{Blood\ Draw\ 1}$ = 1:04) by venipuncture into EDTA tubes, placed on ice, centrifuged for acquisition of plasma, and stored at −80 C for subsequent batch testing. Samples were assayed in duplicate using a high sensitivity ELISA (R&D Systems, Minneapolis, Minn) at the UCLA Inflammatory Biology Core. The range of detection for this assay was 0.20 mg/L to 10.0 pg/mL, and there were no undetectable values in the sample. Intra- and inter-assay CVs were < 9%.

Data Analysis

We fit linear mixed models predicting mood, social disconnection, sleep disturbance, and physical symptoms as a function of our variable of interest, the interaction between change in IL-6 and time. This allowed us to test whether average mood, social disconnection, and sleep differed before and after the vaccine based on the magnitude of IL-6 change from pre- to post-vaccine. Change in IL-6 (ΔIL-6) was computed by subtracting IL-6 concentrations immediately prior to the vaccine from IL-6 concentrations 1-day after the vaccination, such that higher values indicate a greater increase in circulating IL-6. Predictors in each of these models included: study day (1–14), time (a dichotomous variable where 0 = pre-vaccine and 1 = post-vaccine), baseline IL-6 (each participant's pre-vaccination IL-6), ΔIL-6 (a post-diction term that accounts for any association between mood/sleep on pre-vaccine days and change in IL-6), and our variable of interest, Time*ΔIL-6 (the association between change in IL-6 and mood/sleep on post-vaccine days). There is evidence that body mass index (BMI) and sex contribute to differences in circulating markers of inflammation (O'Connor et al., 2009) as well as the way the immune system responds to challenges such as an immunization or a psychological stressor (Edwards et al., 2006b; Fish, 2008; Kitahara et al., 2014; Sun et al., 2012). Therefore, all models controlled for BMI and sex. Whether participants enrolled in the 2015 or 2016 cohort[1] of the study was also included as a covariate. For all analyses, a significance level of 95% or $p < .05$ should be considered reliable, although variations in significance up to $p < .10$ are presented to indicate any possible statistical trends that may inform efforts to replicate and extend these results.

Results

Participants in this study were healthy, ethnically diverse undergraduate students who were representative of their university undergraduate population. See Table 1 for detailed characteristics of the study sample. From pre- to post-vaccine participants demonstrated a significant increase in IL-6 from baseline to post-vaccination, $t(41) = -2.77$, $p = .008$. Overall, 33 participants (80.5%) showed an increase in IL-6, and the mean change in IL-6 was 0.33 pg/mL ($SD = 0.75$; range = −1.44–4.20[2]), $d = 0.45$. See Figure 1 for IL-6 at pre- and post-vaccine for all participants.

[1]We observed significant differences between cohorts such that individuals in the 2016 cohort reported more symptoms of confusion, $p = .050$, less vigor, $p = .049$, greater feelings of social disconnection, $p = .026$, and change in IL-6 from pre- to post-vaccine, $p < .001$, than participants in the 2015 cohort. For this reason, the fixed effect of cohort was included as a covariate in all models.

[2]One participant demonstrated an extreme increase in IL-6 from pre- to post-vaccine, ΔIL-6 = 4.20 pg/mL and was determined to be an outlier. Winsorizing the inflammatory response of this participant does not change the pattern of results. See Figure 2 for fixed effects of primary results with and without winsorizing this participant.

Inflammation before and after influenza vaccination and daily diary reported mood

Table 2 provides descriptive statistics for all daily diary measures on pre-vaccine days. Reports of depressed mood on pre-vaccine days were low. Female participants reported more depressed mood than male participants, $p = .020$. Consistent with our hypotheses, larger increases in IL-6 from pre- to post-vaccine were associated with greater reported depressed mood on post-vaccine days, $p = .039$. While daily reported confusion was also generally low in the sample on pre-vaccine days, individuals demonstrating larger increases in IL-6 from pre- to post-vaccine reported greater confusion on post-vaccine days, $p = .003$. There were no significant associations between change in IL-6 and anger, tension, fatigue, vigor, or positive affect. However, individuals with higher IL-6 at the pre-vaccine blood draw reported lower average daily positive affect, $p = .044$. See Table 3 for unstandardized fixed effects of time and IL-6 on all sickness behavior and features of depression measured in the daily diary.

Inflammation before and after influenza vaccination and daily diary reported social disconnection

Participants in this study generally reported low feelings of social disconnection on pre-vaccine study days. Individuals demonstrating the largest change in IL-6 from pre- to post-vaccine also reported a non-significant increase in feelings of social disconnection on post-vaccine days, $p = .072$.

Inflammation before and after influenza vaccination and daily diary reported sleep

Participants in this study slept an average of 7.12 hours on pre-vaccine days. Change in IL-6 was not associated with changes in sleep duration from pre- to post-vaccine, $p = .64$. Participants in this study reported their average sleep quality as either *Very good* or *Good* on pre-vaccine study days. Participants in the study with high pre-vaccine IL-6 reported greater daily sleep disturbance, $p = .004$, and individuals demonstrating a larger increase in IL-6 from pre- to post-vaccine also reported non-significant increases in sleep disturbance on post-vaccine days, $p = .10$.

Inflammation before and after influenza vaccination and daily diary reported physical symptoms

Change in inflammation from pre- to post-vaccine was not associated with physical symptoms, $p = .69$. Daily reports of physical symptoms were very infrequent or *Absent* on the response scale on pre-vaccine days. Change in IL-6 from pre- to post-vaccine was not associated with post-vaccine physical symptoms, however participants with higher pre-vaccine IL-6 reported more pre-vaccine physical symptoms, $p = .002$.

Discussion

This study documents associations between mild fluctuations in the proinflammatory cytokine IL-6 and features of depression in a sample of healthy, young adults. The majority of participants in this sample demonstrated an increase in IL-6 from immediately before to 1-day after flu vaccine exposure, and while this change was mild, participants varied considerably in the degree of inflammatory change. Consistent with our hypotheses, larger

increases in IL-6 were associated with greater depressed mood and greater confusion in the week following vaccination. These findings align with previous research and with the hypothesized role of inflammation in depression (Dantzer et al., 2008; Dantzer and Kelley, 2007) as well as established experimental models in both animals and humans. Notably, some of the initial observations in preclinical studies were that inflammation interferes with cognitive functioning (Aubert et al., 1995). Further, inflammatory challenge studies in humans using endotoxin (Eisenberger et al., 2009; Reichenberg et al., 2001) and typhoid (Brydon et al., 2008; Harrison et al., 2009a), as well as observational studies (Gimeno et al., 2009; Motivala et al., 2005) have documented associations between inflammation and both cognitive symptoms of depression and sleep disturbance. Our findings extend this literature by demonstrating increases in depressed mood and cognitive symptoms following a mild inflammatory stimulus using a naturalistic and ecologically valid approach.

Further, the results of this study support the use of influenza vaccination as a translational model for interrogating well-established preclinical observations on the role of mild inflammatory changes in depressive symptoms. This model could be used to interrogate sensitivity to these changes in high-risk and vulnerable populations including children, adolescents, older adults, pregnant women, and patients with chronic illness. Inflammatory immune cells and cytokines, including IL-6, can cross the blood-brain interface and activate microglia (Banks et al., 1995; Wohleb et al., 2015). Activation of microglia causes local inflammation which mediates anxiety-like behavior, and primes the immune system for a greater inflammatory response to future stressors (Reader et al., 2015). Repetition of these processes in animals, such as through chronic stress, has been linked to anhedonia, sleep disturbance, and maintenance of anxiety-like behavior (Wohleb et al., 2015). Affective correlates of mild fluctuations in pro-inflammatory cytokines, as demonstrated in this study, may be an indicator of affective sensitivity to increases in peripheral inflammation and thus potentially a neurobiological risk factor for depression.

Contrary to our hypotheses, larger increases in IL-6 were not associated with decreases in daily positive affect or increases in fatigue. Given the subtle changes in both inflammation and daily diary reports of features of depression, we may have lacked power to detect these effects that have been observed in other experimental studies (Eisenberger et al., 2010b; Harrison et al., 2009b; Moieni et al., 2015). It is possible that the effect of inflammation on positive affect and fatigue occurs acutely (i.e., within hours), and is not effectively observed using a daily diary assessment. Indeed, preclinical models have shown that acute inflammatory states interfere with the opioid receptors in the neural structures involved in reward processes that would underlie positive affect (Eisenberger et al., 2010a; Narita et al., 2004). It is also possible that the effect of inflammation on positive affect and fatigue is only observed at higher levels of inflammation than seen here. We did find that higher IL-6 at baseline (immediately prior to vaccination) was associated with lower average daily positive affect. In previous studies, higher trait positive affect has been linked to lower circulating markers of inflammation, IL-6 and CRP, in both adolescents and adults (Chiang et al., 2015; Stellar et al., 2015; Steptoe et al., 2008). A similar pattern was observed for sleep disturbance, such that higher IL-6 at baseline was associated with greater daily reported sleep disturbance. Sleep and inflammation are intimately-linked physiological processes; sleep problems relate to greater inflammation, and interventions that improve sleep are

associated with reductions in inflammatory processes (Irwin et al., 2016; Irwin and Opp, 2017). Therefore, further interrogation of dose, magnitude, and time course of inflammatory challenge is necessary. Some domains of sickness behavior and features of depression may be more sensitive to acute inflammatory signaling, while others may be induced by chronic, sustained elevations in inflammation. These differences further emphasize the value of using different paradigms to examine the role of inflammation in mood and behavior.

An important strength of this study was the use of daily diaries to capture within-subject changes in mood, and the interrogation of multiple domains that relate to depression (e.g., depressed mood, cognitive symptoms, poor sleep quality, positive affect, social disconnection). These findings should be considered preliminary due to the small sample size. Given the number of past studies that have demonstrated an inflammatory response following influenza vaccination (Carty et al., 2006; Christian et al., 2011; McDade et al., 2015; Posthouwer et al., 2004; Tsai et al., 2005) and the within-subject hypotheses of the present study, we did not include a placebo or waitlist control group and therefore no causal conclusions can be drawn. We also did not measure antibody response to the influenza vaccine, and therefore our data cannot speak to the role of change in IL-6 in the potential effectiveness of the vaccine. This study was also conducted in a small, convenience sample of young adults. Further investigations using this paradigm in larger samples are needed. Previous studies have shown that experimentally induced inflammation impacts feelings of social disconnection and sleep disturbance. In this study, the associations between IL-6 response and both of these constructs were in the expected direction but were non-significant. Larger studies would enable us to understand whether these effects only occur following a more robust inflammatory stimulus (e.g., endotoxin) or are subtle effects that require more power to detect. A larger study would facilitate the generalizability of this study's observations as well as identify important moderators of inflammatory responses to influenza vaccination including BMI, sex, and exposure to early life stress (Kuhlman et al., 2017; O'Connor et al., 2009). Finally, we chose to measure the inflammatory response to the influenza vaccine 1 day after vaccination when an inflammatory response would most likely be observable (Carty et al., 2006; Tsai et al., 2005), however one study in pregnant women demonstrated that the inflammatory response to influenza vaccine is higher 2-days post-vaccination than 1-day post-vaccine (Christian et al., 2011). It is possible that some individuals' IL-6 continued to rise beyond our post-vaccine IL-6 measurement. Indeed, there was a modest association between the magnitude of the IL-6 response and the length of the delay between the vaccine and post-vaccine blood draw, $r = .27$, $p = .08$; in other words, IL-6 continued to increase across the day following vaccination. Figure 3 clearly demonstrates that differences in depressed mood between participants with and without an increase in IL-6 are most prominent on the 2nd and 3rd day after vaccination. It will be informative for future studies to determine individual differences in the time course of the inflammatory response to the influenza vaccine as it relates to changes in mood and behavior.

The results of this study provide preliminary evidence that mild, within-subject increases in IL-6 following influenza vaccination are associated with increases in features of depression, specifically depressed mood and cognitive symptoms. These findings are encouraging evidence that the annual influenza vaccine can be used to interrogate the effects of mild

changes in inflammation on mood and behavior in a wide range of populations. The flu vaccine meets risk/benefit ratio criteria by including the tangible benefit of increased protection against influenza infection while also being familiar to most people, recommended annually, cost effective, and widely accessible. Using the influenza vaccine paradigm may help to identify risk factors for depression in high-risk populations and inform psychological and pharmacological interventions targeting inflammation in the pathogenesis of depression.

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Highlights

- Participants demonstrated a significant increase in IL-6 from immediately before to 1-day after influenza vaccine.
- Individuals vary in the magnitude of IL-6 change following influenza vaccine.
- Larger increases in IL-6 were associated with corresponding increases in depressed mood and confusion.
- The annual influenza vaccine may be a useful tool for investigating the role of inflammation in mood and behavior in a wide range of populations.

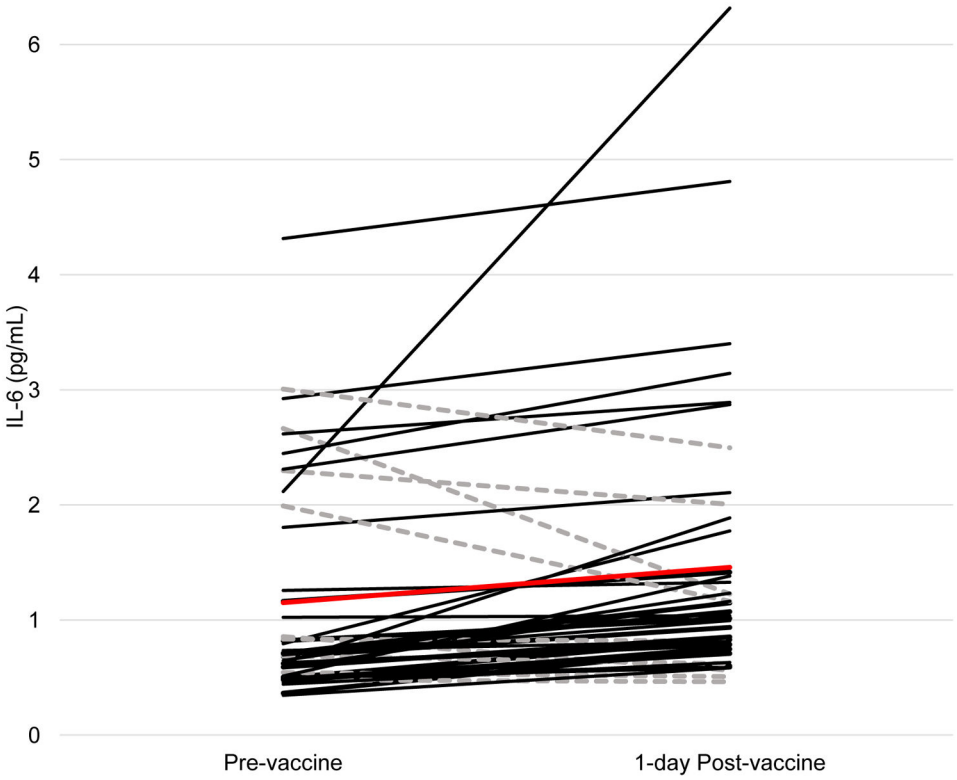


Figure 1. Change in IL-6 from pre- to one-day post-vaccine administration

IL-6 at pre- and post-vaccine for all participants. Black lines indicate participants with an increase in IL-6 from pre- to post-vaccine ($n = 32$), dashed grey lines indicate participants who did not show an increase in IL-6 ($n = 9$), and the red line indicates the mean change in IL-6 across the sample.

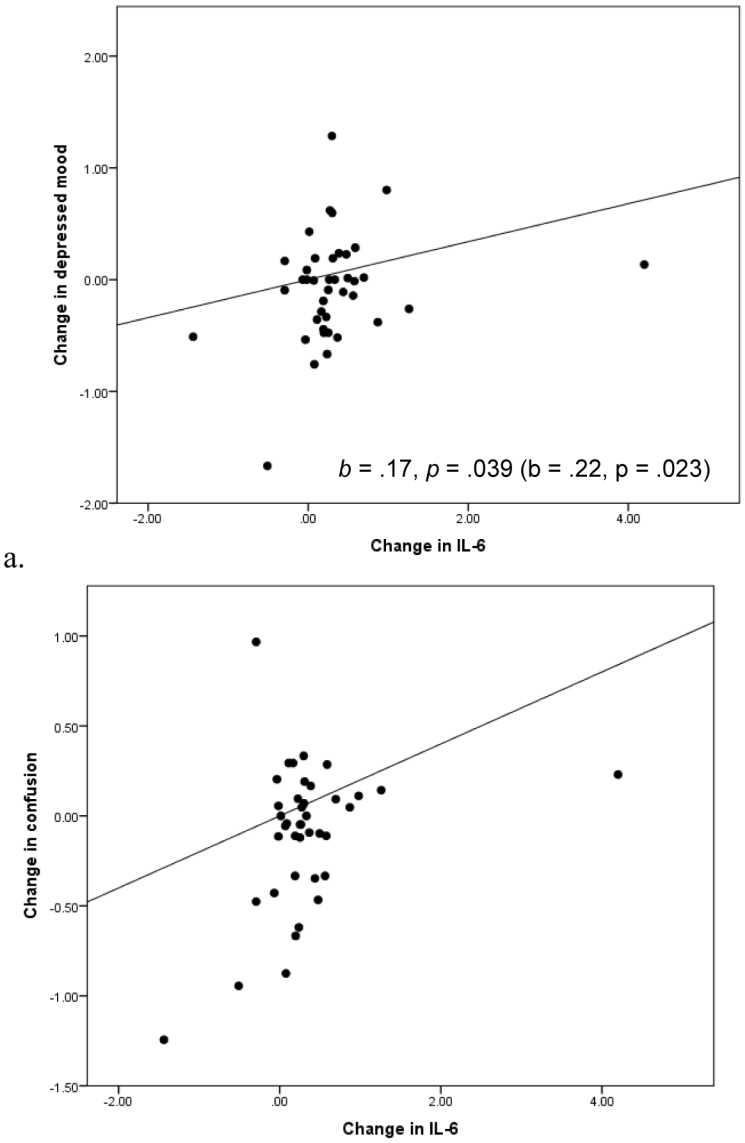


Figure 2. Change in depressed mood and confusion over week following vaccine by IL-6 response

Within-subject change in (a) depressed mood and (b) confusion from pre-vaccine to post-vaccine days by within-subject change in IL-6. Estimates of fixed effects for the Time*ΔIL-6 term in each model are presented in the bottom right corner of each panel.

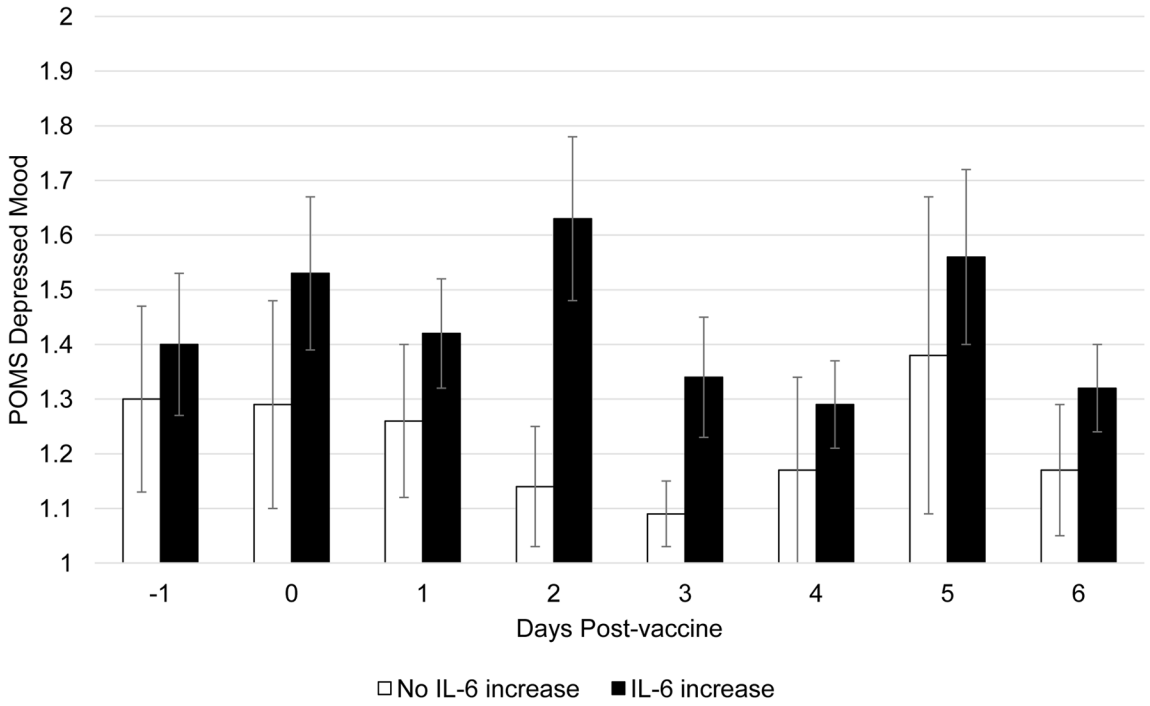


Figure 3. Daily reported depressed mood for participants who did and did not demonstrate an inflammatory response to the flu vaccine

Daily mean (*SE*) of depressed mood following vaccine administration by participants demonstrating an increase in IL-6 from immediately before to 1-day after the vaccine.

Table 1

Sample characteristics and pre- and post-vaccine inflammation.

	M (SD)	% (*n*)
Age	18.49 (0.75)	
Female		73.2 (30)
BMI	24.08 (3.84)	
Race/Ethnicity[1]		
White		41.5 (17)
Asian		58.5 (24)
Hispanic/Latino		22.0 (9)
Maternal Education		
Some high school		14.6 (6)
High school diploma		22.0 (9)
Bachelor's		31.7 (13)
Graduate		31.7 (13)
IL-6 (pg/ml)		
Baseline	1.14 (.95)	
1-day post-vaccine	1.47 (1.22)	
Δ IL-6	0.33 (0.75)	

[1]Groups are not mutually exclusive

Table 2

Mean (SD) of mood, sleep, social disconnection, and physical symptoms on days prior to influenza vaccine.

	M (SD)
Mood	
Depressed mood	1.44 (0.71)
Anger	1.39 (0.62)
Tension	1.49 (0.76)
Fatigue	2.28 (1.12)
Vigor	2.69 (0.83)
Confusion	1.60 (0.68)
Positive affect	3.21 (0.83)
Sleep	
Sleep Disturbance	1.73 (0.69)
Sleep Quantity	7.12 (1.93)
Social Disconnection	1.82 (0.60)
Physical Symptoms	1.13 (0.20)

Table 3

Unstandardized coefficient estimates in models predicting daily diary reported measures of affective well-being by inflammatory increase following influenza vaccine (Time * ΔIL-6)

	Depressed mood	Anger	Tension	Fatigue	Vigor	Confusion	Positive affect	Sleep Disturbance	Sleep Quantity	Social Disconnection	Physical symptoms
	b (SE)	*b (SE)*	*b (SE)*	*b (SE)*	*b (SE)*	*b (SE)*	*b (SE)*	*b (SE)*	*b (SE)*	*b (SE)*	*b (SE)*
Intercept	1.24(0.15)***	1.17 (0.12)***	1.31(0.17)***	2.25(0.28)***	2.77 (0.19)***	1.36(0.16)***	3.08(0.21)***	1.77 (0.13)***	6.78(0.35)***	1.89 (0.14)***	1.09 (0.04)***
Study Day	−0.01 (0.01)	0.01(0.01)	−0.003(0.01)	−0.05(0.02)**	0.01(0.1)	−0.01 (0.01)	0.02(0.01)	−0.004 (0.01)	0.14(0.03)***	−0.01 (0.09)	−0.002(0.003)
BMI	0.001(0.02)	−0.001(0.01)	0.002(0.02)	−0.02(0.03)	0.02(0.02)	0.02 (0.02)	0.03(0.03)	−0.03 (0.02)	−0.03(0.04)	−0.01 (0.02)	−0.001(0.01)
Sex	0.30 (0.13)*	0.14(0.011)	0.20(0.17)	0.29(0.27)	0.12(0.20)	0.25 (0.16)	0.25(0.21)	−0.03 (0.13)	−0.11(0.34)	−0.22 (0.15)	0.12 (0.04)*
Cohort	0.16 (0.11)	0.18(0.09)$^{+}$	0.16(0.15)	0.17(0.23)	−0.35(0.17)*	0.28(0.14)$^{+}$	−0.27(0.18)	−0.03 (0.11)	−0.28(0.29)	0.30 (0.13)*	−0.06 (0.04)
Time	−0.06 (0.09)	−0.13(0.08)	−0.08(0.09)	0.08(0.13)	−0.06(0.11)	−0.09 (0.08)	−0.17(0.10)	−0.01 (0.11)	−1.00(0.28)***	0.04 (0.07)	0.03 (.03)
Baseline IL−6	0.01 (0.06)	−0.01(0.06)	−0.07(0.09)	−0.06(0.13)	−0.19(0.10)$^{+}$	−0.06 (0.08)	−0.22(0.10)*	0.19 (0.06)**	−0.29(0.17)$^{+}$	0.06 (0.07)	0.07(0.02)**
ΔIL−6	−0.17(0.09)$^{+}$	−0.08(0.08)	−0.16(0.11)	−0.31(0.17)$^{+}$	−0.01(0.12)	−0.24(0.10)*	−0.01(0.12)	0.05 (0.08)	−0.04(0.21)	−0.12 (0.09)	−0.02 (0.03)
Time * ΔIL-6[1]	0.17 (0.08)*	0.03(0.06)	0.10(0.07)	0.08(0.12)	−0.10(0.09)	0.20(0.06)**	−0.13(0.09)	0.13 (0.08)$^{+}$	0.14(0.20)	0.11 (0.06)$^{+}$	0.002(0.02)

*** p <.001,

** p < .01,

* p < .05,

$^{+}$ p < .10 (non-significant)

[1] Indicates key parameter of interest.

EXHIBIT 104

COVID-19 is an emerging, rapidly evolving situation.

Get the latest public health information from CDC: https://www.coronavirus.gov
Get the latest research information from NIH: https://www.nih.gov/coronavirus

The National Institute of Mental Health: www.nimh.nih.gov

Depression

Overview

Depression (major depressive disorder or clinical depression) is a common but serious mood disorder. It causes severe symptoms that affect how you feel, think, and handle daily activities, such as sleeping, eating, or working. To be diagnosed with depression, the symptoms must be present for at least two weeks.

Some forms of depression are slightly different, or they may develop under unique circumstances, such as:

Persistent depressive disorder (also called dysthymia) is a depressed mood that lasts for at least two years. A person diagnosed with persistent depressive disorder may have episodes of major depression along with periods of less severe symptoms, but symptoms must last for two years to be considered persistent depressive disorder.
Postpartum depression is much more serious than the "baby blues" (relatively mild depressive and anxiety symptoms that typically clear within two weeks after delivery) that many women experience after giving birth. Women with postpartum depression experience full-blown major depression during pregnancy or after delivery (postpartum depression). The feelings of extreme sadness, anxiety, and exhaustion that accompany postpartum depression may make it difficult for these new mothers to complete daily care activities for themselves and/or for their babies.
Psychotic depression occurs when a person has severe depression plus some form of psychosis, such as having disturbing false fixed beliefs (delusions) or hearing or seeing upsetting things that others cannot hear or see (hallucinations). The psychotic symptoms typically have a depressive "theme," such as delusions of guilt, poverty, or illness.
Seasonal affective disorder is characterized by the onset of depression during the winter months, when there is less natural sunlight. This depression generally lifts during spring and summer. Winter depression, typically accompanied by social withdrawal, increased sleep, and weight gain, predictably returns every year in seasonal affective disorder.
Bipolar disorder (www.nimh.nih.gov//health/topics/bipolar-disorder/index.shtml) is different from depression, but it is included in this list is because someone with bipolar disorder experiences episodes of extremely low moods that meet the criteria for major depression (called "bipolar depression"). But a person with bipolar disorder also experiences extreme high – euphoric or irritable – moods called "mania" or a less severe form called "hypomania."

Examples of other types of depressive disorders newly added to the diagnostic classification of DSM-5 include disruptive mood dysregulation disorder (diagnosed in children and adolescents) and premenstrual dysphoric disorder (PMDD).

Signs and Symptoms

If you have been experiencing some of the following signs and symptoms most of the day, nearly every day, for at least two weeks, you may be suffering from depression:

Persistent sad, anxious, or "empty" mood
Feelings of hopelessness, or pessimism
Irritability
Feelings of guilt, worthlessness, or helplessness
Loss of interest or pleasure in hobbies and activities
Decreased energy or fatigue
Moving or talking more slowly
Feeling restless or having trouble sitting still
Difficulty concentrating, remembering, or making decisions
Difficulty sleeping, early-morning awakening, or oversleeping
Appetite and/or weight changes
Thoughts of death or suicide, or suicide attempts
Aches or pains, headaches, cramps, or digestive problems without a clear physical cause and/or that do not ease even with treatment

Not everyone who is depressed experiences every symptom. Some people experience only a few symptoms while others may experience many. Several persistent symptoms in addition to low mood are required for a diagnosis of major depression, but people with only a few – but distressing – symptoms may benefit from treatment of their "subsyndromal" depression. The severity and frequency of symptoms and how long they last will vary depending on the individual and his or her particular illness. Symptoms may also vary depending on the stage of the illness.

Risk Factors

Depression is one of the most common mental disorders in the U.S. Current research suggests that depression is caused by a combination of genetic, biological, environmental, and psychological factors.

Depression can happen at any age, but often begins in adulthood. Depression is now recognized as occurring in children and adolescents, although it sometimes presents with more prominent irritability than low mood. Many chronic mood and anxiety disorders in adults begin as high levels of anxiety in children.

Depression, especially in midlife or older adults, can co-occur with other serious medical illnesses, such as diabetes, cancer, heart disease, and Parkinson's disease. These conditions are often worse when depression is present. Sometimes medications taken for these physical illnesses may cause side effects that contribute to depression. A doctor experienced in treating these complicated illnesses can help work out the best treatment strategy.

Risk factors include:

Personal or family history of depression
Major life changes, trauma, or stress

Certain physical illnesses and medications

Treatment and Therapies

Depression, even the most severe cases, can be treated. The earlier that treatment can begin, the more effective it is. Depression is usually treated with medications (www.nimh.nih.gov//health/topics/mental-health-medications/index.shtml), psychotherapy (www.nimh.nih.gov//health/topics/psychotherapies/index.shtml), or a combination of the two. If these treatments do not reduce symptoms, electroconvulsive therapy (ECT) and other brain stimulation therapies may be options to explore.

Quick Tip: No two people are affected the same way by depression and there is no "one-size-fits-all" for treatment. It may take some trial and error to find the treatment that works best for you.

Medications

Antidepressants are medicines that treat depression. They may help improve the way your brain uses certain chemicals that control mood or stress. You may need to try several different antidepressant medicines before finding the one that improves your symptoms and has manageable side effects. A medication that has helped you or a close family member in the past will often be considered.

Antidepressants take time – usually 2 to 4 weeks – to work, and often, symptoms such as sleep, appetite, and concentration problems improve before mood lifts, so it is important to give medication a chance before reaching a conclusion about its effectiveness. If you begin taking antidepressants, do not stop taking them without the help of a doctor. Sometimes people taking antidepressants feel better and then stop taking the medication on their own, and the depression returns. When you and your doctor have decided it is time to stop the medication, usually after a course of 6 to 12 months, the doctor will help you slowly and safely decrease your dose. Stopping them abruptly can cause withdrawal symptoms.

Please Note: In some cases, children, teenagers, and young adults under 25 may experience an increase in suicidal thoughts or behavior when taking antidepressants, especially in the first few weeks after starting or when the dose is changed. This warning from the U.S. Food and Drug Administration (FDA) also says that patients of all ages taking antidepressants should be watched closely, especially during the first few weeks of treatment.

If you are considering taking an antidepressant and you are pregnant, planning to become pregnant, or breastfeeding, talk to your doctor about any increased health risks to you or your unborn or nursing child.

To find the latest information about antidepressants, talk to your doctor and visit www.fda.gov.

You may have heard about an herbal medicine called St. John's wort. Although it is a top-selling botanical product, the FDA has not approved its use as an over-the-counter or prescription medicine for depression, and there are serious concerns about its safety (it should never be combined with a prescription antidepressant) and effectiveness. Do not use St. John’s wort before talking to your health care provider. Other natural products sold as dietary supplements, including omega-3 fatty acids and S-adenosylmethionine (SAMe), remain under study but have not yet been proven safe and effective for routine use. For more information on herbal and other complementary approaches and current research, please visit the National Center for Complementary and Integrative Health website.

Psychotherapies

Several types of psychotherapy (also called "talk therapy" or, in a less specific form, counseling) can help people with depression. Examples of evidence-based approaches specific to the treatment of depression include cognitive-behavioral therapy (CBT), interpersonal therapy (IPT), and problem-solving therapy. More information on psychotherapy is available on the NIMH Psychotherapies webpage (www.nimh.nih.gov//health/topics/psychotherapies/index.shtml).

Brain Stimulation Therapies

If medications do not reduce the symptoms of depression, electroconvulsive therapy (ECT) may be an option to explore. Based on the latest research:

- ECT can provide relief for people with severe depression who have not been able to feel better with other treatments.
- Electroconvulsive therapy can be an effective treatment for depression. In some severe cases where a rapid response is necessary or medications cannot be used safely, ECT can even be a first-line intervention.
- Once strictly an inpatient procedure, today ECT is often performed on an outpatient basis. The treatment consists of a series of sessions, typically three times a week, for two to four weeks.
- ECT may cause some side effects, including confusion, disorientation, and memory loss. Usually these side effects are short-term, but sometimes memory problems can linger, especially for the months around the time of the treatment course. Advances in ECT devices and methods have made modern ECT safe and effective for the vast majority of patients. Talk to your doctor and make sure you understand the potential benefits and risks of the treatment before giving your informed consent to undergoing ECT.
- ECT is not painful, and you cannot feel the electrical impulses. Before ECT begins, a patient is put under brief anesthesia and given a muscle relaxant. Within one hour after the treatment session, which takes only a few minutes, the patient is awake and alert.

Other more recently introduced types of brain stimulation therapies used to treat medicine-resistant depression include repetitive transcranial magnetic stimulation (rTMS) and vagus nerve stimulation (VNS). Other types of brain stimulation treatments are under study. You can learn more about these therapies on the NIMH Brain Stimulation Therapies (www.nimh.nih.gov//health/topics/brain-stimulation-therapies/brain-stimulation-therapies.shtml) webpage.

If you think you may have depression, start by making an appointment to see your doctor or health care provider. This could be your primary care practitioner or a health provider who specializes in diagnosing and treating mental health conditions. Visit the NIMH Find Help for Mental Illnesses (www.nimh.nih.gov//health/find-help/index.shtml) if you are unsure of where to start.

Beyond Treatment: Things You Can Do

Here are other tips that may help you or a loved one during treatment for depression:

- Try to be active and exercise.
- Set realistic goals for yourself.
- Try to spend time with other people and confide in a trusted friend or relative.
- Try not to isolate yourself, and let others help you.

Expect your mood to improve gradually, not immediately.
Postpone important decisions, such as getting married or divorced, or changing jobs until you feel better.
Discuss decisions with others who know you well and have a more objective view of your situation.
Continue to educate yourself about depression.

Join a Study

What are Clinical Trials?

Clinical trials are research studies that look at new ways to prevent, detect, or treat diseases and conditions, including depression. During clinical trials, some participants receive treatments under study that might be new drugs or new combinations of drugs, new surgical procedures or devices, or new ways to use existing treatments. Other participants (in the "control group") receive a standard treatment, such as a medication already on the market, an inactive placebo medication, or no treatment. The goal of clinical trials is to determine if a new test or treatment works and is safe. Although individual participants may benefit from being part of a clinical trial, participants should be aware that the primary purpose of a clinical trial is to gain new scientific knowledge so that others may be better helped in the future.

Please Note: Decisions about whether to participate in a clinical trial, and which ones are best suited for a given individual, are best made in collaboration with your licensed health professional.

How do I find a Clinical Trials at NIMH on Depression?

Doctors at NIMH are dedicated to mental health research, including clinical trials of possible new treatments as well as studies to understand the causes and effects of depression. The studies take place at the NIH Clinical Center in Bethesda, Maryland and require regular visits. After the initial phone interview, you will come to an appointment at the clinic and meet with one of our clinicians. Find NIMH studies currently recruiting participants with depression by visiting Join a Research Study: Depression (www.nimh.nih.gov//research/research-conducted-at-nimh/join-a-study/adults/adults-depression.shtml).

How Do I Find a Clinical Trial Near Me?

To search for a clinical trial near you, you can visit ClinicalTrials.gov. This is a searchable registry and results database of federally and privately supported clinical trials conducted in the United States and around the world (search: depression). ClinicalTrials.gov gives you information about a trial's purpose, who may participate, locations, and contact information for more details. This information should be used in conjunction with advice from health professionals.

Learn More

Free Brochures and Shareable Resources

Chronic Illness & Mental Health (www.nimh.nih.gov//health/publications/chronic-illness-mental-health/index.shtml): This brochure discusses chronic illnesses and depression, including symptoms, health effects, treatment, and recovery.

Depression and Older Adults (www.nimh.nih.gov//health/publications/older-adults-and-depression/index.shtml): Depression is not a normal part of aging. This brochure describes the signs, symptoms, and treatment options for depression in older adults.
Perinatal Depression (www.nimh.nih.gov//health/publications/perinatal-depression/index.shtml): A brochure with information about perinatal depression including how it differs from the "baby blues", causes, signs and symptoms, treatment options, and how you or a loved one can get help.
Teen Depression (www.nimh.nih.gov//health/publications/teen-depression/index.shtml): This flier for teens describes depression and how it differs from regular sadness. It also describes symptoms, causes, and treatments, with information on getting help and coping.
Shareable Resources on Depression (www.nimh.nih.gov//health/education-awareness/shareable-resources-on-depression.shtml): Help support depression awareness and education in your community. Use these digital resources, including graphics and messages, to spread the word about depression.

Clinical Trials

Join a Study: Depression – Adults (www.nimh.nih.gov//research/research-conducted-at-nimh/join-a-study/adults/adults-depression.shtml)
Join a Study: Depression – Children (www.nimh.nih.gov//research/research-conducted-at-nimh/join-a-study/children/children-depression.shtml)
Join a Study: Perimenopause-Related Mood Disorders (www.nimh.nih.gov//research/research-conducted-at-nimh/join-a-study/adults/adults-perimenopause-related-mood-disorders.shtml)
Join a Study: Postpartum Depression (PPD) (www.nimh.nih.gov//research/research-conducted-at-nimh/join-a-study/adults/adults-postpartum-depression.shtml)

Federal Resources

Depression: MedlinePlus
Moms' Mental Health Matter: Depression and Anxiety Around Pregnancy (National Institute of Child Health and Human Development)

Research and Statistics

Journal Articles: This webpage provides information on references and abstracts from MEDLINE/PubMed (National Library of Medicine).
Statistics: Major Depression (www.nimh.nih.gov//health/statistics/major-depression.shtml): This webpage provides information on the statistics currently available on the prevalence and treatment of depression among people in the U.S.

Multimedia

Watch Discover NIMH: Personalized and Targeted Brain Stimulation Therapies (www.nimh.nih.gov//news/media/2019/discover-nimh-personalized-and-targeted-brain-stimulation-therapies.shtml): Brain stimulation therapies can be effective treatments for people with depression and other mental disorders. NIMH is supporting studies exploring how to make brain stimulation therapies more personalized while reducing side effects. This video describes transcranial magnetic stimulation and electroconvulsive therapy for treatment-resistant depression.

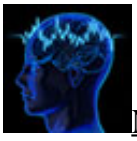
Watch Discover NIMH: Drug Discovery and Development (www.nimh.nih.gov//news/media/2019/discover-nimh-drug-discovery-and-development.shtml): One of the most exciting recent breakthroughs from research funded by the NIMH is the development of a fast-acting medication for treatment-resistant depression based on ketamine. This video shares the story of one of the patients participating in a NIMH clinical trial, and how ketamine infusions changed her life and gave her a sense of purpose. In addition, Dr. Carlos Zarate, a senior clinical investigator in NIMH's Intramural Research Program, describes his groundbreaking research on ketamine.

Last Revised: February 2018

Science News About Depression


Infant Temperament Predicts Personality Over 20 Years Later (www.nimh.nih.gov//news/science-news/2020/infant-temperament-predicts-personality-more-than-20-years-later.shtml)


Fast-Fail Trial Finds Possible Target for Treating Anhedonia (www.nimh.nih.gov//news/science-news/2020/fast-fail-trial-shows-new-approach-to-identifying-brain-targets-for-clinical-treatments.shtml)

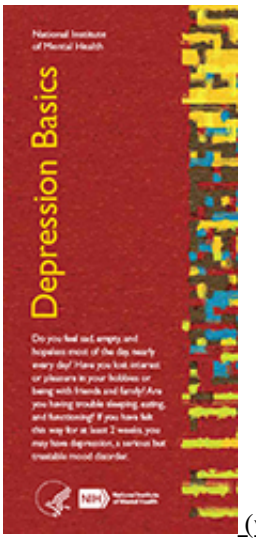

Neural Signature Predicts Antidepressant Response (www.nimh.nih.gov//news/science-news/2020/neural-signature-identifies-people-likely-to-respond-to-antidepressant-medication.shtml)

More (www.nimh.nih.gov//news/science-news/science-news-about-depression.shtml)

Join A Study

Depression Studies for Adults (www.nimh.nih.gov//research/research-conducted-at-nimh/join-a-study/adults/adults-depression.shtml)
Depression Studies for Children (www.nimh.nih.gov//research/research-conducted-at-nimh/join-a-study/children/children-depression.shtml)

Publication About Depression



(www.nimh.nih.gov//health/publications/depression/index.shtml)

Depression Basics (www.nimh.nih.gov//health/publications/depression/index.shtml)

A brochure on depression that explains what it is and how to get help.

More Publications About Depression (www.nimh.nih.gov//health/publications/depression-listing.shtml)

Research Results

Treatment choices for resistant depression – STAR*D trial (www.nimh.nih.gov//funding/clinical-research/practical/stard/index.shtml)
Treatment for Adolescents with Depression Study (TADS) (www.nimh.nih.gov//funding/clinical-research/practical/tads/index.shtml)
Treatment of SSRI-resistant Depression in Adolescents (TORDIA) study (www.nimh.nih.gov//funding/clinical-research/practical/tordia/treatment-of-ssri-resistant-depression-in-adolescents-tordia.shtml)
PubMed: Journal Articles about Depression

Contact Us

The National Institute of Mental Health Information Resource Center

Available in English and Español

Hours: 8:30 a.m. to 5 p.m. Eastern time, M-F

Phone: 1-866-615-6464
TTY: 1-301-443-8431
TTY (toll-free): 1-866-415-8051

Live Online Chat: Talk to a representative
Email: nimhinfo@nih.gov
Fax: 1-301-443-4279

Mail: National Institute of Mental Health
Office of Science Policy, Planning, and Communications
6001 Executive Boulevard, Room 6200, MSC 9663
Bethesda, MD 20892-9663

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EXHIBIT 105

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Children's Mental Health

Anxiety and depression in children: Get the facts

Many children have fears and worries, and may feel sad and hopeless from time to time. Strong fears may appear at different times during development. For example, toddlers are often very distressed about being away from their parents, even if they are safe and cared for. Although some fears and worries are typical in children, persistent or extreme forms of fear and sadness could be due to anxiety or depression.
Learn about anxiety and depression in children.

Facts

- **Anxiety and depression affect many children**[1]
  - 7.1% of children aged 3-17 years (approximately 4.4 million) have diagnosed anxiety.
  - 3.2% of children aged 3-17 years (approximately 1.9 million) have diagnosed depression.
- **Anxiety and depression have increased over time**[2]
  - "Ever having been diagnosed with either anxiety or depression" among children aged 6-17 years increased from 5.4% in 2003 to 8% in 2007 and to 8.4% in 2011–2012.
  - "Ever having been diagnosed with anxiety" among children aged 6-17 years increased from 5.5% in 2007 to 6.4% in 2011–2012.
  - "Ever having been diagnosed with depression" among children aged 6-17 years did not change between 2007 (4.7%) and 2011–2012 (4.9%).

Anxiety

When children do not outgrow the fears and worries that are typical in young children, or when there are so many fears and worries that they interfere with school, home, or play activities, the child may be diagnosed with an anxiety disorder. Examples of different types of anxiety disorders include

- Being very afraid when away from parents (separation anxiety)
- Having extreme fear about a specific thing or situation, such as dogs, insects, or going to the doctor (phobias)
- Being very afraid of school and other places where there are people (social anxiety)
- Being very worried about the future and about bad things happening (general anxiety)

- Having repeated episodes of sudden, unexpected, intense fear that come with symptoms like heart pounding, having trouble breathing, or feeling dizzy, shaky, or sweaty (panic disorder)

Anxiety may present as fear or worry, but can also make children irritable and angry. Anxiety symptoms can also include trouble sleeping, as well as physical symptoms like fatigue, headaches, or stomachaches. Some anxious children keep their worries to themselves and, thus, the symptoms can be missed.

Depression

Occasionally being sad or feeling hopeless is a part of every child's life. However, some children feel sad or uninterested in things that they used to enjoy, or feel helpless or hopeless in situations they are able to change. When children feel persistent sadness and hopelessness, they may be diagnosed with depression.

Examples of behaviors often seen in children with depression include

- Feeling sad, hopeless, or irritable a lot of the time
- Not wanting to do, or enjoy doing, fun things
- Showing changes in eating patterns – eating a lot more or a lot less than usual
- Showing changes in sleep patterns – sleeping a lot more or a lot less than normal
- Showing changes in energy – being tired and sluggish or tense and restless a lot of the time
- Having a hard time paying attention
- Feeling worthless, useless, or guilty
- Showing self-injury and self-destructive behavior

Extreme depression can lead a child to think about suicide or plan for suicide. For youth ages 10-24 years, suicide is among the leading causes of death[1]. Read about youth suicide prevention

Some children may not talk about their helpless and hopeless thoughts, and may not appear sad. Depression might also cause a child to make trouble or act unmotivated, causing others not to notice that the child is depressed, or to incorrectly label the child as a trouble-maker or lazy.

Treatment for Anxiety and Depression

The first step to treatment is to talk with a healthcare provider, such as your child's primary care provider or a mental health specialist, about getting an evaluation. Some of the signs and symptoms of anxiety or depression in children could be caused by other conditions, such as trauma. A mental health professional can develop a therapy plan that works best for the child and family. Behavior therapy includes child therapy, family therapy, or a combination of both. For very young children, involving parents in treatment is key; the school can also be included in the treatment plan. Consultation with a healthcare provider can help determine if medication should be part of the treatment.

If you need help finding treatment, visit MentalHealth.gov .

Managing Symptoms: Staying Healthy

Being healthy is important for all children, and can be especially important for children with depression or anxiety. In addition to getting the right treatment, leading a healthy lifestyle can play a role in managing symptoms of depression or anxiety. Here are some healthy behaviors that may help:

- Having a healthy eating plan centered on fruits, vegetables, whole grains, legumes (beans, peas, and lentils), lean protein sources, and nuts and seeds
- Participating in physical activity each day based on age
- Getting the recommended amount of sleep each night based on age
- Practicing mindfulness or relaxation techniques

More Information

CDC: Children's Mental Health

CDC: Suicide Prevention

CDC: Bullying Research

CDC: Positive Parenting Tips

Stopbullying.gov

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Page last reviewed: March 30, 2020

Content source: National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention

EXHIBIT 106

NCHS Data Brief ■ No. 303 ■ February 2018

Prevalence of Depression Among Adults Aged 20 and Over: United States, 2013–2016

Debra J. Brody, M.P.H., Laura A. Pratt, Ph.D., and Jeffery P. Hughes, M.P.H.

Key findings

Data from the National Health and Nutrition Examination Survey

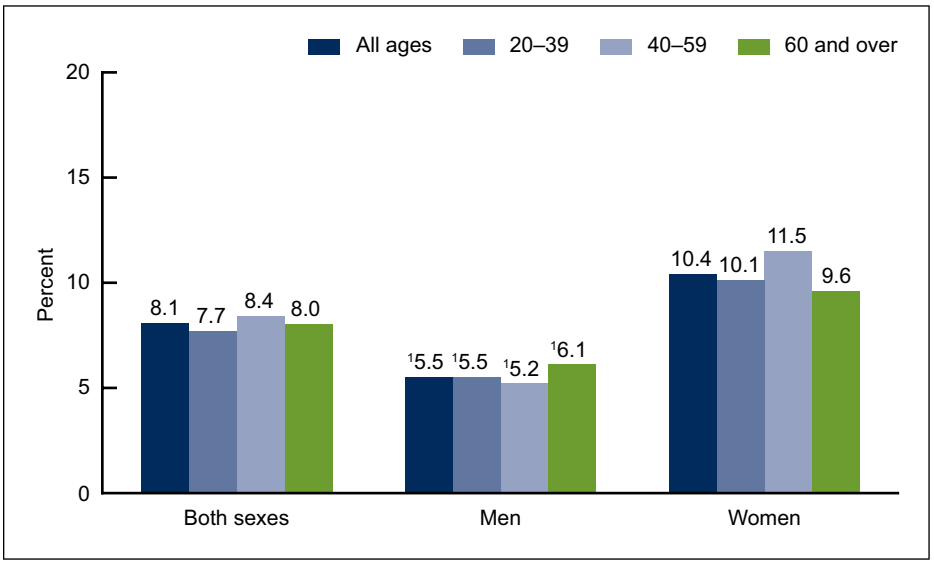
- During 2013–2016, 8.1% of American adults aged 20 and over had depression in a given 2-week period.
- Women (10.4%) were almost twice as likely as were men (5.5%) to have had depression.
- Depression was lower among non-Hispanic Asian adults, compared with Hispanic, non-Hispanic black, or non-Hispanic white adults.
- The prevalence of depression decreased as family income levels increased.
- About 80% of adults with depression reported at least some difficulty with work, home, and social activities because of their depression.
- From 2007–2008 to 2015–2016, the percentage of American adults with depression did not change significantly over time.

Major depression is a common and treatable mental disorder characterized by changes in mood, and cognitive and physical symptoms over a 2-week period (1). It is associated with high societal costs (2) and greater functional impairment than many other chronic diseases, including diabetes and arthritis (3). Depression rates differ by age, sex, income, and health behaviors (4). This report provides the most recent national estimates of depression among adults. Prevalence of depression is based on scores from the Patient Health Questionnaire (PHQ-9), a symptom-screening questionnaire that allows for criteria-based diagnoses of depressive disorders (5). Estimates for non-Hispanic Asian persons are presented for the first time.

Keywords: mental health • NHANES

During 2013–2016, 8.1% of Americans aged 20 and over had depression in a given 2-week period.

Figure 1. Percentage of persons aged 20 and over with depression, by age and sex: United States, 2013–2016



[1]Significantly different from females in same age group.
NOTES: Depression was defined as a score greater than or equal to 10 on the Patient Health Questionnaire. Access data table for Figure 1 at: https://www.cdc.gov/nchs/data/databriefs/db303_table.pdf#1.
SOURCE: NCHS, National Health and Nutrition Examination Survey, 2013–2016.

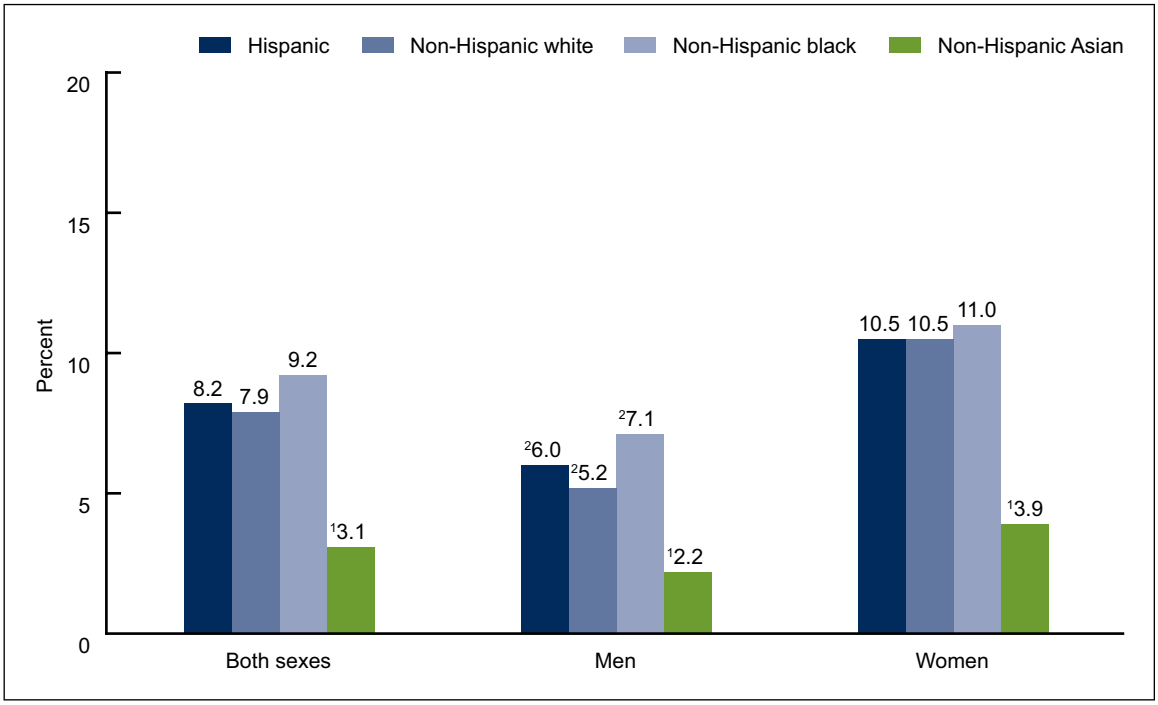
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Centers for Disease Control and Prevention
National Center for Health Statistics

- Overall, women (10.4%) were almost twice as likely to have depression as men (5.5%). This pattern also was observed among each age group (Figure 1).
- Among both men and women, the percentage with depression did not differ statistically across age groups.

The prevalence of depression was lower among non-Hispanic Asian adults than among any other race and Hispanic-origin group.

- Overall, non-Hispanic Asian adults had the lowest prevalence of depression (3.1%) compared with Hispanic (8.2%), non-Hispanic white (7.9%), and non-Hispanic black (9.2%) adults. This pattern was observed among both men and women (Figure 2).
- The prevalence of depression was not statistically different for Hispanic, non-Hispanic white, and non-Hispanic black adults, overall and among both men and women.
- Among all race and Hispanic-origin groups, except non-Hispanic Asian, men had a significantly lower prevalence of depression compared with women.

Figure 2. Percentage of persons aged 20 and over with depression, by race and Hispanic origin and sex: United States, 2013–2016



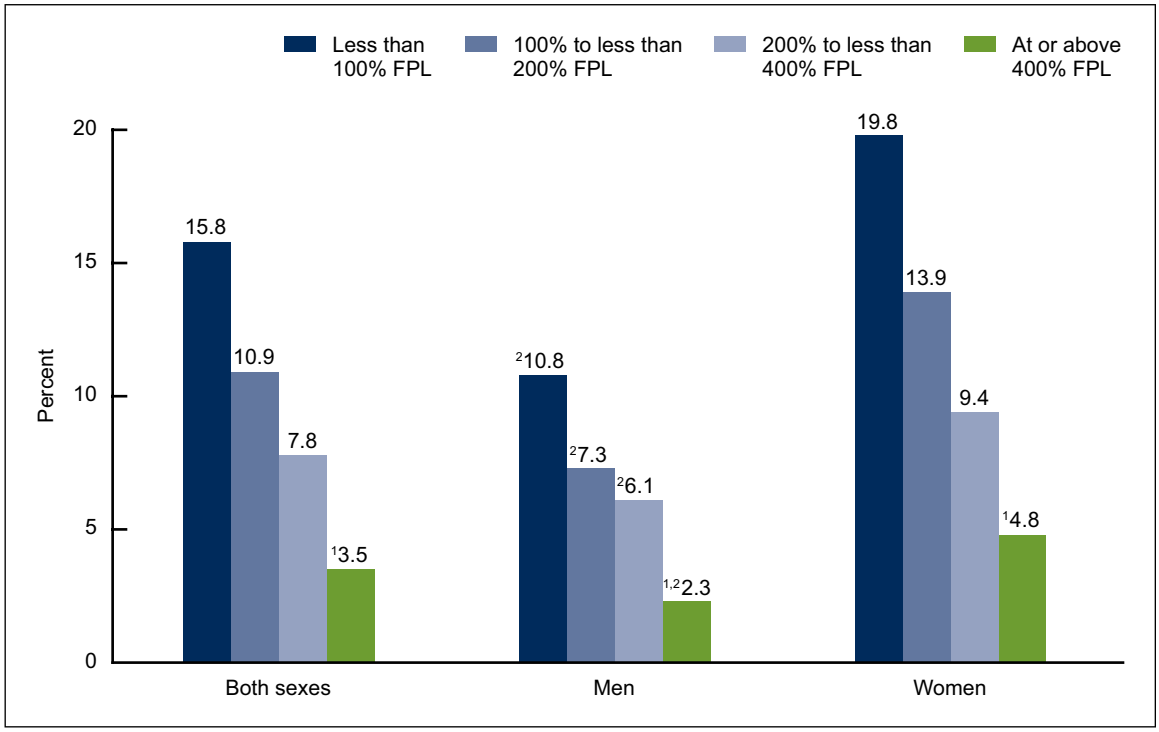
[1]Significantly lower than Hispanic, non-Hispanic white, and non-Hispanic black.
[2]Significantly lower than women of the same race and Hispanic-origin group.
NOTES: Depression was defined as a score greater than or equal to 10 on the Patient Health Questionnaire. Access data table for Figure 2 at: https://www.cdc.gov/nchs/data/databriefs/db303_table.pdf#2.
SOURCE: NCHS, National Health and Nutrition Examination Survey, 2013–2016.

Exhibit 106

The prevalence of depression among adults decreased as family income levels increased.

- Overall, 15.8% of adults from families living below the federal poverty level (FPL) had depression. The prevalence of depression decreased to 3.5% among adults at or above 400% of the FPL (Figure 3).
- Among both men and women, the prevalence of depression decreased with increasing levels of family income.
- Men with family incomes at or above 400% of the FPL had the lowest prevalence of depression (2.3%), while women with family incomes below the FPL had the highest prevalence (19.8%).

Figure 3. Percentage of persons aged 20 and over with depression, by family income level: United States, 2013–2016

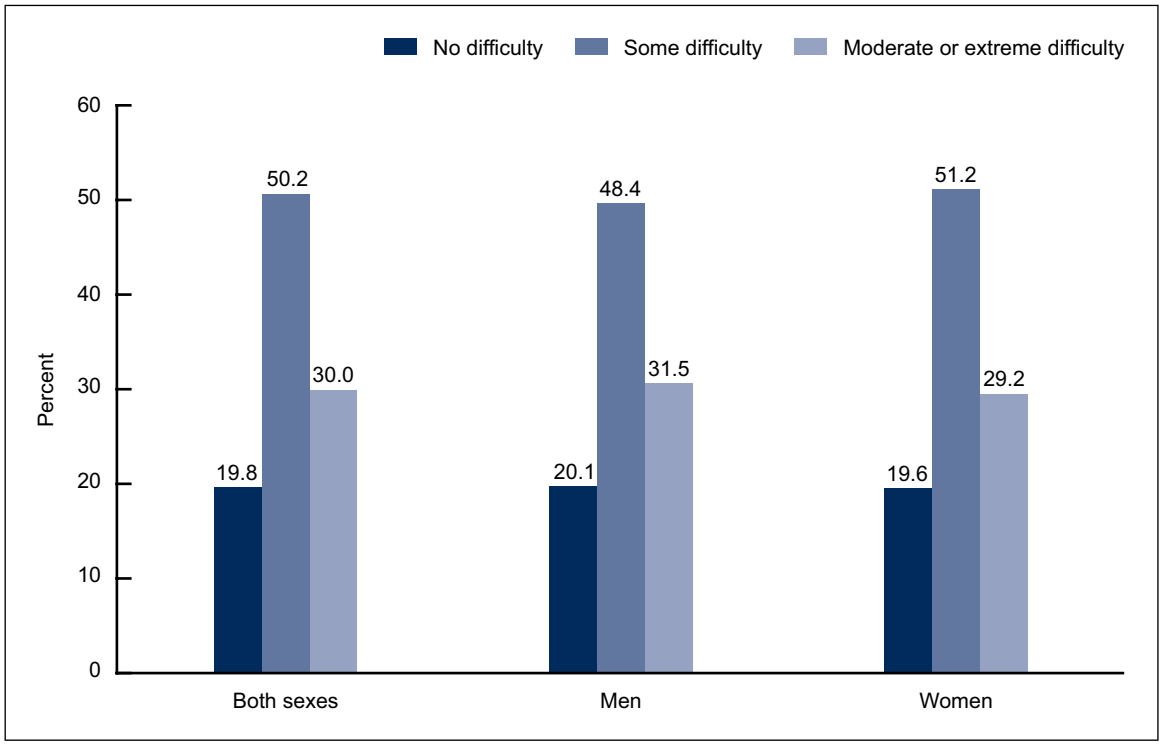


[1]Significant decreasing linear trend.
[2]Significantly lower than women in same family income level.
NOTES: Family income levels are defined by the federal poverty level (FPL). Depression was defined as a score greater than or equal to 10 on the Patient Health Questionnaire. Access data table for Figure 3 at: https://www.cdc.gov/nchs/data/databriefs/db303_table.pdf#3.
SOURCE: NCHS, National Health and Nutrition Examination Survey, 2013–2016.

About 80% of adults with depression reported at least some difficulty with work, home, or social activities because of their depression symptoms.

- 50.2% of adults with depression reported some difficulty with work, home, or social activities because of their depression symptoms (Figure 4).
- 30.0% of adults with depression reported moderate or extreme difficulty with work, home, or social activities because of their depression symptoms.
- The percentage of adults with depression reporting difficulty with work, home, or social activities due to depression symptoms was similar in men and women.

Figure 4. Percentage of persons aged 20 and over with depression who reported difficulty with work, home, or social activities due to depression symptoms: United States, 2013–2016

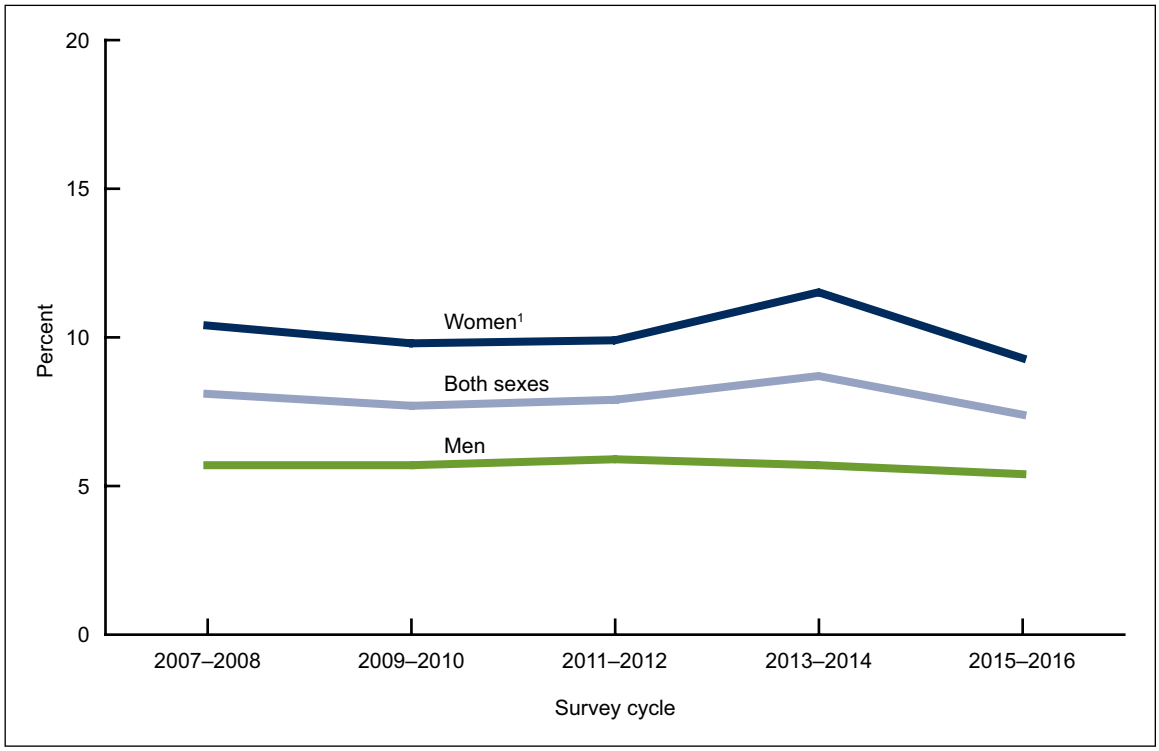


NOTES: Depression was defined as a score greater than or equal to 10 on the Patient Health Questionnaire. Access data table for Figure 4 at: https://www.cdc.gov/nchs/data/databriefs/db303_table.pdf#4.
SOURCE: NCHS, National Health and Nutrition Examination Survey, 2013–2016.

Over a 10-year period, from 2007–2008 to 2015–2016, the percentage of adults with depression did not change significantly.

- Among men, the prevalence of depression was 5.7 % in 2007–2008 and 5.4% in 2015–2016 (Figure 5).
- Among women, the prevalence of depression was 10.4% in 2007–2008 and 9.3% in 2015–2016.

Figure 5. Prevalence of depression among persons aged 20 and over: United States, 2007–2008 to 2015–2016



[1]Women had a higher prevalence of depression than men at every time point.
NOTES: Depression was defined as a score greater than or equal to 10 on the Patient Health Questionnaire. Access data table for Figure 5 at: https://www.cdc.gov/nchs/data/databriefs/db303_table.pdf#5.
SOURCE: NCHS, National Health and Nutrition Examination Survey, 2007–2016.

Summary

During 2013–2016, 8.1% of American adults had depression in a given 2-week period. As observed in other studies (4,6), depression was almost twice as common among women as among men. Depression prevalence did not differ by age. Non-Hispanic Asian adults had the lowest prevalence of depression, a finding noted in other studies (7). Depression prevalence did not vary significantly among the other race and Hispanic-origin groups studied. The proportion of adults with depression increased with decreasing family income level. About 80% of adults with depression reported at least some difficulty with work, home, or social activities due to their depression symptoms. From 2007–2008 to 2015–2016, the prevalence of depression among both men and women showed no significant changes, similar to the results of another major federal survey that tracks depression estimates in the United States (8).

Prevalence estimates reported here do not include populations considered at higher risk for depression (i.e., those in nursing homes or other institutions). Persons currently treated for depression (i.e., medication or therapy) may not have screened positively for depression using the PHQ-9. Finally, some persons with depression may not have been able or willing to participate in the National Health and Nutrition Examination Survey (NHANES). Therefore, these findings may represent conservative estimates of depression among adults in the United States.

Definitions

Depression: Measured using the score from the Patient Health Questionnaire (PHQ-9), a nine-item depression-screening instrument that asks about the frequency of symptoms of depression in the past 2 weeks (5). Response categories of "not at all," "several days," "more than half the days," and "nearly every day" are given a score of 0 to 3. Summary scores ranged from 0 to 27. Depression was defined using a score of 10 or higher, a well-validated cut point used in primary care settings (5).

Difficulties related to depression: Persons with a score of 1 or more on the PHQ-9 symptoms are asked: "How difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?" Responses are 0 (not at all difficult), 1 (somewhat difficult), 2 (moderately difficult), or 3 (extremely difficult). In Figure 4, 1 was defined as "some difficulty," 2 and 3 were defined as "moderate or extreme difficulty."

Percent of federal poverty level: Based on the income-to-poverty ratio, a measure of the annual total family income divided by the poverty guidelines, adjusted for family size.

Data sources and methods

Data from the NHANES 2007–2016 were used for these analyses. Data from two combined cycles (2013–2016) were used to test differences between subgroups. Trends in depression prevalence reflect a 10-year period of five 2-year NHANES survey cycles, 2007–2016.

NHANES is a cross-sectional survey designed to monitor the health and nutritional status of the noninstitutionalized civilian U.S. population (9). The survey consists of home interviews and standardized physical examinations in mobile examination centers (MEC). The PHQ-9 was administered by trained interviewers during a private interview in the MEC. Approximately 89% of MEC-examined adults completed the PHQ-9.

The NHANES sample is selected through a complex, multistage probability design. During 2007–2016, non-Hispanic black, non-Hispanic Asian, and Hispanic persons, among other groups, were oversampled to obtain reliable estimates for these population subgroups. Race and Hispanic origin-specific estimates reflect individuals reporting only one race. Persons reporting another race or multiple races are included in the total but are not reported separately.

Examination sample weights, which account for the differential probabilities of selection, nonresponse, and noncoverage, were incorporated into the estimation process. The standard errors of the percentages were estimated using Taylor series linearization (10), a method that incorporates the sample weights and sample design.

A *t* statistic was used to test for difference between groups. Tests for trends by family income and survey cycle were evaluated using orthogonal polynomials to determine linear or quadratic trends. The significance level for statistical testing was set at $p < 0.05$. All differences reported are statistically significant unless otherwise indicated. All estimates presented are statistically reliable based on a relative standard error of the estimate being at or below 30%. Statistical analyses were conducted using SAS System for Windows (release 9.4; SAS Institute Inc., Cary, N.C.) and SUDAAN (release 11.1; RTI International, Research Triangle Park, N.C.).

About the authors

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EXHIBIT 107

Key Substance Use and Mental Health Indicators in the United States:

Results from the 2018 National Survey on Drug Use and Health

SAMHSA
Substance Abuse and Mental Health Services Administration

(Figure 44). Stated another way, about 1 in 27 adolescents had an SUD in the past year. The percentage of adolescents in 2018 with an SUD was lower than the percentages in 2015 and 2016, but it was similar to the percentage in 2017.

Aged 18 to 25

About 1 in 7 young adults aged 18 to 25 had an SUD in the past year, or about 15.0 percent of young adults (Figure 44). Approximately 5.1 million young adults aged 18 to 25 in 2018 had an SUD in the past year. The percentage of young adults in 2018 with an SUD was similar to the percentages in 2015 to 2017.

Aged 26 or Older

In 2018, approximately 14.2 million adults aged 26 or older had an SUD in the past year. This number corresponds to about 1 in 15 adults in this age group (6.6 percent) with an SUD in the past year (Figure 44). The percentage of adults aged 26 or older in 2018 with an SUD was similar to the percentages in 2015 to 2017.

Major Depressive Episode in the Past Year

Mental disorders are characterized by negative changes in mood, thought, or behavior and are accompanied by distress or impairment. These disorders can make carrying out daily activities difficult and can impair an individual's ability to work or function in school, interact with family, or fulfill other major life functions.

One such mental disorder is major depressive episode (MDE). Respondents were defined as having had an MDE in the past 12 months if they had at least one period of 2 weeks or longer in the past year when they experienced a depressed mood or loss of interest or pleasure in daily activities, accompanied by problems with sleeping, eating, energy, concentration, or self-worth. The MDE questions are based on diagnostic criteria from DSM-5.[45] Some of the wordings of the depression questions for adolescents aged 12 to 17 and adults aged 18 or older differed slightly to make the questions more developmentally appropriate for adolescents. Therefore, the adult and youth estimates for MDE are not directly comparable and are presented separately.[46,47]

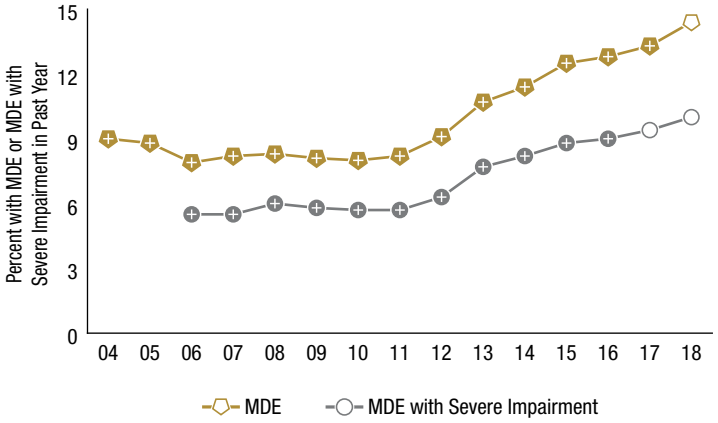
NSDUH also collects data on whether an MDE in the past year caused respondents to experience severe impairment in four major life activities or role domains. These domains are defined separately for adults aged 18 or older and youths aged 12 to 17 to reflect the different roles associated with the two age groups. Adults were defined as having an MDE with severe impairment if their depression caused severe problems with their ability to manage at home or work, have relationships with others, or have a social life.[48] Adolescents were defined as having an MDE with severe impairment if their depression caused severe problems with their ability to do chores at home, do well at work or school, get along with their family, or have a social life.[49]

MDE and MDE with Severe Impairment among Adolescents

In 2018, about 1 in 7 adolescents aged 12 to 17 had a past year MDE (14.4 percent) and 1 in 10 had a past year MDE with severe impairment (10.0 percent) (Figure 45). These percentages correspond to 3.5 million adolescents having had an MDE in the past year and 2.4 million adolescents having had a past year MDE with severe impairment. Thus, more than two thirds of adolescents in 2018 who had a past year MDE (70.0 percent) had an MDE with severe impairment.[23]

The percentage of adolescents aged 12 to 17 in 2018 who had a past year MDE was higher than the percentages in 2004 to 2017 (Figure 45). The percentage of adolescents in 2018 who

Figure 45. Major Depressive Episode (MDE) and MDE with Severe Impairment in the Past Year among Youths Aged 12 to 17: 2004-2018



+ Difference between this estimate and the 2018 estimate is statistically significant at the .05 level.

Figure 45 Table. Major Depressive Episode (MDE) and MDE with Severe Impairment in the Past Year among Youths Aged 12 to 17: 2004-2018

MDE Status	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18
MDE	9.0+	8.8+	7.9+	8.2+	8.3+	8.1+	8.0+	8.2+	9.1+	10.7+	11.4+	12.5+	12.8+	13.3+	14.4
MDE with Severe Impairment	N/A	N/A	5.5+	5.5+	6.0+	5.8+	5.7+	5.7+	6.3+	7.7+	8.2+	8.8+	9.0+	9.4	10.0

N/A = not available.

+ Difference between this estimate and the 2018 estimate is statistically significant at the .05 level.

had a past year MDE with severe impairment also was higher than the percentages in 2006 to 2016 (ranging from 5.5 to 9.0 percent), but it was similar to the percentage in 2017.

MDE and MDE with Severe Impairment among Adults

In 2018, an estimated 7.2 percent of adults aged 18 or older (17.7 million adults) had at least one MDE in the past year (Figure 46), and 4.7 percent of adults (11.5 million adults) had an MDE with severe impairment in the past year (Figure 47). Adults in 2018 who had an MDE with severe impairment correspond to nearly two thirds (65.1 percent) of adults who had a past year MDE.

The percentage of adults aged 18 or older in 2018 who had a past year MDE was higher than the percentages in most years from 2005 to 2016, but it was similar to the percentage in 2017 (Figure 46). The percentage of adults in 2018 with a past year MDE with severe impairment also was higher than the percentages in most years between 2009 and 2016, but it was similar to the percentage in 2017 (Figure 47).

Aged 18 to 25

In 2018, an estimated 4.6 million young adults aged 18 to 25 had a past year MDE, or 13.8 percent of young adults (Figure 46). The percentage of young adults with a past year MDE was greater in 2018 than in the years from 2005 to 2016, but it was similar to the percentage in 2017.

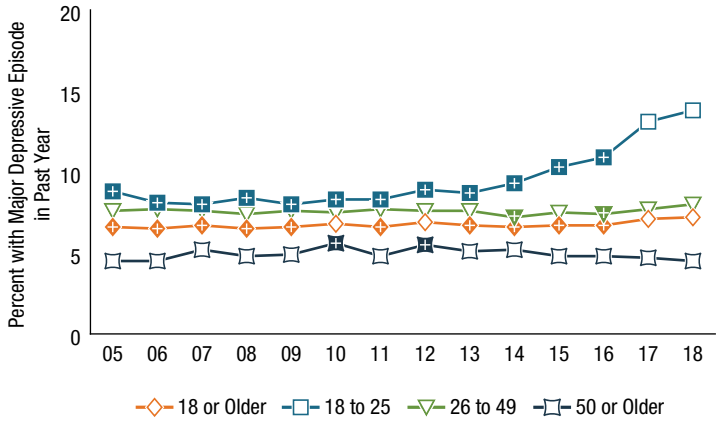
Approximately 3.0 million young adults aged 18 to 25 in 2018 had a past year MDE with severe impairment, or 8.9 percent of young adults (Figure 47). The percentage of young adults with a past year MDE with severe impairment was greater in 2018 than in 2009 to 2016, but it was similar to the percentage in 2017.

Aged 26 to 49

In 2018, about 8.0 million adults aged 26 to 49 had a past year MDE, or 8.0 percent of adults in this age group (Figure 46). The percentage of adults in this age group in 2018 who had a past year MDE was similar to the corresponding percentages in most years from 2005 to 2017.

An estimated 5.3 million adults aged 26 to 49 in 2018 had a past year MDE with severe impairment, or 5.3 percent of adults in this age group (Figure 47). Between 2009 and 2017, the percentages of adults aged 26 to 49 who had a past year MDE with severe impairment ranged from 4.6 to 5.2 percent; the 2018 percentage was either similar to or higher than the earlier percentages. Percentages of adults in this age group who had a past year MDE with severe impairment were similar between 2017 and 2018.

Figure 46. Major Depressive Episode in the Past Year among Adults Aged 18 or Older: 2005-2018



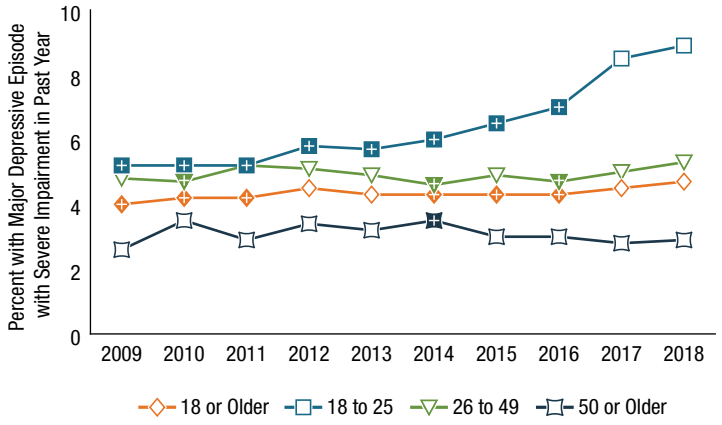
⁺ Difference between this estimate and the 2018 estimate is statistically significant at the .05 level.

Figure 46 Table. Major Depressive Episode in the Past Year among Adults Aged 18 or Older: 2005-2018

Age	05	06	07	08	09	10	11	12	13	14	15	16	17	18
18 or Older	6.6⁺	6.5⁺	6.7⁺	6.5⁺	6.6⁺	6.8	6.6⁺	6.9	6.7⁺	6.6⁺	6.7⁺	6.7⁺	7.1	7.2
18 to 25	8.8⁺	8.1⁺	8.0⁺	8.4⁺	8.0⁺	8.3⁺	8.3⁺	8.9⁺	8.7⁺	9.3⁺	10.3⁺	10.9⁺	13.1	13.8
26 to 49	7.6	7.7	7.6	7.4	7.6	7.5	7.7	7.6	7.6	7.2⁺	7.5	7.4⁺	7.7	8.0
50 or Older	4.5	4.5	5.2	4.8	4.9	5.6⁺	4.8	5.5⁺	5.1	5.2	4.8	4.8	4.7	4.5

⁺ Difference between this estimate and the 2018 estimate is statistically significant at the .05 level.

Figure 47. Major Depressive Episode with Severe Impairment in the Past Year among Adults Aged 18 or Older: 2009-2018



⁺ Difference between this estimate and the 2018 estimate is statistically significant at the .05 level.

Figure 47 Table. Major Depressive Episode with Severe Impairment in the Past Year among Adults Aged 18 or Older: 2009-2018

Age	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
18 or Older	4.0⁺	4.2⁺	4.2⁺	4.5	4.3	4.3⁺	4.3⁺	4.3⁺	4.5	4.7
18 to 25	5.2⁺	5.2⁺	5.2⁺	5.8⁺	5.7⁺	6.0⁺	6.5⁺	7.0⁺	8.5	8.9
26 to 49	4.8	4.7⁺	5.2	5.1	4.9	4.6⁺	4.9	4.7⁺	5.0	5.3
50 or Older	2.6	3.5	2.9	3.4	3.2	3.5⁺	3.0	3.0	2.8	2.9

⁺ Difference between this estimate and the 2018 estimate is statistically significant at the .05 level.

EXHIBIT 108

COVID-19 is an emerging, rapidly evolving situation.

Get the latest public health information from CDC: https://www.coronavirus.gov
Get the latest research information from NIH: https://www.nih.gov/coronavirus

The National Institute of Mental Health: www.nimh.nih.gov

Anxiety Disorders

Overview

Occasional anxiety is an expected part of life. You might feel anxious when faced with a problem at work, before taking a test, or before making an important decision. But anxiety disorders involve more than temporary worry or fear. For a person with an anxiety disorder, the anxiety does not go away and can get worse over time. The symptoms can interfere with daily activities such as job performance, school work, and relationships.

There are several types of anxiety disorders, including generalized anxiety disorder, panic disorder, and various phobia-related disorders.

Signs and Symptoms

Generalized Anxiety Disorder

People with generalized anxiety disorder (GAD) display excessive anxiety or worry, most days for at least 6 months, about a number of things such as personal health, work, social interactions, and everyday routine life circumstances. The fear and anxiety can cause significant problems in areas of their life, such as social interactions, school, and work.

Generalized anxiety disorder symptoms include:

- Feeling restless, wound-up, or on-edge
- Being easily fatigued
- Having difficulty concentrating; mind going blank
- Being irritable
- Having muscle tension
- Difficulty controlling feelings of worry
- Having sleep problems, such as difficulty falling or staying asleep, restlessness, or unsatisfying sleep

Panic Disorder

People with panic disorder have recurrent unexpected panic attacks. Panic attacks are sudden periods of intense fear that come on quickly and reach their peak within minutes. Attacks can occur unexpectedly or can be brought on by a trigger, such as a feared object or situation.

During a panic attack, people may experience:

- Heart palpitations, a pounding heartbeat, or an accelerated heartrate
- Sweating
- Trembling or shaking
- Sensations of shortness of breath, smothering, or choking
- Feelings of impending doom
- Feelings of being out of control

People with panic disorder often worry about when the next attack will happen and actively try to prevent future attacks by avoiding places, situations, or behaviors they associate with panic attacks. Worry about panic attacks, and the effort spent trying to avoid attacks, cause significant problems in various areas of the person's life, including the development of agoraphobia (see below).

Phobia-related disorders

A *phobia* is an intense fear of—or aversion to—specific objects or situations. Although it can be realistic to be anxious in some circumstances, the fear people with phobias feel is out of proportion to the actual danger caused by the situation or object.

People with a phobia:

- May have an irrational or excessive worry about encountering the feared object or situation
- Take active steps to avoid the feared object or situation
- Experience immediate intense anxiety upon encountering the feared object or situation
- Endure unavoidable objects and situations with intense anxiety

There are several types of phobias and phobia-related disorders:

Specific Phobias (sometimes called simple phobias): As the name suggests, people who have a specific phobia have an intense fear of, or feel intense anxiety about, specific types of objects or situations. Some examples of specific phobias include the fear of:

- Flying
- Heights
- Specific animals, such as spiders, dogs, or snakes
- Receiving injections
- Blood

Social anxiety disorder (previously called social phobia): People with social anxiety disorder have a general intense fear of, or anxiety toward, social or performance situations. They worry that actions or behaviors associated with their anxiety will be negatively evaluated by others, leading them to feel embarrassed. This worry often causes people with social anxiety to avoid social situations. Social anxiety disorder can manifest in a range of situations, such as within the workplace or the school environment.

Agoraphobia: People with agoraphobia have an intense fear of two or more of the following situations:

- Using public transportation

Being in open spaces
Being in enclosed spaces
Standing in line or being in a crowd
Being outside of the home alone

People with agoraphobia often avoid these situations, in part, because they think being able to leave might be difficult or impossible in the event they have panic-like reactions or other embarrassing symptoms. In the most severe form of agoraphobia, an individual can become housebound.

Separation anxiety disorder: Separation anxiety is often thought of as something that only children deal with; however, adults can also be diagnosed with separation anxiety disorder. People who have separation anxiety disorder have fears about being parted from people to whom they are attached. They often worry that some sort of harm or something untoward will happen to their attachment figures while they are separated. This fear leads them to avoid being separated from their attachment figures and to avoid being alone. People with separation anxiety may have nightmares about being separated from attachment figures or experience physical symptoms when separation occurs or is anticipated.

Selective mutism: A somewhat rare disorder associated with anxiety is *selective mutism*. Selective mutism occurs when people fail to speak in specific social situations despite having normal language skills. Selective mutism usually occurs before the age of 5 and is often associated with extreme shyness, fear of social embarrassment, compulsive traits, withdrawal, clinging behavior, and temper tantrums. People diagnosed with selective mutism are often also diagnosed with other anxiety disorders.

Risk Factors

Researchers are finding that both genetic and environmental factors contribute to the risk of developing an anxiety disorder. Although the risk factors for each type of anxiety disorder can vary, some general risk factors for all types of anxiety disorders include:

Temperamental traits of shyness or behavioral inhibition in childhood
Exposure to stressful and negative life or environmental events in early childhood or adulthood
A history of anxiety or other mental illnesses in biological relatives
Some physical health conditions, such as thyroid problems or heart arrhythmias, or caffeine or other substances/medications, can produce or aggravate anxiety symptoms; a physical health examination is helpful in the evaluation of a possible anxiety disorder.

Treatments and Therapies

Anxiety disorders are generally treated with psychotherapy, medication, or both. There are many ways to treat anxiety and people should work with their doctor to choose the treatment that is best for them.

Psychotherapy

Psychotherapy or “talk therapy” can help people with anxiety disorders. To be effective, psychotherapy must be directed at the person’s specific anxieties and tailored to his or her needs.

Cognitive Behavioral Therapy

Cognitive Behavioral Therapy (CBT) is an example of one type of psychotherapy that can help people with anxiety disorders. It teaches people different ways of thinking, behaving, and reacting to anxiety-producing and fearful objects and situations. CBT can also help people learn and practice social skills, which is vital for treating social anxiety disorder.

Cognitive therapy and exposure therapy are two CBT methods that are often used, together or by themselves, to treat social anxiety disorder. Cognitive therapy focuses on identifying, challenging, and then neutralizing unhelpful or distorted thoughts underlying anxiety disorders. Exposure therapy focuses on confronting the fears underlying an anxiety disorder to help people engage in activities they have been avoiding. Exposure therapy is sometimes used along with relaxation exercises and/or imagery.

CBT can be conducted individually or with a group of people who have similar difficulties. Often "homework" is assigned for participants to complete between sessions.

Medication

Medication does not cure anxiety disorders but can help relieve symptoms. Medication for anxiety is prescribed by doctors, such as a psychiatrist or primary care provider. Some states also allow psychologists who have received specialized training to prescribe psychiatric medications. The most common classes of medications used to combat anxiety disorders are anti-anxiety drugs (such as benzodiazepines), antidepressants, and beta-blockers.

Anti-Anxiety Medications

Anti-anxiety medications can help reduce the symptoms of anxiety, panic attacks, or extreme fear and worry. The most common anti-anxiety medications are called benzodiazepines. Although benzodiazepines are sometimes used as first-line treatments for generalized anxiety disorder, they have both benefits and drawbacks.

Some benefits of benzodiazepines are that they are effective in relieving anxiety and take effect more quickly than antidepressant medications often prescribed for anxiety. Some drawbacks of benzodiazepines are that people can build up a tolerance to them if they are taken over a long period of time and they may need higher and higher doses to get the same effect. Some people may even become dependent on them.

To avoid these problems, doctors usually prescribe benzodiazepines for short periods of time, a practice that is especially helpful for older adults, people who have substance abuse problems, and people who become dependent on medication easily.

If people suddenly stop taking benzodiazepines, they may have withdrawal symptoms, or their anxiety may return. Therefore, benzodiazepines should be tapered off slowly. When you and your doctor have decided it is time to stop the medication, the doctor will help you slowly and safely decrease your dose.

For long-term use, benzodiazepines are often considered a second-line treatment for anxiety (with antidepressants being considered a first-line treatment) as well as an "as-needed" treatment for any distressing flare-ups of symptoms.

A different type of anti-anxiety medication is *buspirone*. Buspirone is a non-benzodiazepine medication

specifically indicated for the treatment of chronic anxiety, although it does not help everyone.

Antidepressants

Antidepressants are used to treat depression, but they can also be helpful for treating anxiety disorders. They may help improve the way your brain uses certain chemicals that control mood or stress. You may need to try several different antidepressant medicines before finding the one that improves your symptoms and has manageable side effects. A medication that has helped you or a close family member in the past will often be considered.

Antidepressants can take time to work, so it's important to give the medication a chance before reaching a conclusion about its effectiveness. If you begin taking antidepressants, do not stop taking them without the help of a doctor. When you and your doctor have decided it is time to stop the medication, the doctor will help you slowly and safely decrease your dose. Stopping them abruptly can cause withdrawal symptoms.

Antidepressants called selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are commonly used as first-line treatments for anxiety. Less-commonly used — but effective — treatments for anxiety disorders are older classes of antidepressants, such as tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs).

Please Note: In some cases, children, teenagers, and young adults under 25 may experience an increase in suicidal thoughts or behavior when taking antidepressant medications, especially in the first few weeks after starting or when the dose is changed. Because of this, patients of all ages taking antidepressants should be watched closely, especially during the first few weeks of treatment.

Beta-Blockers

Although beta-blockers are most often used to treat high blood pressure, they can also be used to help relieve the physical symptoms of anxiety, such as rapid heartbeat, shaking, trembling, and blushing. These medications, when taken for a short period of time, can help people keep physical symptoms under control. They can also be used "as needed" to reduce acute anxiety, including as a preventive intervention for some predictable forms of performance anxieties.

Choosing the Right Medication

Some types of drugs may work better for specific types of anxiety disorders, so people should work closely with their doctor to identify which medication is best for them. Certain substances such as caffeine, some over-the-counter cold medicines, illicit drugs, and herbal supplements may aggravate the symptoms of anxiety disorders or interact with prescribed medication. Patients should talk with their doctor, so they can learn which substances are safe and which to avoid.

Choosing the right medication, medication dose, and treatment plan should be done under an expert's care and should be based on a person's needs and their medical situation. Your doctor may try several medicines before finding the right one.

You and your doctor should discuss:

- How well medications are working or might work to improve your symptoms

Benefits and side effects of each medication
Risk for serious side effects based on your medical history
The likelihood of the medications requiring lifestyle changes
Costs of each medication
Other alternative therapies, medications, vitamins, and supplements you are taking and how these may affect your treatment; a combination of medication and psychotherapy is the best approach for many people with anxiety disorders
How the medication should be stopped (Some drugs can't be stopped abruptly and must be tapered off slowly under a doctor's supervision).

For more information, please visit Mental Health Medications Health Topic webpage (www.nimh.nih.gov//health/topics/mental-health-medications/index.shtml). Please note that any information on this website regarding medications is provided for educational purposes only and may be outdated. Diagnosis and treatment decisions should be made in consultation with your doctor. Information about medications changes frequently. Please visit the U.S. Food and Drug Administration website for the latest information on warnings, patient medication guides, or newly approved medications.

Support Groups

Some people with anxiety disorders might benefit from joining a self-help or support group and sharing their problems and achievements with others. Internet chat rooms might also be useful, but any advice received over the internet should be used with caution, as Internet acquaintances have usually never seen each other and what has helped one person is not necessarily what is best for another. You should always check with your doctor before following any treatment advice found on the internet. Talking with a trusted friend or member of the clergy can also provide support, but it is not necessarily a sufficient alternative to care from a doctor or other health professional.

Stress Management Techniques

Stress management techniques and meditation can help people with anxiety disorders calm themselves and may enhance the effects of therapy. Research suggests that aerobic exercise can help some people manage their anxiety; however, exercise should not take the place of standard care and more research is needed.

Join a Study

Clinical trials are research studies that look at new ways to prevent, detect, or treat diseases and conditions, including anxiety disorders. During clinical trials, treatments might be new drugs or new combinations of drugs, new surgical procedures or devices, new psychotherapies, or new ways to use existing treatments. The goal of clinical trials is to determine if a new test or treatment works and is safe.

Although individual participants may benefit from being part of a clinical trial, participants should be aware that the primary purpose of a clinical trial is to gain new scientific knowledge so that others may be better helped in the future. **Decisions about whether to apply for a clinical trial and which ones are best suited for a given individual are best made in collaboration with a licensed health professional**.

To learn more about clinical trials, please visit the NIH Clinical Research Trials and You website. To find a

clinical trial, visit ClinicalTrials.gov.

Learn More

Free Brochures and Shareable Resources

Generalized Anxiety Disorder (GAD): When Worry Gets Out of Control (www.nimh.nih.gov//health/publications/generalized-anxiety-disorder-gad/index.shtml): A brochure on GAD that explains the signs, symptoms, and treatment
Obsessive-Compulsive Disorder: When Unwanted Thoughts Take Over (www.nimh.nih.gov//health/publications/obsessive-compulsive-disorder-when-unwanted-thoughts-take-over/index.shtml): A brochure on OCD that explains the signs, symptoms, and treatments
Panic Disorder: When Fear Overwhelms (www.nimh.nih.gov//health/publications/panic-disorder-when-fear-overwhelms/index.shtml): A brochure on panic disorder that explains the signs, symptoms, and treatments
Social Anxiety Disorder: More Than Just Shyness (www.nimh.nih.gov//health/publications/social-anxiety-disorder-more-than-just-shyness/index.shtml): This brochure discusses symptoms, causes, and treatments for social anxiety disorder (also called social phobia).
Shareable Resources on Anxiety Disorders (www.nimh.nih.gov//health/education-awareness/shareable-resources-on-anxiety-disorders.shtml): Help support anxiety awareness and education in your community. Use these digital resources, including graphics and messages, to spread the word about anxiety disorders.

Multimedia

Watch: Bullying Exerts Psychological Effects into Adulthood (www.nimh.nih.gov//news/media/2013/bullying-exerts-psychiatric-effects-into-adulthood.shtml): Once considered a childhood rite of passage, bullying is no longer seen as benign. Its effects linger well into adulthood. Bullies and victims alike are at risk for psychiatric problems such as anxiety, depression, substance misuse, and suicide when they become adults, according to a study partially funded by the NIMH that was published in the April 2013 issue of *JAMA Psychiatry*.
See: **Multimedia about Anxiety Disorders (www.nimh.nih.gov//news/media/index-anxiety-disorders.shtml)**

Federal Resources

Anxiety Disorders (MedlinePlus – also en Español)
Specific Phobias (U.S. Department of Veterans Affairs)

Research and Statistics

Join a Study: Adults - Anxiety Disorders (www.nimh.nih.gov//research/research-conducted-at-nimh/join-a-study/adults/adults-anxiety-disorders.shtml)
Join a Study: Children - Anxiety Disorders (www.nimh.nih.gov//research/research-conducted-at-nimh/join-a-study/children/children-anxiety-disorders.shtml)
Journal Articles: References and abstracts from MEDLINE/PubMed (National Library of Medicine).
Statistics: Anxiety Disorder (www.nimh.nih.gov//health/statistics/any-anxiety-disorder.shtml): This webpage provides information on the statistics currently available on the prevalence and treatment of anxiety

among people in the U.S.

Last Revised: July 2018

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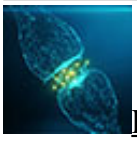
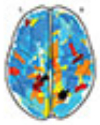
Science News About Anxiety Disorders


Infant Temperament Predicts Personality Over 20 Years Later (www.nimh.nih.gov//news/science-news/2020/infant-temperament-predicts-personality-more-than-20-years-later.shtml)


Fast-Fail Trial Finds Possible Target for Treating Anhedonia (www.nimh.nih.gov//news/science-news/2020/fast-fail-trial-shows-new-approach-to-identifying-brain-targets-for-clinical-treatments.shtml)


Differences in Brain Activity in Children with Anhedonia (www.nimh.nih.gov//news/science-news/2019/nih-study-reveals-differences-in-brain-activity-in-children-with-anhedonia.shtml)

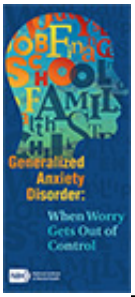
More (www.nimh.nih.gov//news/science-news/science-news-about-anxiety-disorders.shtml)

Join A Study

Anxiety Studies for Adults (www.nimh.nih.gov//research/research-conducted-at-nimh/join-a-study/adults/adults-anxiety-disorders.shtml)

Anxiety Studies for Children (www.nimh.nih.gov//research/research-conducted-at-nimh/join-a-study/children/children-anxiety-disorders.shtml)

Featured Publications About Anxiety Disorders



(www.nimh.nih.gov//health/publications/generalized-anxiety-disorder-gad/index.shtml)

Generalized Anxiety Disorder: When Worry Gets Out of Control

(www.nimh.nih.gov//health/publications/generalized-anxiety-disorder-gad/index.shtml)

This brochure discusses signs and symptoms, diagnosis, and treatment options for generalized anxiety disorder (GAD).

(www.nimh.nih.gov//health/publications/panic-disorder-when-fear-overwhelms/index.shtml)

Panic Disorder: When Fear Overwhelms (www.nimh.nih.gov//health/publications/panic-disorder-when-fear-overwhelms/index.shtml)

This brochure discusses symptoms, causes, and treatments for panic disorder, a type of anxiety disorder associated with sudden and repeated attacks of fear.

More Publications About Anxiety Disorders (www.nimh.nih.gov//health/publications/anxiety-disorders-listing.shtml)

Research Results

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EXHIBIT 109

Facts & Statistics

Did You Know?

- Anxiety disorders are the most common mental illness in the U.S., affecting 40 million adults in the United States age 18 and older, or 18.1% of the population every year.
- Anxiety disorders are highly treatable, yet only 36.9% of those suffering receive treatment.
- People with an anxiety disorder are three to five times more likely to go to the doctor and six times more likely to be hospitalized for psychiatric disorders than those who do not suffer from anxiety disorders.
- Anxiety disorders develop from a complex set of risk factors, including genetics, brain chemistry, personality, and life events.

Anxiety and Depression (http://www.adaa.org/understanding-anxiety/depression)

It's not uncommon for someone with an anxiety disorder to also suffer from depression or vice versa. Nearly one-half of those diagnosed with depression are also diagnosed with an anxiety disorder.

Find out more about depression. (http://www.adaa.org/understanding-anxiety/depression)

Facts

Generalized Anxiety Disorder (GAD) (/understanding-anxiety/generalized-anxiety-disorder-gad)
GAD affects 6.8 million adults, or 3.1% of the U.S. population, yet only 43.2% are receiving treatment.
Women are twice as likely to be affected as men. GAD often co-occurs with major depression.

Panic Disorder (/understanding-anxiety/panic-disorder-agoraphobia) (PD)
PD affects 6 million adults, or 2.7% of the U.S. population.
Women are twice as likely to be affected as men.

Social Anxiety Disorder (/understanding-anxiety/social-anxiety-disorder)
SAD affects 15 million adults, or 6.8% of the U.S. population.
SAD is equally common among men and women andtypically begins around age 13.
According to a 2007 ADAA survey, 36% of people with social anxiety disorder report experiencing symptoms for 10 or more years before seeking help.

Specific Phobias (/understanding-anxiety/specific-phobias)
Specific phobias affect 19 million adults, or 8.7% of the U.S. population.
Women are twice as likely to be affected as men.
Symptoms typically begin in childhood; the average age-of-onset is 7 years old.
Obsessive-compulsive disorder (OCD) and posttraumatic stress disorder (PTSD) are closely related to anxiety disorders, which some may experience at the same time, along with depression.

Obsessive-Compulsive Disorder (OCD) (http://www.adaa.org/understanding-anxiety/obsessive-compulsive-disorder-ocd)
OCD affects 2.2 million adults, or 1.0% of the U.S. population.
OCD is equally common among men and women.
The average age of onset is 19, with 25 percent of cases occurring by age 14. One-third of affected adults first experienced symptoms in childhood.

Posttraumatic Stress Disorder (PTSD) (http://www.adaa.org/understanding-anxiety/posttraumatic-stress-disorder-ptsd)
PTSD affects 7.7 million adults, or 3.5% of the U.S. population.
Women are more likely to be affected than men.
Rape is the most likely trigger of PTSD: 65% of men and 45.9% of women who are raped will develop the disorder.
Childhood sexual abuse is a strong predictor of lifetime likelihood for developing PTSD.

Major Depressive Disorder (http://www.adaa.org/understanding-anxiety/depression)
The leading cause of disability in the U.S. for ages 15 to 44.3.
MDD affects more than 16.1 million American adults, or about 6.7%of the U.S. population age 18 and older in a given year.
While major depressive disorder can develop at any age, the median age at onset is 32.5 years old.
More prevalent in women than in men.

Persistent depressive disorder, or PDD, (https://www.adaa.org/understanding-anxiety/depression) (formerly called dysthymia) is a form of depression that usually continues for at least two years.
Affects approximately 1.5 percent of the U.S. population age 18 and older in a given year. (about 3.3 million American adults). Only 61.7% of adults with MDD are receiving treatment. The average age of onset is 31 years old.

(Source: National Institute of Mental Health)

Related Illnesses (http://www.adaa.org/understanding-anxiety/related-illnesses)
Many people with an anxiety disorder also have a co-occurring disorder or physical illness, which can make their symptoms worse and recovery more difficult. It's essential to be treated for both disorders.

Obsessive-compulsive disorder (OCD) and posttraumatic stress disorder (PTSD) are closely related to anxiety disorders, which some may experience at the same time, along with depression.

Read on to learn more about the co-occurrence of anxiety and these disorders:

- Bipolar disorder (../../understanding-anxiety/related-illnesses/bipolar-disorder)
- Eating disorders (../../understanding-anxiety/related-illnesses/eating-disorders)
- Headaches (../../understanding-anxiety/related-illnesses/headaches)
- Irritable bowel syndrome (IBS) (../../understanding-anxiety/related-illnesses/irritable-bowel-syndrome-ibs)
- Sleep disorders (../../understanding-anxiety/related-illnesses/sleep-disorders)
- Substance abuse (../../understanding-anxiety/related-illnesses/substance-abuse)
- Adult ADHD (attention deficit/hyperactive disorder) (../../understanding-anxiety/related-illnesses/other-related-conditions/adult-adhd)
- BDD (body dysmorphic disorder) (../../understanding-anxiety/related-illnesses/other-related-conditions/body-dysmorphic-disorder-bdd)
- Chronic pain (../../understanding-anxiety/related-illnesses/other-related-conditions/chronic-pain)
- Fibromyalgia (../../understanding-anxiety/related-illnesses/other-related-conditions/fibromyalgia)
- Stress (../../understanding-anxiety/related-illnesses/other-related-conditions/stress)

Children (http://www.adaa.org/living-with-anxiety/children)
Anxiety disorders affect 25.1% of children between 13 and 18 years old. Research shows that untreated children with anxiety disorders are at higher risk to perform poorly in school, miss out on important social experiences, and engage in substance abuse.

- See statistics for anxiety disorders among children (http://www.nimh.nih.gov/statistics/1ANYANX_child.shtml) from the National Institute of Mental Health.

Anxiety disorders also often co-occur with other disorders such as depression, eating disorders, and attention-deficit/hyperactivity disorder (ADHD).

- Childhood anxiety disorders (../../living-with-anxiety/children/childhood-anxiety-disorders)
- Anxiety and depression (../../living-with-anxiety/children/anxiety-and-depression)
- Treatment (../../living-with-anxiety/children/treatment)
- Tips for parents and caregivers (../../living-with-anxiety/children/tips-parents-and-caregivers)
- Anxiety disorders at school (../../living-with-anxiety/children/anxiety-disorders-school)
- School refusal (../../living-with-anxiety/children/school-refusal)

Older Adults (http://www.adaa.org/living-with-anxiety/older-adults)
Anxiety is as common among older adults as among the young. Generalized anxiety disorder (GAD) (../../understanding-anxiety/generalized-anxiety-disorder-gad) is the most common anxiety disorder among older adults, though anxiety disorders in this population are frequently associated with traumatic events such as a fall or acute illness. Read the best way to treat anxiety disorders (../../living-with-anxiety/older-adults/treatment) in older adults.

Worldwide Statistics

Depression is the leading cause of disability worldwide. Almost 75% of people with mental disorders remain untreated in developing countries with almost 1 million people taking their lives each year. In addition, according to the World Health Organization (WHO), 1 in 13 globally suffers from anxiety. The WHO reports that anxiety disorders are the most common mental disorders worldwide with specific phobia, major depressive disorder and social phobia being the most common anxiety disorders.[2]

Treatment Options (http://www.adaa.org/finding-help/treatment)

Anxiety disorders are treatable, and the vast majority of people with an anxiety disorder can be helped with professional care. Several standard approaches have proved effective:

- Therapy (../../finding-help/treatment/therapy)
- Medication (../../finding-help/treatment/medication)
- Complementary and alternative treatment (../../finding-help/treatment/complementary-alternative-treatment)
- Transcranial Magnetic Stimulation (https://www.adaa.org/finding-help/transcranial-magnetic-stimulation)

Learn about online therapy (https://www.betterhelp.com/) at BetterHelp.com.

Source:

- National Institute of Mental Health (https://www.nimh.nih.gov/health/statistics/prevalence/index.shtml)
- World Health Organization: Mental Health (http://www.who.int/mental_health/advocacy/en/#Factsheets)

(https://adaa.org/resources-professionals/press-room)
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(https://www.youtube.com/user/GotAnxiety)

Founded in 1979, ADAA is an international nonprofit organization dedicated to the prevention, treatment, and cure of anxiety, depression, OCD, PTSD, and co-occurring disorders through education, practice, and research.

(https://www.guidestar.org/profile/52-1248820)

(https://www.opm.gov/combined-federal-campaign/)

(https://www.nimh.nih.gov/outreach/partnership-program/national-partners.shtml?utm_source=multiple&utm_medium=widget&utm_campaign=button_nationalPartners_h)

(https://www.mhlg.org)

(http://www.hmr.org/)

EXHIBIT 110

COVID-19 is an emerging, rapidly evolving situation.

Get the latest public health information from CDC: https://www.coronavirus.gov
Get the latest research information from NIH: https://www.nih.gov/coronavirus

The National Institute of Mental Health: www.nimh.nih.gov

Obsessive-Compulsive Disorder

Overview

Obsessive-Compulsive Disorder (OCD) is a common, chronic, and long-lasting disorder in which a person has uncontrollable, reoccurring thoughts (*obsessions*) and/or behaviors (*compulsions*) that he or she feels the urge to repeat over and over.

Signs and Symptoms

People with OCD may have symptoms of obsessions, compulsions, or both. These symptoms can interfere with all aspects of life, such as work, school, and personal relationships.

Obsessions are repeated thoughts, urges, or mental images that cause anxiety. Common symptoms include:

- Fear of germs or contamination
- Unwanted forbidden or taboo thoughts involving sex, religion, or harm
- Aggressive thoughts towards others or self
- Having things symmetrical or in a perfect order

Compulsions are repetitive behaviors that a person with OCD feels the urge to do in response to an obsessive thought. Common compulsions include:

- Excessive cleaning and/or handwashing
- Ordering and arranging things in a particular, precise way
- Repeatedly checking on things, such as repeatedly checking to see if the door is locked or that the oven is off
- Compulsive counting

Not all rituals or habits are compulsions. Everyone double checks things sometimes. But a person with OCD generally:

- Can't control his or her thoughts or behaviors, even when those thoughts or behaviors are recognized as excessive
- Spends at least 1 hour a day on these thoughts or behaviors
- Doesn’t get pleasure when performing the behaviors or rituals, but may feel brief relief from the anxiety the thoughts cause

Experiences significant problems in their daily life due to these thoughts or behaviors

Some individuals with OCD also have a tic disorder. Motor tics are sudden, brief, repetitive movements, such as eye blinking and other eye movements, facial grimacing, shoulder shrugging, and head or shoulder jerking. Common vocal tics include repetitive throat-clearing, sniffing, or grunting sounds.

Symptoms may come and go, ease over time, or worsen. People with OCD may try to help themselves by avoiding situations that trigger their obsessions, or they may use alcohol or drugs to calm themselves. Although most adults with OCD recognize that what they are doing doesn't make sense, some adults and most children may not realize that their behavior is out of the ordinary. Parents or teachers typically recognize OCD symptoms in children.

If you think you have OCD, talk to your doctor about your symptoms. If left untreated, OCD can interfere in all aspects of life.

Risk Factors

OCD is a common disorder that affects adults, adolescents, and children all over the world. Most people are diagnosed by about age 19, typically with an earlier age of onset in boys than in girls, but onset after age 35 does happen. For statistics on OCD in adults, please see the NIMH Obsessive-Compulsive Disorder (www.nimh.nih.gov//health/statistics/obsessive-compulsive-disorder-ocd.shtml) webpage.

The causes of OCD are unknown, but risk factors include:

Genetics

Twin and family studies have shown that people with first-degree relatives (such as a parent, sibling, or child) who have OCD are at a higher risk for developing OCD themselves. The risk is higher if the first-degree relative developed OCD as a child or teen. Ongoing research continues to explore the connection between genetics and OCD and may help improve OCD diagnosis and treatment.

Brain Structure and Functioning

Imaging studies have shown differences in the frontal cortex and subcortical structures of the brain in patients with OCD. There appears to be a connection between the OCD symptoms and abnormalities in certain areas of the brain, but that connection is not clear. Research is still underway. Understanding the causes will help determine specific, personalized treatments to treat OCD.

Environment

An association between childhood trauma and obsessive-compulsive symptoms has been reported in some studies. More research is needed to understand this relationship better.

In some cases, children may develop OCD or OCD symptoms following a streptococcal infection—this is called Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS). For more information, please read NIMH's fact sheet on PANDAS

(www.nimh.nih.gov//health/publications/pandas/index.shtml).

Treatments and Therapies

OCD is typically treated with medication, psychotherapy, or a combination of the two. Although most patients with OCD respond to treatment, some patients continue to experience symptoms.

Sometimes people with OCD also have other mental disorders, such as anxiety, depression, and body dysmorphic disorder, a disorder in which someone mistakenly believes that a part of their body is abnormal. It is important to consider these other disorders when making decisions about treatment.

Medication

Serotonin reuptake inhibitors (SRIs), which include selective serotonin reuptake inhibitors (SSRIs) are used to help reduce OCD symptoms.

SRIs often require higher daily doses in the treatment of OCD than of depression and may take 8 to 12 weeks to start working, but some patients experience more rapid improvement.

If symptoms do not improve with these types of medications, research shows that some patients may respond well to an antipsychotic medication. Although research shows that an antipsychotic medication may help manage symptoms for people who have both OCD and a tic disorder, research on the effectiveness of antipsychotics to treat OCD is mixed.

If you are prescribed a medication, be sure you:

- Talk with your doctor or a pharmacist to make sure you understand the risks and benefits of the medications you're taking.
- Do not stop taking a medication without talking to your doctor first. Suddenly stopping a medication may lead to "rebound" or worsening of OCD symptoms. Other uncomfortable or potentially dangerous withdrawal effects are also possible.
- Report any concerns about side effects to your doctor right away. You may need a change in the dose or a different medication.
- Report serious side effects to the U.S. Food and Drug Administration (FDA) MedWatch Adverse Event Reporting program online or by phone at 1-800-332-1088. You or your doctor may send a report.

Other medications have been used to treat OCD, but more research is needed to show the benefit of these options. For basic information about these medications, you can visit the NIMH Mental Health Medications (www.nimh.nih.gov//health/topics/mental-health-medications/index.shtml) webpage. For the most up-to-date information on medications, side effects, and warnings, visit the FDA website.

Psychotherapy

Psychotherapy can be an effective treatment for adults and children with OCD. Research shows that certain types of psychotherapy, including cognitive behavior therapy (CBT) and other related therapies (e.g., habit reversal training) can be as effective as medication for many individuals. Research also shows that a type of

CBT called Exposure and Response Prevention (EX/RP) – spending time in the very situation that triggers compulsions (e.g. touching dirty objects) but then being prevented from undertaking the usual resulting compulsion (e.g. handwashing) – is effective in reducing compulsive behaviors in OCD, even in people who did not respond well to SRI medication.

As with most mental disorders, treatment is usually personalized and might begin with either medication or psychotherapy, or with a combination of both. For many patients, EX/RP is the add-on treatment of choice when SRIs or SSRIs medication does not effectively treat OCD symptoms or vice versa for individuals who begin treatment with psychotherapy.

Other Treatment Options

In 2018, the FDA approved Transcranial Magnetic Stimulation (TMS) as an adjunct in the treatment of OCD in adults.

NIMH is supporting research into other new treatment approaches for people whose OCD does not respond well to the usual therapies. These new approaches include combination and add-on (augmentation) treatments, as well as novel techniques such as deep brain stimulation. You can learn more about brain stimulation therapies (www.nimh.nih.gov//health/topics/brain-stimulation-therapies/brain-stimulation-therapies.shtml) on the NIMH website.

Finding Treatment

For general information on mental health and to locate treatment services in your area, call the Substance Abuse and Mental Health Services Administration (SAMHSA) Treatment Referral Helpline at 1-800-662-HELP (4357). SAMHSA also has a Behavioral Health Treatment Locator on its website that can be searched by location. You can also visit the NIMH's Help for Mental Illnesses (www.nimh.nih.gov//health/find-help/index.shtml) page for more information and resources.

Join a Study

Clinical trials are research studies that look at new ways to prevent, detect, or treat diseases and conditions. The goal of clinical trials is to determine if a new test or treatment works and is safe. Although individual participants may benefit from being part of a clinical trial, participants should be aware that the primary purpose of a clinical trial is to gain new scientific knowledge so that others may be better helped in the future.

Researchers at NIMH and around the country conduct many studies with patients and healthy volunteers. We have new and better treatment options today because of what clinical trials uncovered years ago. Be part of tomorrow's medical breakthroughs. Talk to your doctor about clinical trials, their benefits and risks, and whether one is right for you.

To learn more about participating in clinical trials, visit the NIMH Clinical Trials page (www.nimh.nih.gov//health/trials/index.shtml).

Learn More

Free Booklets and Brochures

Obsessive-Compulsive Disorder: When Unwanted Thoughts Take Over (www.nimh.nih.gov//health/publications/obsessive-compulsive-disorder-when-unwanted-thoughts-take-over/index.shtml)**:** A brochure that offers basic information about OCD, including signs and symptoms, treatment, and finding help. Also available en Español (www.nimh.nih.gov//health/publications/espanol/trastorno-obsesivo-compulsivo/index.shtml).

Federal Resources

Obsessive-Compulsive Disorder (MedlinePlus – also en Español)

Research and Statistics

Journal Articles: This webpage provides information on references and abstracts from MEDLINE/PubMed (National Library of Medicine).
OCD Clinical Trials: This webpage includes clinical trials on OCD funded by the National Institutes of Health and being conducted across the country.
OCD Statistics: Adults (www.nimh.nih.gov//health/statistics/obsessive-compulsive-disorder-ocd.shtml): This webpage lists information on the prevalence of OCD among adults.

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Science News About Obsessive-Compulsive Disorder (OCD)


PANS/PANDAS Treatment Guidelines (www.nimh.nih.gov//news/science-news/2017/guidelines-published-for-treating-pans-pandas.shtml)

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Obsessive-Compulsive Disorder Studies

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Obsessive-Compulsive Disorder: When Unwanted Thoughts or Irresistible Actions Take Over (www.nimh.nih.gov//health/publications/obsessive-compulsive-disorder-when-unwanted-thoughts-take-over/index.shtml)

This brochure discusses signs and symptoms, diagnosis, and treatment options for obsessive-compulsive disorder (OCD), a chronic disorder in which a person has uncontrollable, reoccurring thoughts and behaviors.

More Publications About Obsessive-Compulsive Disorder (OCD) (www.nimh.nih.gov//health/publications/ocd-listing.shtml)

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EXHIBIT 111

OPEN ACCESS

Obsessive-compulsive disorder in children and adolescents

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ABSTRACT

Obsessive-compulsive disorder (OCD) in childhood and adolescence is an impairing condition, associated with a specific set of distressing symptoms incorporating repetitive, intrusive thoughts (obsessions) and distressing, time-consuming rituals (compulsions). This review considers current knowledge of causes and mechanisms underlying OCD, as well as assessment and treatment. Issues relating to differential diagnosis are summarised, including the challenges of distinguishing OCD from autism spectrum disorders and tic disorders in youth. The recommended treatments, namely cognitive behaviour therapy and serotonin reuptake inhibiting/selective serotonin reuptake inhibitor medications, are outlined along with the existing evidence-based and factors associated with treatment resistance. Finally, novel clinical developments that are emerging in the field and future directions for research are discussed.

EPIDEMIOLOGY

Obsessive-compulsive disorder (OCD) is a psychiatric condition characterised by persistent and unwanted intrusive thoughts, images and urges (obsessions) and repetitive behaviours or mental acts (compulsions) (see table 1). Once considered to be rare in youth, epidemiological studies have found an estimated prevalence of 0.25%–4% among children and adolescents.[1–3] Left untreated symptoms may wax and wane but typically follow a chronic course[4 5] and cause marked functional impairment across multiple domains, including at home, school and socially.[6] Furthermore, paediatric OCD is associated with increased risk of other psychiatric disorders in adulthood.[7 8]

AETIOLOGY

The aetiology of paediatric OCD remains relatively poorly understood, despite considerable research to date. Data from twin, family and segregation studies strongly support a genetic component.[9] Twin studies have shown that genetic factors explain 45%–65% of the variance of OCD in children,[10] pointing to a higher heritability in OCD relative to most other anxiety disorders and depression in youth.[11] Interestingly, the heritability of OCD appears to be greater in paediatric compared with adult cohorts,[10] supporting the notion of early-onset OCD as a putative developmental subtype of the disorder. The results of genome-wide association studies[12 13] and meta-analyses of candidate gene studies[14] suggest that the genetic influence on OCD is polygenic, with many genes involved which individually exert a relatively small effect on the phenotype. In particular, genes within the serotonergic, dopaminergic and glutamatergic system appear to influence OCD.[15]

Neuropsychological models of OCD propose that OCD arises from alterations to frontostriatal circuitry. Hyperactivation of the orbitofrontal cortex has been proposed to mediate persistent thoughts about threat and harm (ie, obsessions), which in turn lead to attempts to neutralise the perceived threat (ie, compulsions). There is robust evidence from functional neuroimaging studies of increased activation in the lateral and medial orbitofrontal cortex in both children and adults with OCD.[15] Interestingly, orbitofrontal brain dysfunction has also been found in unaffected relatives of patients with OCD, who are at genetic risk of OCD.[16] Importantly, treatment studies have demonstrated reduced activation in the orbitofrontal cortex following cognitive behaviour therapy (CBT) for OCD,[15] demonstrating some degree of plasticity.

While genetic factors clearly influence the expression of OCD, environmental factors also play a significant role, but remarkably little is known about these effects. Few prospective studies have been conducted, and results have been inconsistent. For example, one longitudinal study found that social isolation, physical abuse and negative emotionality were specific predictors of an adult OCD diagnosis.[17] In contrast, a recent retrospective study found no evidence for an association between adverse childhood experiences and OCD, although such experiences were related to certain comorbidities, including depression.[18]

There has been emerging clinical evidence over the past 10–15 years of a subgroup of children who experience sudden onset OCD and/or tics after streptococcal infection. This group of children was originally given the acronym PANDAS (paediatric autoimmune neuropsychiatric disorders associated with streptococcus),[19] but more recently the term PANS (paediatric acute-onset neuropsychiatric syndrome) has been used in preference, as it is felt to capture both the sudden onset and the uncertainty about aetiology.[20] These children tend to have more widespread neuropsychiatric difficulties than other children with OCD, including enuresis, deterioration in handwriting and impulsivity. The exact mechanism of sudden onset neuropsychiatric disorder is unknown, but there has been interest in delivering therapies that target immune and infectious causes. However, other small studies suggest that OCD in this population responds as well to standard treatments, and effectiveness of prophylactic antibiotics has been inconsistent.

DIAGNOSTIC CRITERIA AND CLASSIFICATION

The diagnosis of OCD in young people is broadly similar to adults (see box 1 for the International Classification of Diseases (ICD) diagnostic criteria).

Table 1 Description of obsessions and compulsions

	Obsessions	Compulsions
Definition	Recurrent, unwanted and persistent thoughts, images or urges that cause marked distress	Repetitive behaviours or mental acts that are often driven by rigid rules and performed in an attempt to reduce anxiety
Common themes	Contamination	Washing and cleaning
	Aggressive/harm	Checking
	Sexual	Reassurance seeking
	Religious	Repeating
	Making things 'just right'	Ordering and arranging

However, it has been noted that children are less likely to have insight into the irrationality of their obsessions and compulsions,[21] presumably due to underdeveloped meta-cognitive skills. Furthermore, in children, it is important to differentiate true compulsions from normal routines or ritualised behaviours, which are typically transient and no cause for concern. For example, many children display specific routines at bedtime such as saying goodnight in a particular way to their parents and/or toys.[22] In order to be considered a compulsion, a behaviour must be distressing and/or impairing.

Historically OCD has been considered to be an anxiety disorder. Indeed, OCD is listed as a 'neurotic, stress-related and somatoform disorder' along with anxiety disorders in ICD-10, and similarly it was classified as an anxiety disorder in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III, DSM-III-R and DSM-IV. However, in light of accumulating evidence for key differences in the phenomenology and aetiology of OCD compared with other anxiety disorders,[23] its classification has changed within DSM-5 and it now falls within the new 'OCD and related disorders' section. This section also includes a number of other disorders that are characterised by repetitive thinking and repetitive behaviour, such as body dysmorphic disorder, hoarding disorder and trichotillomania.

Box 1 International Classification of Diseases-10 diagnostic criteria for obsessive-compulsive disorder

1. Either obsessions or compulsions or both present on most days for a period of 2 weeks.
2. Obsessions (unwanted ideas, images or impulses that repeatedly enter a person's mind) and compulsions (repetitive stereotyped behaviours or mental acts driven by rules that must be applied rigidly) share the following features:
   - Patient is aware that these originate from their own mind.
   - They are repetitive, unpleasant and distressing to the patient. At least one is perceived as excessive or unreasonable ('egodystonic').
   - At least one is resisted unsuccessfully, even though others may be present that the sufferer no longer resists.
   - Thought of carrying out the obsession or compulsion is not intrinsically pleasurable (simple relief of tension momentarily on completion of the thought/act is not regarded as pleasure in this sense).
3. The symptoms must be disabling. Even young children will have some insight into the senselessness of the thoughts and behaviours.

ASSESSMENT AND DIAGNOSIS

OCD typically goes undetected for many years before an accurate diagnosis is made.[24] Delays in detection in young people may reflect embarrassment and attempts to conceal symptoms, poor insight and/or difficulty differentiating true OCD from normative rituals during development.[25] Furthermore, while OCD is often associated with a characteristic set of symptoms (eg, excessive washing, repeated checking), the disorder is strikingly heterogeneous; two individuals with OCD may present with entirely non-overlapping symptom profiles, which can present a diagnostic challenge. Nevertheless, the majority of paediatric OCD cases be identified using a six-question screening instrument, the Short OCD Screener (SOCS), recommended by the National Institute for Health and Clinical Excellence (see box 2).[26] The SOCS has been found to have a sensitivity of 97% (95% CI 0.91 to 0.98) in detecting OCD. As it is not a diagnostic instrument, further assessment is required in individuals who screen positive including taking a detailed history of obsessions and compulsions, a developmental history and a separate interview with the young person.[27] The latter is particularly important given that 'taboo' obsessions, such as sexual obsessions, are common and the young person may be reluctant to disclose them in front of relatives.[28]

DIFFERENTIAL DIAGNOSIS

Differential diagnosis can be challenging, particularly in paediatric populations; three of the most complex differential diagnoses are outlined below.

Restricted interests and stereotyped behaviours are a core feature of autism spectrum disorders (ASDs) and may result in both cognitive preoccupations and repetitive behaviours. Stereotyped behaviours can manifest as a phenocopy of compulsions (eg, ordering and arranging toys) and it is crucial to delineate ASD-related behaviours from true compulsions in order to inform treatment. In contrast to autism-related stereotyped behaviours, compulsions are usually (a) preceded by an obsession, (b) associated with relief in anxiety and (c) egodystonic (ie, unwanted and inconsistent with the individual's fundamental values) and the behaviour itself is not experienced as being intrinsically pleasurable. Of course, a young person may present with both ASD and OCD, and indeed prevalence rates of OCD are significantly elevated among individuals with ASD.[29]

Box 2 Short obsessive-compulsive disorder screener

1. Do you wash or clean a lot?
2. Do you check things a lot?
3. Is there any thought that keeps bothering you that you would like to get rid of but cannot?
4. Do your daily activities take a long time to finish? (eg, getting ready for school)
5. Are you concerned about putting things in a special order or are you very upset by mess?
6. Do these problems trouble you?

Detecting and treating OCD in the context of ASD can significantly improve functioning and quality of life.[30]

Another common differential diagnosis is OCD and tic disorders. Up to 59% of children and adolescents with OCD meet criteria for a diagnosis of a tic disorder at some point during their lifetime.[31] Individuals with comorbid tic disorders may display an earlier age of onset of OCD and a different symptom profile compared with those without tic disorders.[32] Complex tics, in particular, can be difficult to differentiate from compulsions: as with autism-related stereotyped behaviours, the behaviour itself can appear identical to a compulsion (eg, touching and tapping). However, while tics are largely involuntary, compulsions are performed deliberately to relieve anxiety. The level of complexity of the behaviour may also help to differentiate tics from compulsions; even complex tics are relatively straightforward behaviours (eg, a brief tapping action), whereas compulsions are often more elaborate and performed according to a rule (eg, tapping four times with the left hand and four times with the right hand). Differentiating an OCD component is important, as OCD treatments are effective in children with tics and OCD, and OCD can be the most impairing aspect of their condition.[33]

A third differential diagnosis that can be challenging is psychosis and OCD. The bizarre nature of obsessional thoughts can often raise queries of psychotic phenomena, especially in cases where the young person has limited insight into the irrationality of their obsessions. For example, a proportion of young people with OCD present with 'transformation obsessions', which refers to a fear of turning into someone or something else or acquiring unwanted characteristics.[34] These unusual symptoms can easily be confused with delusions, leading to inappropriate treatment.[34] Similarly, aggressive obsessions such as a fear of being harmed can appear similar to paranoia. In cases of OCD, the individual may have some insight into the irrationality of their fears; the obsessional thought is unlikely to be part of a broader delusional set of beliefs (eg, a plot of how and why others would want to harm them); and other symptoms of OCD are likely to be present upon questioning whereas other symptoms of psychosis (such as hallucinations and thought-disorder) are absent.

TREATMENT

There are two treatments with an established evidence base in the treatment of paediatric OCD, namely CBT incorporating exposure with response prevention (E/RP) and selective serotonin reuptake inhibitors (SSRIs).[35] CBT for paediatric OCD is a relatively short-term treatment, usually consisting of 12–20 weekly sessions. The main therapeutic strategy is E/RP, which involves the young person gradually confronting their feared situations (eg, touching dirty door handles) and refraining from carrying out compulsions (eg, handwashing) in an attempt to neutralise their anxiety or feared outcome. Instead, the young person is encouraged to wait until their anxiety comes down naturally, and then to repeatedly practice the same E/RP task until their anxiety extinguishes altogether (ie, habituation). E/RP tasks are set up in graded way, as guided by a hierarchy, and are carried out in sessions with the therapist and in between sessions as homework.

Randomised controlled trials (RCTs) have demonstrated that CBT is an efficacious treatment for paediatric OCD. The treatment is associated with a 40%–65% reduction in symptoms[36] and can be effective for children as young as 3 years when delivered in a developmentally appropriate format.[37] Gains appear to be relatively enduring and have been shown to be maintained up to 18-month follow-up.[38] Encouragingly, similar outcomes have been observed in community clinics (ie, non-research settings), suggesting that CBT protocols are effective in routine clinical practice.[39 40]

In line with the robust evidence base, there is international consensus that CBT should be offered to all young people with OCD and should be the first-line treatment in mild to moderate cases of OCD.[35 41] In more severe cases or where young people fail to respond to CBT, medication should be considered in addition to CBT. RCTs have shown a range of SSRIs (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram) to be effective in the treatment of paediatric OCD; they are associated with a 29%–44% reduction in symptoms and appear to be well tolerated and safe.[36] Few comparative treatment trials of different SSRIs have been undertaken, so there is little or no evidence to suggest that any one SSRI is more effective than another. However, in the UK, currently only sertraline and fluvoxamine are licensed for use in children, with sertraline recommended because of its favourable side effect profile.

Only one study to date has directly compared the efficacy of CBT versus SSRI medication in paediatric OCD.[42] This study found that CBT and sertraline were associated with comparable levels of symptom reduction, but that combined CBT and SSRI treatment was associated with superior outcomes. More recently, the same group has investigated the extent to which CBT improves outcomes among young people receiving SRIs for OCD.[43] They found that the individuals who received CBT compared with medication management alone had better outcomes, indicating that the combination of CBT and medication is superior to medication as a monotherapy in paediatric OCD. Interestingly, young people who received brief CBT instructions did not show any better response than those who received medication alone, suggesting that a truncated form of CBT is not effective in this population.

TREATMENT-RESISTANT OCD

A proportion of young people with OCD do not respond to CBT or SSRIs, and an even larger proportion make gains but are left with clinically significant residual symptoms. A number of studies have attempted to identify predictors of treatment response in an attempt to understand the mechanisms underlying treatment resistance. Perhaps, most attention has been given to the impact of comorbidity on treatment response. Comorbidity is common in paediatric OCD, with up to 80% meeting diagnostic criteria for an additional psychiatric disorder.[42] Although some comorbidities, such as depression and anxiety disorders, do not appear to affect response to CBT or SSRIs, others may have an impact. For example, individuals with comorbid tic disorders tend to have a poorer response to SSRIs but respond equally well to CBT compared with those without tics.[44] Externalising disorders (oppositional defiant disorder and conduct disorder) have been shown to predict a worse response to SSRIs and CBT,[44] and there is some suggestion that individuals presenting with this dual diagnosis would benefit from modified treatment approaches, such as CBT combined with parent management training.[45] Similarly, it has been suggested that individuals with ASDs respond less well to CBT for OCD, highlighting the need for modified CBT protocols in this group.[46]

Children with OCD who fail to respond to a course of CBT and an initial SSRI administered for at least 12 weeks at the maximum tolerated dose should usually have additional trials of at least one other SSRI. The tricyclic drug clomipramine (a non-SSRI) may be a useful medication to trial in resistant cases where two or more

SSRIs have failed, although it is less well tolerated than SSRIs. There is also some RCT evidence in adults, and emerging evidence in children that augmentation of SSRI medication with a low dose of a dopamine antagonist can improve response rate, with up to 50% of previous non-responders showing improvement.[47] However, studies have variable outcomes, and a recent RCT in adults who had been non-responsive to SSRIs demonstrated that delivering high-quality exposure-based CBT was more efficacious than risperidone augmentation.[48] The key message again for treatment in children with OCD is that they should have access to exposure-based CBT and that risperidone augmentation is a less-favourable option.

FUTURE DIRECTIONS

A major clinical challenge is the dissemination of good quality CBT to young people with OCD. Unfortunately, the vast majority of OCD sufferers fail to access CBT due to geographical barriers and/or a shortage of appropriately trained therapists.[49] In recent years, research has begun to focus on developing evidence-based methods for increasing the availability of, and access to, CBT. Novel approaches that have shown promise include CBT delivered via telephone[50] or web-camera[51] and internet CBT with minimal therapist input.[52] While further validation is required, these methods have the potential to transform service delivery for this population.

In addition to efforts to disseminate current evidence-based treatments for paediatric OCD, recent research has also focused on ways of enhancing CBT in order to improve outcomes, particularly for the significant minority who do not benefit from existing CBT protocols. For example, family conflict and parental blame have been shown to be associated with poorer CBT outcome in young people with OCD[53] and pilot data suggest that family therapy specifically aimed at targeting these dynamics is an effective adjunct to CBT in families that present with these difficulties.[54] With respect to pharmacological developments, in recent years there has been increasing interest in the use of d-cycloserine (DCS) as a potential augmentation strategy for CBT for OCD. DCS is a partial *N*-methyl-D-aspartate receptor agonist and animal studies have shown that DCS enhances extinction learning, which has raised the question of whether DCS could augment exposure-based therapies for anxiety disorders. However, findings remain mixed with some studies demonstrating an augmentation effect of DCS on CBT for OCD,[55] but not others.[56] These discrepancies may reflect methodological differences between studies, and further research is needed to establish the possible value of DCS in treating OCD in youth.

CONCLUSIONS

OCD commonly starts in childhood, and in addition to causing significant distress and impairment in children, it can persist into adult life where the WHO ranks it as one of the most impairing illnesses.[57] National guidelines exist for the assessment and treatment of OCD, and children should be offered interventions according to guidelines incorporating these evidence-based treatments. A substantial proportion of children and adolescents will respond with full or partial remission to CBT, which may be combined with an SRI/SSRI. Unfortunately, inadequate provision of CBT means limitations in access to treatments, and current research aims to establish more accessible and economic formats of CBT. Ongoing research into the genetic and biological basis of OCD and its relationship with infections/autoimmunity may also in time increase understanding of mechanisms and offer new treatment possibilities.

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EXHIBIT 112

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

Children's Mental Health

Obsessive-Compulsive Disorder in Children

Many children occasionally have thoughts that bother them, and they might feel like they have to do something about those thoughts, even if their actions don't actually make sense. For example, they might worry about having bad luck if they don't wear a favorite piece of clothing. For some children, the thoughts and the urges to perform certain actions persist, even if they try to ignore them or make them go away. Children may have an obsessive-compulsive disorder (OCD) when unwanted thoughts, and the behaviors they feel they must do because of the thoughts, happen frequently, take up a lot of time (more than an hour a day), interfere with their activities, or make them very upset. The thoughts are called obsessions. The behaviors are called compulsions.

Symptoms

Having OCD means having obsessions, compulsions, or both.

Examples of obsessive or compulsive behaviors include:

- Having unwanted thoughts, impulses, or images that occur over and over and which cause anxiety or distress.
- Having to think about or say something over and over (for example, counting, or repeating words over and over silently or out loud)
- Having to do something over and over (for example, handwashing, placing things in a specific order, or checking the same things over and over, like whether a door is locked)
- Having to do something over and over according to certain rules that must be followed exactly in order to make an obsession go away.

Children do these behaviors because they have the feeling that the behaviors will prevent bad things from happening or will make them feel better. However, the behavior is not typically connected to actual danger of something bad happening, or the behavior is extreme, such as washing hands multiple times per hour.

A common myth is that OCD means being really neat and orderly. Sometimes, OCD behaviors may involve cleaning, but many times someone with OCD is too focused on one thing that must be done over and over, rather than on being organized. Obsessions and compulsions can also change over time.

Learn more about ODC

Treatment for OCD

The first step to treatment is to talk with a healthcare provider to arrange an evaluation. A comprehensive evaluation by a mental health professional will determine if the anxiety or distress involves memories of a traumatic event that actually happened, or if the fears are based on other thoughts or beliefs. The mental health professional should also determine whether someone with OCD has a current or past tic disorder. Anxiety or depression and disruptive behaviors may also occur with OCD.

For Healthcare Providers

Learn about the guidelines for diagnosing and treating OCD

Treatments can include behavior therapy and medication. Behavior therapy, specifically cognitive-behavioral therapy, helps the child change negative thoughts into more positive, effective ways of thinking, leading to more effective behavior. Behavior therapy for OCD can involve gradually exposing children to their fears in a safe setting; this helps them learn that bad things do not really occur when they don't do the behavior, which eventually decreases their anxiety. Behavior therapy alone can be effective, but some children are treated with a combination of behavior therapy and medication. Families and schools can help children manage stress by being part of the therapy process and learning how to respond supportively without accidentally making obsessions or compulsions more likely to happen again.

Get help finding treatment

Here are tools to find a healthcare provider familiar with treatment options:

- Psychologist Locator , a service of the American Psychological Association (APA) Practice Organization.
- Child and Adolescent Psychiatrist Finder , a research tool by the American Academy of Child and Adolescent Psychiatry (AACAP).
- Find a Cognitive Behavioral Therapist , a search tool by the Association for Behavioral and Cognitive Therapies.
- If you need help finding treatment facilities, visit MentalHealth.gov .

Prevention of OCD

It is not known exactly why some children develop OCD. There is likely to be a biological and neurological component, and some children with OCD also have Tourette syndrome or other tic disorders. There are some studies that suggest that health problems during pregnancy and birth may make OCD more likely, which is one of many important reasons to support the health of women during pregnancy.

Learn about preventing problems during pregnancy

Page last reviewed: March 30, 2020

Content source: National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention

EXHIBIT 113

NCHS Data Brief ■ No. 330 ■ November 2018

Suicide Mortality in the United States, 1999–2017

Holly Hedegaard, M.D., Sally C. Curtin, M.A., and Margaret Warner, Ph.D.

Key findings

Data from the National Vital Statistics System, Mortality

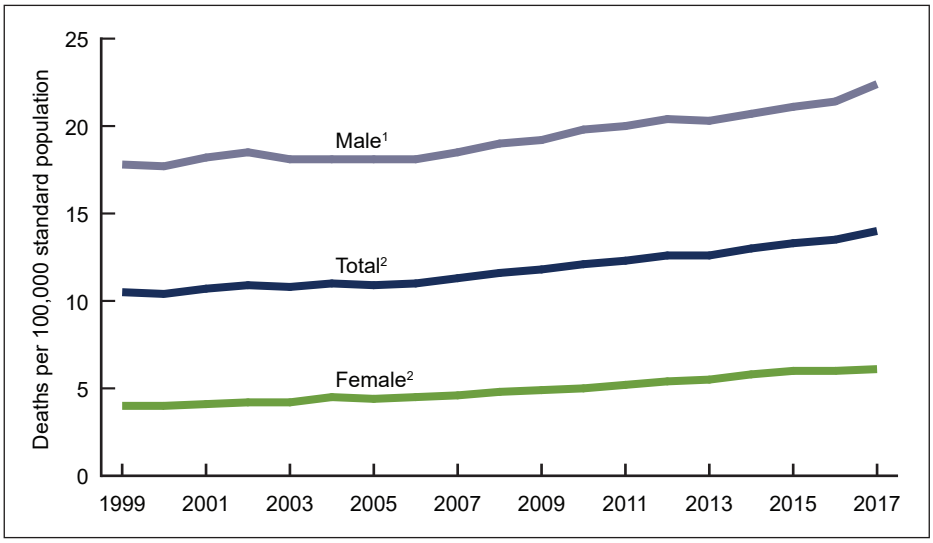
- From 1999 through 2017, the age-adjusted suicide rate increased 33% from 10.5 to 14.0 per 100,000.
- Suicide rates were significantly higher in 2017 compared with 1999 among females aged 10–14 (1.7 and 0.5, respectively), 15–24 (5.8 and 3.0), 25–44 (7.8 and 5.5), 45–64 (9.7 and 6.0), and 65–74 (6.2 and 4.1).
- Suicide rates were significantly higher in 2017 compared with 1999 among males aged 10–14 (3.3 and 1.9, respectively), 15–24 (22.7 and 16.8), 25–44 (27.5 and 21.6), 45–64 (30.1 and 20.8) and 65–74 (26.2 and 24.7).
- In 2017, the age-adjusted suicide rate for the most rural (noncore) counties was 1.8 times the rate for the most urban (large central metro) counties (20.0 and 11.1 per 100,000, respectively).

Since 2008, suicide has ranked as the 10th leading cause of death for all ages in the United States (1). In 2016, suicide became the second leading cause of death for ages 10–34 and the fourth leading cause for ages 35–54 (1). Although the Healthy People 2020 target is to reduce suicide rates to 10.2 per 100,000 by 2020 (2), suicide rates have steadily increased in recent years (3,4). This data brief uses final mortality data from the National Vital Statistics System (NVSS) to update trends in suicide mortality from 1999 through 2017 and to describe differences by sex, age group, and urbanization level of the decedent's county of residence.

From 1999 through 2017, suicide rates increased for both males and females, with greater annual percentage increases occurring after 2006.

- From 1999 through 2017, the age-adjusted suicide rate increased 33% from 10.5 per 100,000 standard population to 14.0 (Figure 1). The rate

Figure 1. Age-adjusted suicide rates, by sex: United States, 1999–2017



[1]Stable trend from 1999 through 2006; significant increasing trend from 2006 through 2017, $p < 0.001$.
[2]Significant increasing trend from 1999 through 2017 with different rates of change over time, $p < 0.001$.
NOTES: Suicides are identified using *International Classification of Diseases, Tenth Revision* underlying cause-of-death codes U03, X60–X84, and Y87.0. Age-adjusted death rates were calculated using the direct method and the 2000 U.S. standard population. Access data table for Figure 1 at: https://www.cdc.gov/nchs/data/databriefs/db330_tables-508.pdf#1.
SOURCE: NCHS, National Vital Statistics System, Mortality.

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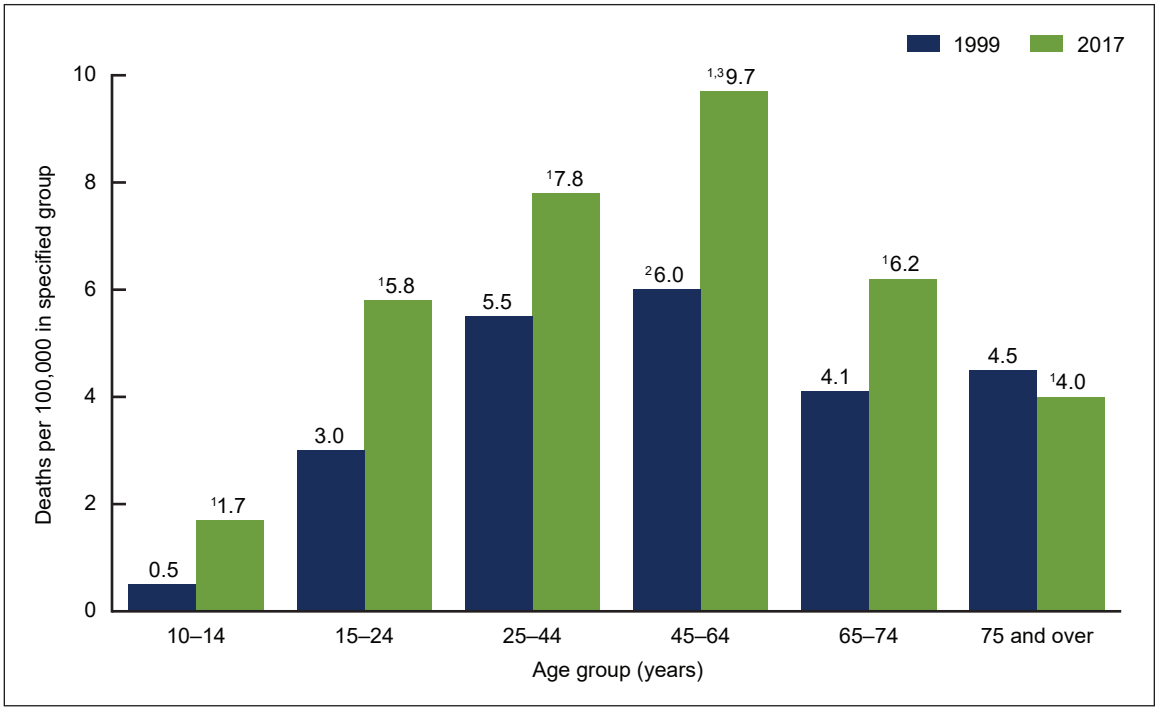
increased on average by about 1% per year from 1999 through 2006 and by 2% per year from 2006 through 2017.

- For males, the rate increased 26% from 17.8 in 1999 to 22.4 in 2017. The rate did not significantly change from 1999 to 2006, then increased on average by about 2% per year from 2006 through 2017.
- For females, the rate increased 53% from 4.0 in 1999 to 6.1 in 2017. The rate increased on average by 2% per year from 1999 through 2007 and by 3% per year from 2007 through 2017.

Suicide rates for females aged 10–74 were higher in 2017 than in 1999.

- Suicide rates for females were highest for those aged 45–64 in both 1999 (6.0 per 100,000) and 2017 (9.7) (Figure 2).
- Suicide rates were significantly higher in 2017 compared with 1999 among females aged 10–14 (1.7 and 0.5, respectively), 15–24 (5.8 and 3.0), 25–44 (7.8 and 5.5), 45–64 (9.7 and 6.0), and 65–74 (6.2 and 4.1).
- The suicide rate in 2017 for females aged 75 and over (4.0) was significantly lower than the rate in 1999 (4.5).

Figure 2. Suicide rates for females, by age group: United States, 1999 and 2017



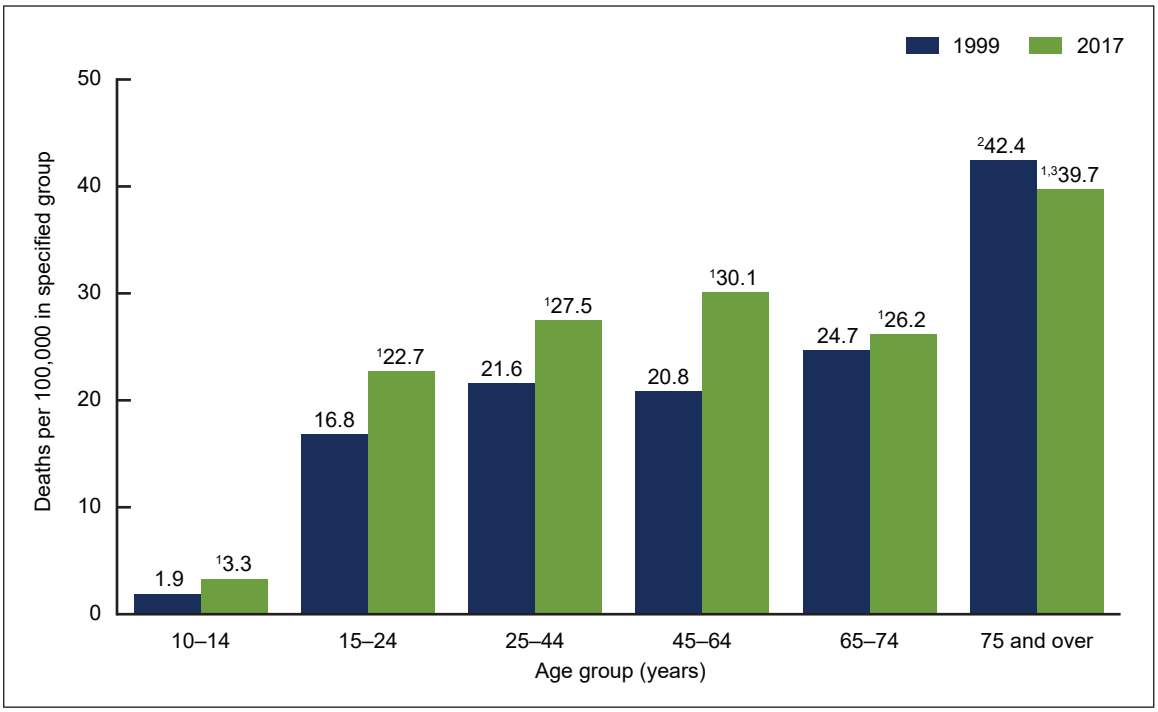
[1]Significantly different from 1999 rate, $p < 0.05$.
[2]Significantly higher than rates for all other age groups in 1999, $p < 0.05$.
[3]Significantly higher than rates for all other age groups in 2017, $p < 0.05$.
NOTES: Suicides are identified using *International Classification of Diseases, Tenth Revision* underlying cause-of-death codes U03, X60–X84, and Y87.0.
Access data table for Figure 2 at: https://www.cdc.gov/nchs/data/databriefs/db330_tables-508.pdf#2.
SOURCE: NCHS, National Vital Statistics System, Mortality.

Exhibit 113

Suicide rates for males aged 10–74 were higher in 2017 than in 1999.

- Suicide rates for males were highest for those aged 75 and over in both 1999 (42.4 per 100,000) and 2017 (39.7) (Figure 3).
- Suicide rates were significantly higher in 2017 compared with 1999 among males aged 10–14 (3.3 and 1.9, respectively), 15–24 (22.7 and 16.8), 25–44 (27.5 and 21.6), 45–64 (30.1 and 20.8), and 65–74 (26.2 and 24.7).
- The suicide rate in 2017 for males aged 75 and over (39.7) was significantly lower than the rate in 1999 (42.4).

Figure 3. Suicide rates for males, by age group: United States, 1999 and 2017

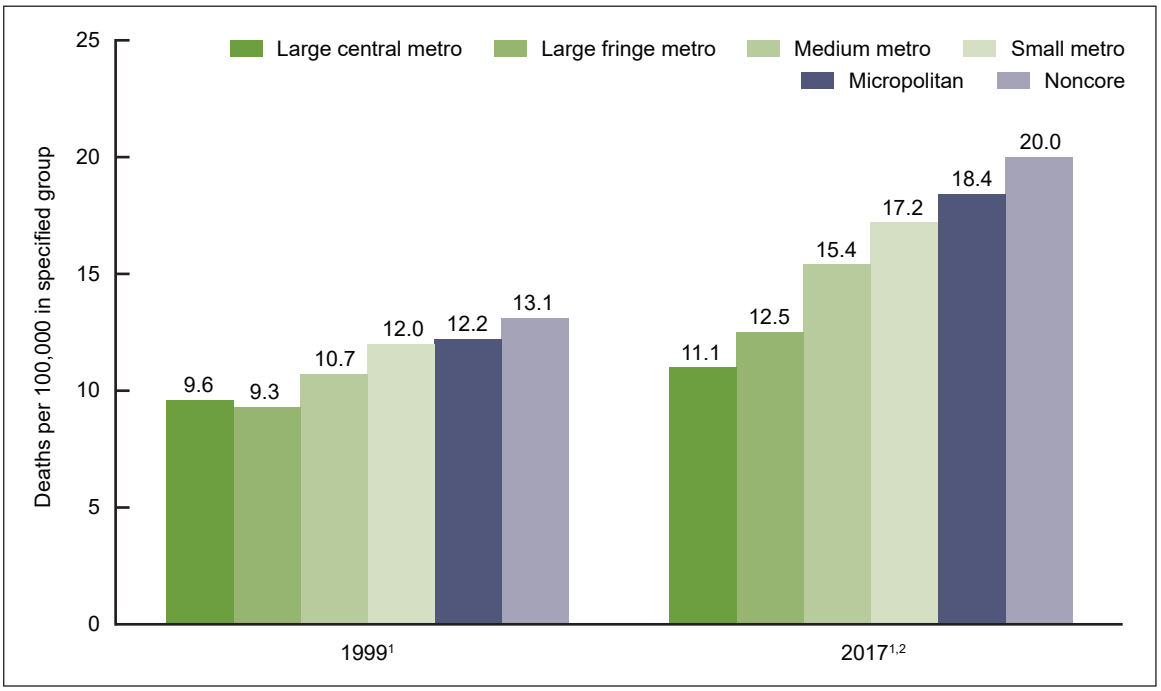


[1]Significantly different from 1999 rate, $p < 0.05$.
[2]Significantly higher than rates for all other age groups in 1999, $p < 0.05$.
[3]Significantly higher than rates for all other age groups in 2017, $p < 0.05$.
NOTES: Suicides are identified using *International Classification of Diseases, Tenth Revision* underlying cause-of-death codes U03, X60–X84, and Y87.0.
Access data table for Figure 3 at: https://www.cdc.gov/nchs/data/databriefs/db330_tables-508.pdf#3.
SOURCE: NCHS, National Vital Statistics System, Mortality.

The difference in age-adjusted suicide rates between the most rural and most urban counties was greater in 2017 than in 1999.

- In both 1999 and 2017, the age-adjusted suicide rate increased with decreasing urbanization (Figure 4). In 1999, the age-adjusted suicide rate for the most rural (noncore) counties (13.1 per 100,000) was 1.4 times the rate for the most urban (large central metro) counties (9.6). This difference increased in 2017, with the suicide rate for the most rural counties (20.0 per 100,000) increasing to 1.8 times the rate for the most urban counties (11.1).
- The age-adjusted suicide rate for the most urban counties in 2017 (11.1 per 100,000) was 16% higher than the rate in 1999 (9.6).
- The age-adjusted suicide rate for the most rural counties in 2017 (20.0 per 100,000) was 53% higher than the rate in 1999 (13.1).

Figure 4. Age-adjusted suicide rates, by county urbanization level: United States, 1999 and 2017



[1]Significantly increasing suicide rates by decreasing urbanization, $p < 0.05$.
[2]Significantly higher than 1999 rate for each level of urbanization, $p < 0.05$.
NOTES: Suicides are identified using *International Classification of Diseases, Tenth Revision* underlying cause-of death codes U03, X60–X84, and Y87.0. Age-adjusted death rates are calculated using the direct method and the 2000 U.S. standard population. Classification of the decedent's county of residence is based on the 2006 NCHS Urban–Rural Classification Scheme for Counties, available from: https://www.cdc.gov/nchs/data/series/sr_02/sr02_154.pdf. Categories are presented from most urban (large central metro) to least urban (small metro), and from rural (micropolitan) to most rural (noncore). Access data table for Figure 4 at: https://www.cdc.gov/nchs/data/databriefs/db330_tables-508.pdf#4.
SOURCE: NCHS, National Vital Statistics System, Mortality.

Summary

This report highlights trends in suicide rates from 1999 through 2017. During this period, the age-adjusted suicide rate increased 33% from 10.5 per 100,000 in 1999 to 14.0 in 2017. The average annual percentage increase in rates accelerated from approximately 1% per year from 1999 through 2006 to 2% per year from 2006 through 2017. The age-adjusted rate of suicide among females increased from 4.0 per 100,000 in 1999 to 6.1 in 2017, while the rate for males increased from 17.8 to 22.4. Compared with rates in 1999, suicide rates in 2017 were higher for males and females in all age groups from 10 to 74 years. The differences in age-adjusted suicide rates between the most rural (noncore) and most urban (large central metro) counties was greater in 2017 than in 1999. In 1999, the age-adjusted suicide rate for the most rural counties (13.1 per 100,000) was 1.4 times the rate for the most urban counties (9.6), while in 2017, the age-adjusted suicide rate for the most rural counties (20.0) was 1.8 times the rate for the most urban counties (11.1). The age-adjusted suicide rate for the most urban counties in 2017 (11.1 per 100,000) was 16% higher than the rate in 1999 (9.6), while the rate for the most rural counties in 2017 (20.0) was 53% higher than the rate in 1999 (13.1).

Data sources and methods

Data were analyzed using the NVSS multiple cause-of-death mortality files for 1999 through 2017 (5). Suicide deaths were identified using *International Classification of Diseases, Tenth Revision* (ICD–10) underlying cause-of-death codes U03, X60–X84, and Y87.0 (6). Age-adjusted death rates were calculated using the direct method and the 2000 U.S. standard population (7). Suicides for persons aged 5–9 years were included in the total numbers and age-adjusted rates but not shown as part of the age-specific numbers or rates, due to the small number of suicide deaths among this age group.

Urbanization level of the decedent's county of residence was categorized using the 2006 NCHS Urban–Rural Classification Scheme for Counties (8). Counties were classified into six urbanization levels based on metropolitan–nonmetropolitan status, population distribution, and other factors. The six urbanization levels ranged from the most urban (large central metro) to the most rural (noncore). Metropolitan counties include large central counties, the fringes of large counties (suburbs), medium counties, and small counties. Nonmetropolitan counties (i.e., rural counties) include micropolitan statistical areas and noncore areas, including open countryside, rural towns (populations of less than 2,500), and areas with populations of 2,500–49,999 that are not part of larger labor market areas (metropolitan areas).

Trends in age-adjusted death rates were evaluated using the Joinpoint Regression Program (9). The Joinpoint software was used to fit weighted least-squares regression models to the estimated proportions on the linear scale. The default settings allowed for as few as four observed time points in the beginning, ending, and middle line segments, including the joinpoints. Using these settings, a maximum of three joinpoints were searched for using the grid search algorithm and permutation test, and an overall alpha level of 0.05 (10). Pairwise comparisons of rates in Figures 2–4 were conducted using the *z* test statistic with an alpha level of 0.05 (7).

About the authors

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10. Ingram DD, Malec DJ, Makuc DM, Kruszon-Moran D, Gindi RM, Albert M, et al. National Center for Health Statistics Guidelines for Analysis of Trends. National Center for Health Statistics. Vital Health Stat 2(179). 2018. Available from: https://www.cdc.gov/nchs/data/series/sr_02/sr02_179.pdf.

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Exhibit 113

EXHIBIT 114

Letters

RESEARCH LETTER

Trends in Emergency Department Visits for Nonfatal Self-inflicted Injuries Among Youth Aged 10 to 24 Years in the United States, 2001-2015

In the United States, youth have the highest burden of nonfatal self-inflicted injury (ie, deliberate physical harm against oneself, inclusive of suicidal and nonsuicidal intent) requiring medical attention.[1] One study found that emergency department (ED) visits for these injuries during the 1993 to 2008 period varied by age group, ranging from 1.1 to 9.6 per 1000 ED visits, with adolescents aged 15 to 19 years exhibiting the highest rates.[1] Self-inflicted injury is one of the strongest risk factors for suicide—the second-leading cause of death among those aged 10 to 24 years during 2015.[2] This study examined trends in nonfatal self-inflicted injuries treated in hospital EDs among US children, adolescents, and young adults aged 10 to 24 years (hereafter referred to as youth).

Methods | The National Electronic Injury Surveillance System—All Injury Program (NEISS-AIP) collects data on all first-time visits for nonfatal injuries treated in 66 US hospital EDs through stratified probability sampling, allowing for the derivation of national estimates.[3] Self-inflicted injuries were identified by reviewing injury cause narratives and other coded data within ED records. This study used publicly available secondary data and was exempted by the CDC from institutional review board review.

Self-inflicted injury ED visit rates were calculated from 2001 through 2015 by sex, age (10-14, 15-19, and 20-24 years), along with injury method (poisoning, sharp object, blunt object), and 95% CIs using US Census population estimates as denominators. Rates were weighted to obtain nationally representative estimates and age-adjusted to the 2000 US Census population. Trends in self-inflicted injury ED visit rates were assessed using joinpoint regression software (Surveillance Research Program, National Cancer Institute), version 4.3.1.0. The annual percentage change described the rate of change for each linear segment.

Results | From 2001 to 2015, NEISS-AIP captured 43 138 youth self-inflicted injury ED visits. The overall weighted age-adjusted rate for this group showed no statistically significant trend until 2008, increasing 5.7% (95% CI, 3.0%-8.4%) annually thereafter and reaching 303.7 per 100 000 population (95% CI, 254.1-353.3) in 2015 (**Table**). Age-adjusted trends for males overall and across age groups remained stable throughout 2001-2015 (**Figure**, Table). Overall age-adjusted rates for females demonstrated no statistically significant trend before 2009, yet increased 8.4% (95% CI, 5.6%-11.2%) yearly from 2009 to 2015. After 2009, rates among females aged 10 to 14 years increased 18.8% (95% CI, 12.1%-25.8%) per year—from 109.8 (95% CI, 69.9-149.7) in 2009 to 317.7 (95% CI, 230.3-405.1) per 100 000 population in 2015. Rates among females aged 15 to 19 years showed a 7.2% (95% CI, 3.8%-10.8%) increase per year during 2008-2015. Rates among females aged 20 to 24 years exhibited a 2.0% (95% CI, 0.8%-3.1%) increase per year throughout 2001-2015 (Figure, Table).

Trends for all self-inflicted injury methods were stable for males. Poisoning was the most common method of self-inflicted injury for females, with rates remaining stable until 2007 and increasing 5.3% (95% CI, 0.5%-10.4%) annually thereafter. Female rates for self-inflicted injuries by sharp object increased 7.1% (95% CI, 5.2%-8.9%) annually throughout 2001-2015; female rates for blunt object injuries were stable during 2006-2015 (Table).

Discussion | Youth self-inflicted injury ED visit rates were relatively stable before 2008. However, rates among females significantly increased thereafter—particularly among females aged 10 to 14 years, who experienced an 18.8% annual increase from 2009 to 2015. This study only included ED cases; thus, rates were underestimated. Also, limited statistical power could have resulted in some trends not showing statistical significance. Findings are consistent with previously reported upward trends in youth suicide rates during 1999-2014, in which rates increased most notably after 2006 with females aged 10 to 14 years experiencing the greatest increase.[4] Findings also coincide with increased reports of depression among youth, especially young girls.[5] Other potential underlying reasons for the observed increasing trends, particularly among young females, warrant further study.

These findings underscore the need for the implementation of evidence-based, comprehensive suicide and self-harm prevention strategies within health systems and communities. These strategies include strengthening access to and delivery of care for suicidal youth within health systems and creating protective environments, promoting youth connectedness, teaching coping and problem-solving skills, and identifying and supporting at-risk youth within communities.[6]

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Correction: This article was corrected for an error in the Figure title on December 26, 2017.

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Author Contributions: Dr Mercado had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Exhibit 114

Table. Trends in Nonfatal Self-inflicted Injury Emergency Department (ED) Visit Rates (per 100 000) Among Youth Aged 10 to 24 Years in the United States, 2001-2015[a]

	2001		2015		Segment 1[a]		Segment 2[a]		Segment 3[a]	
	Unweighted Nonfatal Self-inflicted Injury ED Visits, No.	Weighted Rate (95% CI)	Unweighted Nonfatal Self-inflicted Injury ED Visits, No.	Weighted Rate (95% CI)	Period	APC (95% CI)	Period	APC (95% CI)	Period	APC (95% CI)
Male										
Age group, y										
10-14	93	33.9 (21.4 to 46.4)	180	44.1 (22.9 to 65.3)	2001 to 2015	1.0 (−2.0 to 4.1)				
15-19	387	213.7 (150.4 to 277.0)	531	256.5 (176.9 to 336.1)	2001 to 2015	0.5 (−0.9 to 1.8)				
20-24	350	240.7 (165.6 to 315.8)	407	243.8 (181.7 to 305.9)	2001 to 2015	−0.1 (−1.3 to 1.2)				
Injury type[b]										
Poisoning	460	89.5 (69.9 to 109.1)	359	74.1 (55.2 to 93.0)	2001 to 2008	−6.3 (−10.4 to −2.1)	2008 to 2011	10.6 (−19.4 to 51.9)	2011 to 2015	−4.3 (−14.0 to 6.4)
Sharp object	228	45.2 (33.4 to 57.1)	347	50.7 (38.5 to 62.8)	2001 to 2015	1.1 (−0.3 to 2.5)				
Blunt object	35	6.0 (3.1 to 8.9)	101	11.8 (7.3 to 16.3)	2001 to 2015	1.3 (−2.5 to 5.2)				
Overall trend	830	160.8 (114.9 to 206.7)	1118	184.3 (135.1 to 233.5)	2001 to 2015	0.5 (−0.5 to 1.6)				
Age-adjusted overall trend	830	160.2 (127.9 to 192.5)	1118	179.2 (144.9 to 213.5)	2001 to 2015	0.3 (−0.7 to 1.4)				
Female										
Age group, y										
10-14	286	119.4 (78.4 to 160.4)	1033	317.7 (230.3 to 405.1)	2001 to 2004	9.7 (−8.1 to 30.9)	2004 to 2009	−4.3 (−13.1 to 5.4)	2009 to 2015	18.8 (12.1 to 25.8)
15-19	725	389.3 (271.7 to 506.9)	1356	632.5 (465.9 to 799.1)	2001 to 2004	11.0 (−2.8 to 26.7)	2004 to 2008	−4.6 (−14.1 to 5.9)	2008 to 2015	7.2 (3.8 to 10.8)
20-24	355	228.0 (150.4 to 305.6)	556	346.2 (253.1 to 439.3)	2001 to 2015	2.0 (0.8 to 3.1)				
Injury type[b]										
Poisoning	988	170.9 (135.0 to 206.8)	987	203.3 (167.1 to 239.5)	2001 to 2007	−6.4 (−13.0 to 0.8)	2007 to 2015	5.3 (0.5 to 10.4)		
Sharp object	261	54.1 (40.5 to 67.7)	1021	136.3 (103.5 to 169.0)	2001 to 2015	7.1 (5.2 to 8.9)				
Blunt object	19	2.5 (0.5 to 4.5)	104	11.2 (7.3 to 15.0)	2001 to 2006	36.1 (15.7 to 60.0)	2006 to 2015	−0.7 (−4.9 to 3.6)		
Overall trend	1366	244.3 (171.8 to 316.8)	2945	430.8 (325.5 to 536.1)	2001 to 2004	9.1 (0.2 to 18.8)	2004 to 2009	−1.6 (−5.7 to 2.8)	2009 to 2015	7.9 (5.0 to 10.8)
Age-adjusted overall trend	1366	245.5 (196.5 to 294.5)	2945	434.0 (363.2 to 504.8)	2001 to 2004	9.0 (0 to 18.8)	2004 to 2009	−1.9 (−6.2 to 2.5)	2009 to 2015	8.4 (5.6 to 11.2)
Overall										
Age-adjusted overall trend		**201.6 (163.8 to 239.4)**		**303.7 (254.1 to 353.3)**	**2001 to 2004**	**7.9 (−2.4 to 19.4)**	**2004 to 2008**	**−3.7 (−11.0 to 4.1)**	**2008 to 2015**	**5.7 (3.0 to 8.4)**

Abbreviation: APC, annual percentage change.

[a] Joinpoint regression was used to determine nonfatal self-inflicted injury emergency department visit rate trends overall and by sex or age-group. Trends are presented as linear segments connected at the joinpoints (ie, at the years when the slope of each trend changed significantly). The number and location of joinpoints for each trend is determined statistically. Therefore, the periods for each linear segment within each trend may vary. If no joinpoint was identified for a trend, then that trend remained linear for the entire 2001-2015 period; in those instances, the APC is presented in Segment 1 only and left blank for all other segments.

[b] Insufficient sample size to analyze the trends for other types of self-inflicted injury. Blunt object–related injuries include "Injuries resulting from being struck by (hit) or crushed by a human, animal, or inanimate object or force other than a vehicle or machinery." This does not include falls from heights, such as buildings and bridges.

Concept and design: Mercado, Holland, Leemis, Stone.
Acquisition, analysis, or interpretation of data: Mercado, Holland, Leemis, Wang.
Drafting of the manuscript: Mercado, Holland, Leemis, Wang.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Holland, Wang.
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Supervision: Mercado.
Other - subject matter expertise: Stone.

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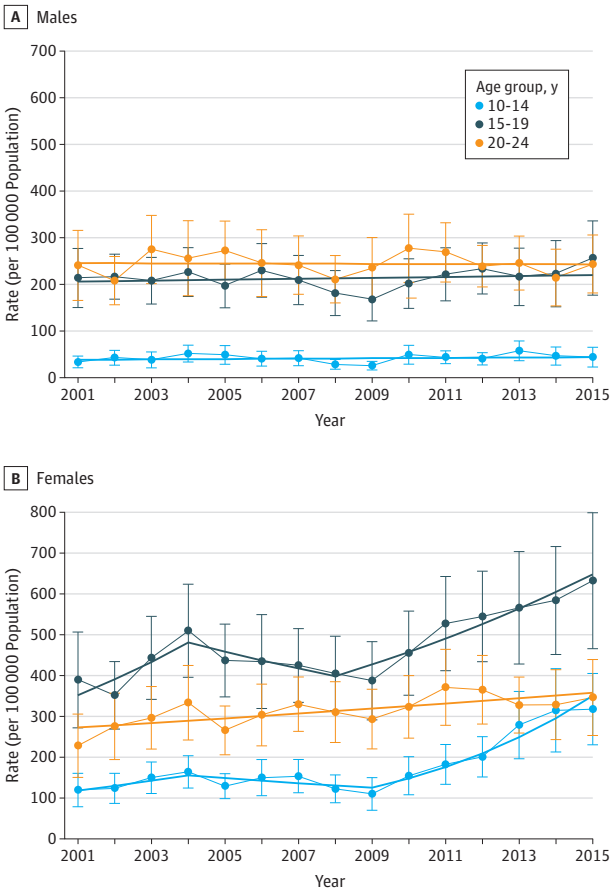
Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the CDC.

Exhibit 114

Figure. Nonfatal Self-Inflicted Injury Emergency Department Visits Among Youth Aged 10 to 24 Years in the United States, 2001-2015



Data markers indicate observed rates and solid colored lines indicate modeled rates. The error bars represent the 95% CIs of the observed rates. A, No significant trends for annual percentage change by age group were noted for males. B, Among females, the significant trends for annual percentage change by age group were 2009 to 2015 (18.8 [95% CI, 12.1-25.8]) for 10 to 14 years, 2008 to 2015 (7.2 [95% CI, 3.8-10.8]) for 15 to 19 years, and 2001 to 2015 (2.0 [95% CI, 0.8-3.1]) for 20 to 24 years.

Additional Contributions: The data used in this report originated from the National Electronic Injury Surveillance System All Injury Program, operated by the US Consumer Product Safety Commission and whose data are made available by CDC's web-based Injury Statistics Query and Reporting System, supported by CDC's National Center for Injury Prevention and Control. We thank Tadesse Haileyesus, MS (CDC's National Center for Injury Prevention and Control), for providing technical support. He did not receive compensation for his contribution.

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COMMENT & RESPONSE

Consequences of Reductions in Hospital Readmissions

To the Editor The Patient Protection and Affordable Care Act established the Hospital Readmissions Reduction Program (HRRP) with public reporting of 30-day risk-standardized readmission rates and financial penalties for hospitals with higher-than-expected readmissions. Concerns have been raised regarding unintended consequences, particularly for patients with heart failure (HF).[1,2] Incentives to reduce readmissions may perversely encourage inappropriate care strategies, such as discouraging appropriate triage for emergency care.[1,2] The financial penalties have been shown to fall disproportionately on academic medical centers and safety-net hospitals, which provide care disproportionately for patients with lower socioeconomic status and minorities. These penalties may hinder the ability of these hospitals to provide care for these vulnerable populations, potentially resulting in unintended consequences.[2]

The analysis of fee-for-service Medicare beneficiaries hospitalized with HF along with other conditions covered by the HRRP from 2008 to 2014 by Dr Dharmarajan and colleagues found that reductions in paired monthly hospital 30-day readmissions were weakly but statistically significantly correlated with reductions in 30-day mortality rates after discharge. This finding could indicate that 30-day postdischarge mortality was not increased by efforts to reduce rehospitalizations.[3] However, the assessment for unintended consequences needs to consider the effect on all patients and all hospitals exposed, not just those from hospitals with declining readmissions. During the course of the study, after HRRP implementation, 30-day risk-adjusted postdischarge mortality in Medicare beneficiaries hospitalized with HF increased from 7.9% in 2008 to 9.2% in 2014, a 1.3% absolute increase and 16.5% relative increase. In 2014, because 385 222 Medicare beneficiaries were hospitalized with HF, a 1.3% absolute increase in mortality would represent a considerable number of excess HF patient deaths associated with HRRP implementation. Furthermore, in the decade prior to HRRP, 30-day risk-adjusted mortality rates in patients with HF had steadily declined by 16.4%,[4] so the magnitude of this potential adverse consequence might be considerably greater.

Rather than providing any measure of reassurance, we believe the question of harm remains. These findings suggest that the HRRP policies targeting readmissions after HF hospitalization may have been associated with the serious unintended consequence of higher mortality. If confirmed, these data represent the worst-case scenario regarding the potential effect of HRRP. Consideration needs to be given to more rigorous assessment of this question, and if proven to be harmful, action to mitigate those components that may have contributed to the increase in HF mortality should be implemented.

Gregg C. Fonarow, MD
Clyde W. Yancy, MD, MSc

Exhibit 114

EXHIBIT 115

National Institute of Diabetes and Digestive and Kidney Diseases

What is Diabetes?

In this section:

Diabetes is a disease that occurs when your blood glucose, also called blood sugar, is too high. Blood glucose is your main source of energy and comes from the food you eat. Insulin, a hormone made by the pancreas, helps glucose from food get into your cells to be used for energy. Sometimes your body doesn't make enough—or any—insulin or doesn't use insulin well. Glucose then stays in your blood and doesn't reach your cells.

Over time, having too much glucose in your blood can cause health problems. Although diabetes has no cure, you can take steps to manage your diabetes and stay healthy.

Sometimes people call diabetes "a touch of sugar" or "borderline diabetes." These terms suggest that someone doesn't really have diabetes or has a less serious case, but every case of diabetes is serious.

Diabetes affects just about everyone, from the over 110 million Americans with or at risk for the disease to the many more people who care for them.

What are the different types of diabetes?

The most common types of diabetes are type 1, type 2, and gestational diabetes.

Type 1 diabetes

If you have type 1 diabetes, your body does not make insulin. Your immune system attacks and destroys the cells in your pancreas that make insulin. Type 1 diabetes is usually diagnosed in children and young adults, although it can appear at any age. People with type 1 diabetes need to take insulin every day to stay alive.

Type 2 diabetes

If you have type 2 diabetes, your body does not make or use insulin well. You can develop type 2 diabetes at any age, even during childhood. However, this type of diabetes occurs most often in middle-aged and older people. Type 2 is the most common type of diabetes.

Gestational diabetes

Gestational diabetes develops in some women when they are pregnant. Most of the time,

this type of diabetes goes away after the baby is born. However, if you've had gestational diabetes, you have a greater chance of developing type 2 diabetes later in life. Sometimes diabetes diagnosed during pregnancy is actually type 2 diabetes.

Other types of diabetes

Less common types include monogenic diabetes, which is an inherited form of diabetes, and cystic fibrosis-related diabetes.

How common is diabetes?

As of 2015, 30.3 million people in the United States, or 9.4 percent of the population, had diabetes. More than 1 in 4 of them didn't know they had the disease. Diabetes affects 1 in 4 people over the age of 65. About 90-95 percent of cases in adults are type 2 diabetes.[1]

Who is more likely to develop type 2 diabetes?

You are more likely to develop type 2 diabetes if you are age 45 or older, have a family history of diabetes, or are overweight. Physical inactivity, race, and certain health problems such as high blood pressure also affect your chance of developing type 2 diabetes. You are also more likely to develop type 2 diabetes if you have prediabetes or had gestational diabetes when you were pregnant. Learn more about risk factors for type 2 diabetes.

What health problems can people with diabetes develop?

Over time, high blood glucose leads to problems such as

- heart disease
- stroke
- kidney disease
- eye problems
- dental disease
- nerve damage
- foot problems

You can take steps to lower your chances of developing these diabetes-related health

problems.

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December 2016

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Contact Us

The National Institute of Diabetes and Digestive and Kidney Diseases
Health Information Center

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TTY: 1-866-569-1162
Hours: 8:30 a.m. to 5 p.m. eastern time, M-F

EXHIBIT 116

Back to **Statistics**

Statistics About Diabetes

Overall numbers

- **Prevalence**: In 2018, 34.2 million Americans, or 10.5% of the population, had diabetes.
  - Nearly 1.6 million Americans have type 1 diabetes, including about 187,000 children and adolescents
- **Undiagnosed**: Of the 34.2 million adults with diabetes, 26.8 million were diagnosed, and 7.3 million were undiagnosed.
- **Prevalence in seniors**: The percentage of Americans age 65 and older remains high, at

26.8%, or 14.3 million seniors (diagnosed and undiagnosed).

- **New cases**: 1.5 million Americans are diagnosed with diabetes every year.
- **Prediabetes**: In 2015, 88 million Americans age 18 and older had prediabetes.

Diabetes in youth

- About 210,000 Americans under age 20 are estimated to have diagnosed diabetes, approximately 0.25% of that population.
- In 2014—2015, the annual incidence of diagnosed diabetes in youth was estimated at 18,200 with type 1 diabetes, 5,800 with type 2 diabetes.

Diabetes by race/ethnicity

The rates of diagnosed diabetes in adults by race/ethnic background are:

- 7.5% of non-Hispanic whites
- 9.2% of Asian Americans
- 12.5% of Hispanics

- 11.7% of non-Hispanic blacks
- 14.7% of American Indians/Alaskan Natives

The breakdown among Asian Americans:

- 5.6% of Chinese
- 10.4% of Filipinos
- 12.6% of Asian Indians
- 9.9% of other Asian Americans

The breakdown among Hispanic adults:

- 8.3% of Central and South Americans
- 6.5% of Cubans
- 14.4% of Mexican Americans
- 12.4% of Puerto Ricans

Deaths

Diabetes was the seventh leading cause of death in the United States in 2017 based on the 83,564 death certificates in which diabetes was listed as the underlying cause of death. In 2017, diabetes was mentioned as a cause of death in a total of 270,702 certificates.

Diabetes may be underreported as a cause of death. Studies have found that only about 35% to 40% of people with diabetes who died had diabetes listed anywhere on

the death certificate and about 10% to 15% had it listed as the underlying cause of death.

Cost of diabetes

Updated March 22, 2018

$327 billion: Total cost of diagnosed diabetes in the United States in 2017

$237 billion was for direct medical costs

$90 billion was in reduced productivity

After adjusting for population age and sex differences, average medical expenditures among people with diagnosed diabetes were 2.3 times higher than what expenditures would be in the absence of diabetes.

Read more about the results of our study "*Economic Costs of Diabetes in the U.S. in 2017*."

For additional information

For additional information, read the *CDC National Diabetes Statistics Report, 2020*.

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EXHIBIT 117

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Prevalence of Type 1 and Type 2 Diabetes Among Children and Adolescents From 2001 to 2009

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Role of the Sponsors: The sponsors were voting members of the steering committee, had full access to the data, but had no role in the data analysis. Authors who were employed by the sponsor (Drs Saydah and Imperatore, CDC, and Linder, NIDDK) reviewed and approved the manuscript, and participated in the decision to submit the manuscript for publication.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention and the National Institute of Diabetes and Digestive and Kidney Diseases.

Previous Presentation: These data were presented in abstract form at the American Diabetes Association 72nd Annual Scientific Sessions in Philadelphia, PA, in June, 2012.

Additional Contributions: The Writing Group thanks the many youth, their families, and their clinicians whose participation made this study possible.

Correction: This article was corrected on September 3, 2014, to clarify that the study participants were from Alberta, Canada.

Author Video Interview at jama.com

Author Contributions: Drs Dabelea and Mayer-Davis had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Dabelea, Mayer-Davis, Saydah, Imperatore, Badaru, Liese, Merchant, Lawrence, Dolan, Hamman.
Acquisition, analysis, or interpretation of data: Dabelea, Mayer-Davis, Saydah, Linder, Divers, Bell, Talton, Crume, Liese, Merchant, Reynolds, Dolan, Liu, Hamman.
Drafting of the manuscript: Dabelea, Mayer-Davis, Badaru, Lawrence, Dolan, Liu.
Critical revision of the manuscript for important intellectual content: Mayer-Davis, Saydah, Imperatore, Linder, Divers, Bell, Talton, Crume, Liese, Merchant, Lawrence, Reynolds, Dolan, Hamman.
Statistical analysis: Dabelea, Mayer-Davis, Divers, Talton, Liese, Lawrence.
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Study supervision: Dabelea, Mayer-Davis, Saydah, Imperatore, Divers, Merchant.

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Abstract

IMPORTANCE—Despite concern about an "epidemic," there are limited data on trends in prevalence of either type 1 or type 2 diabetes across US race and ethnic groups.

OBJECTIVE—To estimate changes in the prevalence of type 1 and type 2 diabetes in US youth, by sex, age, and race/ethnicity between 2001 and 2009.

DESIGN, SETTING, AND PARTICIPANTS—Case patients were ascertained in 4 geographic areas and 1 managed health care plan. The study population was determined by the 2001 and 2009 bridged-race intercensal population estimates for geographic sites and membership counts for the health plan.

MAIN OUTCOMES AND MEASURES—Prevalence (per 1000) of physician-diagnosed type 1 diabetes in youth aged 0 through 19 years and type 2 diabetes in youth aged 10 through 19 years.

RESULTS—In 2001, 4958 of 3.3 million youth were diagnosed with type 1 diabetes for a prevalence of 1.48 per 1000 (95% CI, 1.44–1.52). In 2009, 6666 of 3.4 million youth were diagnosed with type 1 diabetes for a prevalence of 1.93 per 1000 (95% CI, 1.88–1.97). In 2009, the highest prevalence of type 1 diabetes was 2.55 per 1000 among white youth (95% CI, 2.48–2.62) and the lowest was 0.35 per 1000 in American Indian youth (95% CI, 0.26–0.47) and type 1 diabetes increased between 2001 and 2009 in all sex, age, and race/ethnic subgroups except for those with the lowest prevalence (age 0–4 years and American Indians). Adjusted for completeness of ascertainment, there was a 21.1% (95% CI, 15.6%–27.0%) increase in type 1 diabetes over 8 years. In 2001, 588 of 1.7 million youth were diagnosed with type 2 diabetes for a prevalence of 0.34 per 1000 (95% CI, 0.31–0.37). In 2009, 819 of 1.8 million were diagnosed with type 2 diabetes for a prevalence of 0.46 per 1000 (95% CI, 0.43–0.49). In 2009, the prevalence of type 2 diabetes was 1.20 per 1000 among American Indian youth (95% CI, 0.96–1.51); 1.06 per 1000 among black youth (95% CI, 0.93–1.22); 0.79 per 1000 among Hispanic youth (95% CI, 0.70–0.88); and 0.17 per 1000 among white youth (95% CI, 0.15–0.20). Significant increases occurred between 2001 and 2009 in both sexes, all age-groups, and in white, Hispanic, and black youth, with no significant changes for Asian Pacific Islanders and American Indians. Adjusted for completeness of ascertainment, there was a 30.5% (95% CI, 17.3%–45.1%) overall increase in type 2 diabetes.

CONCLUSIONS AND RELEVANCE—Between 2001 and 2009 in 5 areas of the United States, the prevalence of both type 1 and type 2 diabetes among children and adolescents increased. Further studies are required to determine the causes of these increases.

Information on recent trends in the prevalence of type 1 and type 2 diabetes in the United States is limited. Imperatore et al[1] reported that the predicted increase in the number of

youth living with type 1 and type 2 diabetes by the year 2050 would be primarily among youth of minority race/ethnic groups. Worldwide, from 1990 to 2008, the incidence of type 1 diabetes has been increasing by 2.8% to 4.0% per year,[2] similar to that observed in the United States[3] for both non-Hispanic white (hereafter called white) and Hispanic youth. However, a recent report from Finland, with the world's highest incidence, suggested a possible leveling off of the increase from 2005–2011.[4] Due to the very low mortality among youth with type 1 diabetes in the United States,[5] an increase in the incidence of type 1 diabetes will likely result in an increase in prevalence.

Type 2 diabetes is increasingly diagnosed in youth and now accounts for 20% to 50% of new-onset diabetes case patients,[6] disproportionately affecting minority race/ethnic groups.[7–9] Although few longitudinal studies have been conducted, it has been suggested that the increase in type 2 diabetes in youth is a result of an increase in the frequency of obesity in pediatric populations.[10] Obesity in youth has been increasing since the 1960s though recent data suggest a plateau.[11]

There are a limited number of population-based studies of youth-onset type 2 diabetes. Most have involved American Indians and Native Canadians and showed high prevalence.[7,12,13] Similarly, type 2 diabetes incidence rates rose among non-Hispanic black (hereafter called black), Hispanic, and white children with insulin-treated, non–type 1 diabetes from 1994 to 2003.[14]

We explored whether overall prevalence of type 1 and type 2 diabetes among US youth changed from 2001[15] to 2009[13] and whether it changed by sex, age, and race/ethnicity. Understanding changes in prevalence according to population subgroups is important to inform clinicians about care that will be needed for the pediatric population living with diabetes and may provide direction for other studies designed to determine the causes of the observed changes.

Methods

A SEARCH description has been published[16] as have previous prevalence[13,15] and incidence results.[17] We report herein on changes in prevalence estimates between 2001 and 2009, the only years in which prevalence was assessed. Methods of case ascertainment and prevalence estimation were the same in the 2 periods, including a 22-month window of ascertainment. Data were collected from 5 centers located in California (Kaiser Permanente Southern California, excluding San Diego [7 counties]), Colorado [14 counties, including Denver], Ohio [8 counties, including Cincinnati], South Carolina [4 counties, including Columbia], and Washington state [5 counties, including Seattle])[15] as well as data from selected American Indian reservations in Arizona and New Mexico. The study was approved by the institutional review board (IRB) at each center. Because we attempted to identify 100% of case patients, identification was conducted with an approved Health Insurance Portability and Accountability Act waiver of consent. Active surveillance used networks of pediatric and adult endocrinologists and other clinicians, hospitals, and health plans in the study areas. Case patients identified by *International Classification of Diseases, Ninth Revision*, were validated by verifying the diagnosis of diabetes with a physician to remove

miscoded case patients. Duplicated case patients were removed using combinations of name or initials (depending on IRB approval), date of birth, date of diagnosis, sex, and race/ethnicity. After eligibility was verified based on residence and age, the case patient was registered with the coordinating center. Diabetes type diagnosed as type 1, type 1a, or type 1b by the clinician was considered *type 1 diabetes* and diabetes diagnosed as type 2 was included as *type 2 diabetes*. All other types, including secondary forms, were excluded for this analysis (165 patients in 2001 and 191 in 2009).

Study Population

Case patients included all youth younger than 20 years who had been diagnosed with nongestational diabetes and who were prevalent in 2001 and 2009 on December 31 in 2001 and 2009 and who resided in the geographic study area or were members of the participating health plans. Active duty military personnel or those who were institutionalized were not eligible. Race/ethnicity was based on self-report or medical records and on geocoding (ie, assignment of a US Census 2010 data–derived race/ethnicity proportion) for the youth who had missing data (4.2% in 2001 and 2.6% in 2009). We report type 2 diabetes prevalence only for those aged 10 through 19 years because there were not enough children younger than 10 years to establish stable rates (5 in 2001; 19 in 2009).

The study population included youth younger than 20 years residing in the geographic study areas or who were members of participating health plans in 2001 and 2009. For the geographically based sites, the population was defined by the 2001 and 2009 bridged-race intercensal population estimates.[18] For California, addresses were geocoded to the census-block level and the race/ethnic–specific proportions were applied to estimate the racial and ethnic composition of youth by age and sex. Patients of the Indian Health Service for the preceding 3 years determined the American Indian study population. Estimates were then pooled across all 5 sites. Race/ethnic categories included: Hispanic, white, black, Asian Pacific Islanders, and American Indians and were determined by first identifying any residents of Hispanic ethnicity and then by applying race-bridging methods[18] to multiracial youth to ascertain the probability of belonging to each of the 4 other racial groups. The study population of those aged 17 through 19 years had counts of active duty military personal removed.

Data Collection

Demographic information, date of diagnosis, and diabetes type were obtained from medical records. We validated clinician diagnoses of diabetes type through an etiologic assessment of diabetes type, defined as presence of at least 1 diabetes autoantibody (glutamic acid decarboxylase or insulinoma associated antibody) using harmonized assays[19] for type 1 diabetes and in the absence of diabetes autoantibodies and in the presence of insulin resistance based on a clamp validated index[20] for type 2 diabetes. This information came from an in-person research visit available on youth who had provided written informed consent or assent. Because no visits were made to patients at the time of diagnosis in the years 2001 and 2009, data from the 2 closest incident years (2002, 2008) were used. Patients with diabetes onset in 2002 or 2008 were identified using the same methods as those in 2001 and 2009. To assess generalizability, selected demographic characteristics of the SEARCH

study population were compared with the US population using US Census 2000 and 2010 summary files.

Statistical Analyses

Prevalence was expressed as cases of type 1 or 2 diabetes per 1000 youth pooled across all sites with 95% CIs. Statistical tests for trends used a 2-sided skew-corrected inverted score test assuming a binomial distribution.[21] Assuming a significance level of 5%, we had more than 90% power to detect a change in prevalence of 0.07 per 1000 youth for the overall population and of 0.12 per 1000 youth for subgroup analyses. To assess trends over time it is important to determine whether case patients were identified with the same completeness of ascertainment in both years. This was estimated for the 4 geographic-based sites using the capture-recapture method.[22] For each center, case patients were identified from multiple sources (from 13 to 41). A source was defined as any location from which case patients were reported. Matching across sources to identify potential duplicate records was performed at the center level using personal health identifiers. Once matching was accomplished, the sources were further grouped into 2 modes of ascertainment (clinicians and inpatient hospital system records). Using the number of duplicate and case patients unique to one or the other source allowed calculation of the total estimated case patients in the geographic region.[22] The percentage completeness of ascertainment for each site was taken as the number of observed case patients divided by the total estimated number from the capture-recapture method. Pooled estimates used a global logarithmic-linear model and maximum likelihood analysis[23] using SAS version 9.3 (SAS Institute Inc). The 95% CIs computed for the capture-recapture adjusted prevalence estimates account for the variation in the estimates. Approximately 20% of the study population was ascertained in membership-based sites where it was impossible to assess completeness of ascertainment using capture-recapture analyses due to the lack of independent sources of case patient ascertainment.

Results

Type 1 Diabetes

In 2001, 4958 patients with type 1 diabetes were identified from a population of 3 345 783; the respective case patients and population were 6666 and 3 458 974 in 2009 (Table 1). Prevalence was 1.48 per 1000 (95% CI, 1.44–1.52) in 2001 and 1.93 per 1000 (95% CI, 1.88–1.97) in 2009, representing an increase of 30.0% (95% CI, 25.4%–34.9%) over the 8-year period. Statistically significant increases were observed within each age, race/ethnic, and sex subgroup evaluated except for youth age 0 through 4 years and American Indians, which were the 2 population subgroups with the lowest prevalence of type 1 diabetes in 2001 and 2009. The greatest prevalence increase was observed in those aged 15 through 19 years.

Type 2 Diabetes

Table 2 shows the prevalence of type 2 diabetes for 2001 and 2009 among youth aged 10 to 19 years. In 2001, 588 of 1 725 846 and in 2009, 819 of 1 781 260 had type 2 diabetes. The overall prevalence was 0.34 per 1000 (95% CI, 0.31–0.37) in 2001 and 0.46 per 1000 (95% CI, 0.43–0.49) in 2009, representing a relative increase of 35% (95% CI, 21.4%–50.0%). A

statistically significant increase was seen in both sexes, in those aged 10 through 14 years and 15 through 19 years, and in white, black, and Hispanic youth. No significant changes were seen in Asian Pacific Islander or American Indian youth. The prevalence of type 2 diabetes was higher in both periods among those aged 15 through 19 years than among those aged 10 through 14 years and higher among females than among males; larger absolute increases were seen in these groups over time ($P < .001$, Table 2).

Completeness of Case Ascertainment

The overall completeness for type 1 diabetes was estimated to be 92.5% (95% CI, 91.8%–93.3%) in 2001 and 99.3% (95% CI, 99.2%–99.5%) in 2009. For type 2 diabetes it was estimated to be 92.9% (95% CI, 90.6%–95.2%) in 2001 and 96.1% (95% CI, 94.6%–97.6%) in 2009 (Table 3). After adjustment for completeness of ascertainment, type 1 diabetes prevalence for 2001 was 1.60 per 1000 (95% CI, 1.54–1.67) and for 2009 was 1.94 per 1000 (95% CI, 1.89–2.00), representing an adjusted increase of 21.1% (95% CI, 15.6%–27.0%). After adjustment for completeness of ascertainment, type 2 diabetes prevalence for 2001 was 0.37 per 1000 (95% CI, 0.34–0.40) and in 2009 it was 0.48 per 1000 (95% CI, 0.45–0.51), representing an adjusted increase of 30.5% (95% CI, 17.3%–45.1%).

Etiologic Criteria

We also explored whether similar proportions of case patients diagnosed by clinicians with type 1 or type 2 diabetes in the 2 years met etiologic criteria for diabetes type.[20] Among those with type 1 diabetes, 84.2% had positive antibodies in 2002 and 85.7%, in 2008 ($P = .50$; Table 4). Among those with type 2 diabetes, 82.1% in 2001 and 88.7% in 2009 ($P = .23$) met the etiologic criteria. Similar small differences by age group and by race/ethnicity did not reach statistical significance, except for white youth with type 2 diabetes: 55.6% in 2002 and 90.9% in 2008 met etiologic criteria ($P = .01$). Except for this subgroup, trends in the accuracy of diagnosis of diabetes type were stable over time.

Representativeness of the SEARCH Population

Table 5 shows that for race/ethnicity, age, parental educational attainment, and median household income, the proportional distribution for 2001 and 2009 was very similar to the US census for 2000 and 2010. Thus, we were satisfied that the study areas reasonably represented the US population.

Discussion

Type 1 Diabetes

Over the 8-year period, the adjusted prevalence of type 1 diabetes increased 21.1% (95% CI, 15.6%–27.0%) among US youth. Increases were observed in both sexes; in white, black, Hispanic, and Asian Pacific Islander youth; and in those aged 5 years or older. Historically, type 1 diabetes has been considered a disease that affects primarily white youth; however, our findings highlight the increasing burden of type 1 diabetes experienced by youth of minority racial/ethnic groups as well.

Increases in the prevalence of type 1 diabetes could reflect increases in disease incidence, decreases in mortality, or both. Mortality due to diabetes in youth is low (1.05 per million for aged ≤19 years in 2008–2009[5]); therefore, an increase in type 1 diabetes incidence is the most likely primary explanation. Increases in the incidence of type 1 diabetes have been observed around the world,[24] and more recently, increases among white, Hispanic, and black youth in the United States have been reported.[3,25] A doubling of incidence rates from 1978 to 2007 was reported in Sweden,[26] although declining cumulative incidence was observed in the 2000–2006 birth cohorts. Similarly, a Finnish report showed that even though the incidence increased from 1989 to 2005, no further increase in incidence of type 1 diabetes occurred between 2005 and 2011.[4]

Through the year 2000, published prevalence estimates from around the world ranged from 0.03 to 1.83 per 1000,[27,28] whereas after 2000, estimated prevalence ranged from 0.06 to 4.8 per 1000[15,29,30] compared with our estimate of 1.93 per 1000 in 2009. Overall prevalence of type 1 diabetes was 1.58 per 1000 in Philadelphia schools, somewhat lower than our estimates, and race/ethnic specific differences were all lower than what we found: 0.73 per 1000 among white, 0.56 among black, and 0.50 among Hispanic youth.[29] These estimates are difficult to compare because of differences in ascertainment methods, race/ethnicity, and age composition of the populations across studies. Few studies have projected changes in prevalence of type 1 diabetes among contemporary youth. Based on SEARCH data, Imperatore et al[1] modeled the number of youth who would have type 1 diabetes in 2010 and 2050, which was estimated to nearly triple, from 179 387 in 2010 to 587 477 in 2050, due to large increases in the numbers of minority race/ ethnic groups. The increase in prevalence among US minorities documented herein is of concern, given that minority youth are more likely to have poor glycemic control,[31] known to be associated with the serious complications of type 1 diabetes.

Type 2 Diabetes

We also report, to our knowledge, the only multiethnic data on changes in the prevalence of type 2 diabetes in youth. The prevalence of type 2 diabetes in 2009 among adolescents aged 10 through 19 years was 0.46 per 1000 or 0.046%, with highest prevalence in American Indians, followed by black, Hispanic, and Asian Pacific Islander youth, with lowest prevalence in white youth, a pattern that is almost the inverse of that seen in type 1 diabetes. Prevalence was somewhat lower than reported in fifth- to 12th-grade students in Ohio (0.08%, previously diagnosed type 2 diabetes),[32] although a higher proportion of black students were included in that study. It was also lower than the screening results in the Studies to Treat or Prevent Pediatric Type 2 Diabetes[33] (STOPP-T2D) involving eighth-grade students, which documented a 0.5% prevalence of elevated screening glucose levels; however, only a single screening test was used. Compared with our estimate of 0.46 per 1000, the reported prevalence among sixth graders in the HEALTHY study (0.2 per 1000)[34] was lower, as was prevalence among students in the Philadelphia schools (0.35 per 1000 overall[29]), which also reported substantially lower race/ethnicity specific estimates (0.03 per 1000 white; 0.28 per 1000 black; and 0.05 per 1000 Hispanic youth).

We showed that the overall prevalence of type 2 diabetes between 2001 and 2009 increased by 30.5% when adjusted for differences in completeness of ascertainment. Increases occurred in white, Hispanic, and black youth, whereas no changes were found in Asian Pacific Islander and American Indian youth. Projections suggest that the number of youth with type 2 diabetes will increase from 22 820 in 2010 to 84 131 in 2050, a 4-fold increase.[1] Our data also suggest that there was little change in the pattern of diagnosis of diabetes type that clinicians used over this period, with the exception of white youth. We can only speculate about whether changes in the awareness of type 2 diabetes in youth over time may have accounted for this change. Because a lower proportion of white youth met the etiologic criteria in the first period, the rates for 2001 may have been overestimated, and therefore we may have underestimated the increase in type 2 diabetes among white youth.

There are limited population-based data on temporal trends of type 2 diabetes in youth. In Cincinnati, Ohio, type 2 diabetes incidence increased 10-fold, from 1982 to 1994 (average annual change, 41.7%).[35] Annual incidence rates from 1994 to 2003 increased by 3.7% among white, 3.9% among black, and 9.6% among Hispanic children with insulin-treated, non–type 1 diabetes in Chicago[14]; however, these case patients represent an unknown proportion of all case patients. Among aboriginal youth in Alberta, Canada,[12] a 14% average annual increase was reported in Chicago between 1995 and 2007 in youth younger than 20 years. Dabelea et al[7] showed an increase in prevalence of type 2 diabetes in Pima Indian youth aged 10 through 19 years in both sexes, with the highest prevalence in females. In Pima, the estimated average annual increase ranged from 1.9% to 10%, whereas we estimated the average annual increase at 4.4% overall, similar to that seen among the Pima Indians.

Studies in Europe[36,37] indicate that type 2 diabetes remains rare in largely white populations, and 1 report showed no trend[38]; however, we observed a significant prevalence increase in white youth. Although differences in obesity rates between US and European youth are likely contributors, the full explanation for these discrepancies deserves further study.

Several reasons for the increasing type 2 diabetes prevalence are possible. Most likely are real changes in population risk for type 2 diabetes, such as minority population growth, obesity, exposure to diabetes in utero,[39] and perhaps endocrine-disrupting chemicals.[40] Similarly, changing awareness of type 2 diabetes in youth leading to different diagnostic practices may have contributed to the increases.

Our study has limitations and strengths. We only included youth with diagnosed diabetes, which will miss youth who may meet diagnostic criteria for type 2 diabetes if screened, although this is much less of a limitation for youth with type 1 diabetes. However, the number of undiagnosed cases of type 2 diabetes is likely to be small.[32,34] We only included 2 years of data and rates may vary from year to year. Also, the last year of data was 2009, 5 years ago, so we are not able to comment on whether current prevalence has changed. There were relatively small numbers of youth in some groups by race/ethnicity (especially American Indian and Asian Pacific Islanders) making these estimates of changes in prevalence less precise. Our observation period was relatively short and further surveillance

will produce better estimates of changes. Strengths of the study include large numbers of youth identified using consistent methods from 2 periods; the population-based nature of the study; the racial/ethnic composition of the populations, which was similar in distribution to the United States; and the ability to show that our findings were not overly influenced by changes in case ascertainment or in clinician's diagnostic patterns of diabetes type.

The increases in prevalence reported herein are important because such youth with diabetes will enter adulthood with several years of disease duration, difficulty in treatment,[41] an increased risk of early complications, and increased frequency of diabetes during reproductive years, which may further increase diabetes in the next generation.[7]

Conclusions

Between 2001 and 2009 in 5 areas of the United States, there was an increase in the prevalence of both type 1 and type 2 diabetes among children and adolescents. Further studies are required to determine the causes of these increases.

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Table 1

Prevalence of Type 1 Diabetes by Demographic Characteristics

	2001 Population			2009 Population				
	No. of Youth		Prevalence per 1000 (95% CI)	No. of Youth		Prevalence per 1000 (95% CI)	Difference in Prevalence (95% CI)	*P* Value
	Cases With Diabetes	General Population		Cases With Diabetes	General Population			
Total[a]	4958	3 345 783	1.48 (1.44 to 1.52)	6666	3 458 974	1.93 (1.88 to 1.97)	0.45 (0.41 to 0.48)	<.001
Sex								
Females	2420	1 635 589	1.48 (1.42 to 1.54)	3263	1 692 112	1.93 (1.86 to 2.00)	0.45 (0.40 to 0.49)	<.001
Males	2538	1 710 194	1.48 (1.43 to 1.54)	3403	1 766 862	1.93 (1.86 to 1.99)	0.44 (0.40 to 0.49)	<.001
Age, y[b]								
0-≤4	217	787 251	0.28 (0.24 to 0.31)	241	832 791	0.29 (0.26 to 0.33)	0.01 (−0.01 to 0.04)	.30
5-≤9	977	832 686	1.17 (1.10 to 1.25)	1143	844 923	1.35 (1.28 to 1.43)	0.18 (0.13 to 0.23)	<.001
10-≤14	1727	885 604	1.95 (1.86 to 2.04)	2335	867 403	2.69 (2.59 to 2.80)	0.74 (0.67 to 0.81)	<.001
15-≤19	2037	840 242	2.42 (2.32 to 2.53)	2947	913 857	3.22 (3.11 to 3.34)	0.80 (0.72 to 0.88)	<.001
Race/ethnicity								
White	3718	1 996 971	1.86 (1.80 to 1.92)	4804	1 885 451	2.55 (2.48 to 2.62)	0.69 (0.64 to 0.73)	<.001
Black	471	365 146	1.29 (1.18 to 1.41)	621	383 198	1.62 (1.50 to 1.75)	0.33 (0.25 to 0.42)	<.001
Hispanic	625	647 656	0.96 (0.89 to 1.04)	1042	809 267	1.29 (1.21 to 1.37)	0.32 (0.27 to 0.38)	<.001
Asian Pacific Islander	107	212 708	0.50 (0.42 to 0.61)	156	260 846	0.60 (0.51 to 0.70)	0.09 (0.03 to 0.16)	.006
American Indian	37	123 303	0.30 (0.22 to 0.42)	42	120 212	0.35 (0.26 to 0.47)	0.05 (−0.03 to 0.12)	.19

[a] Differences in the number of youth reported with type 1 diabetes in 2001[15] and in this report are due to exclusion of 1 prior study site in both years (Hawaii) and continued data cleaning.

[b] Age on December 23, 2001, and December 31, 2009.

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Table 2

Prevalence of Type 2 Diabetes per 1000 by Demographic Characteristics

	2001 Population			2009 Population				
	No. of Youth			No. of Youth				
	Cases With Diabetes	General Population	Prevalence per 1000 (95% CI)	Cases With Diabetes	General Population	Prevalence per 1000 (95% CI)	Difference in Prevalence (95% CI)	*P* Value
Total[a]	588	1 725 846	0.34 (0.31 to 0.37)	819	1 781 260	0.46 (0.43 to 0.49)	0.12 (0.10 to 0.14)	<.001
Sex								
Females	356	843 168	0.42 (0.38 to 0.47)	505	871 465	0.58 (0.53 to 0.63)	0.16 (0.12 to 0.19)	<.001
Males	232	882 678	0.26 (0.23 to 0.30)	314	909 to 795	0.35 (0.31 to 0.39)	0.08 (0.06 to 0.11)	<.001
Age, y[b]								
10-≤14	136	885 604	0.15 (0.13 to 0.18)	198	867 403	0.23 (0.20 to 0.26)	0.07 (0.05 to 0.09)	<.001
15-≤19	452	840 242	0.54 (0.49 to 0.59)	621	913 857	0.68 (0.63 to 0.74)	0.14 (0.10 to 0.18)	<.001
Race/ethnicity								
White	150	1 046 084	0.14 (0.12 to 0.17)	172	985 818	0.17 (0.15 to 0.20)	0.03 (0.01 to 0.05)	<.001
Black	177	186 637	0.95 (0.82 to 1.10)	209	196 723	1.06 (0.93 to 1.22)	0.12 (0.02 to 0.22)	.02
Hispanic	144	318 238	0.45 (0.39 to 0.53)	317	402 691	0.79 (0.70 to 0.88)	0.33 (0.27 to 0.39)	<.001
Asian Pacific Islander	39	110 560	0.35 (0.26 to 0.48)	46	133 455	0.34 (0.26 to 0.46)	−0.01 (−0.09 to 0.06)	.73
American Indian	78	64 327	1.22 (0.98 to 1.52)	75	62 573	1.20 (0.96 to 1.51)	−0.01 (−0.21 to 0.17)	.83

[a] Differences in the number of youth reported with type 2 diabetes in 2001[15] and in this report are due to exclusion of 1 prior study site in both years (Hawaii) and continued data cleaning. Differences from 2009 previously published[13] are due to exclusion of youth 10 y or younger at onset and continued data cleaning.

[b] Age on December 23, 2001, and December 31, 2009.

Table 3

Estimated Completeness of Case Ascertainment for Youth With Diabetes Using Capture-Recapture for 4 Geographic Sites Combined, by Year, Age Group, Sex, and Race/Ethnicity

	% Completeness (95% CI)	
Diabetes	**2001**	**2009**
Overall		
Type 1	92.5 (91.8–93.3)	99.3 (99.2–99.5)
Type 2	92.9 (90.6–95.2)	96.1 (94.6–97.6)
Age, y		
Type 1		
0-≤4	93.7 (92.9–94.6)	99.6 (99.6–99.7)
5-≤9	93 (92.5–93.4)	99.5 (99.5–99.6)
10-≤14		
Type 1	93.2 (92.8–93.5)	99.4 (99.4–99.4)
Type 2	96 (95.2–96.8)	96.8 (96.4–97.2)
15-≤19		
Type 1	91.7 (91.3–92)	96.5 (96.2–96.8)
Type 2	91.7 (90.9–92.6)	94.6 (93.8–95.5)
Sex		
Female		
Type 1	93.1 (92.8–93.3)	99.4 (99.3–99.4)
Type 2	94 (93.3–94.7)	96.8 (96.4–97.1)
Male		
Type 1	92 (91.7–92.3)	99.3 (99.3–99.3)
Type 2	90.8 (89.4–92.2)	94.3 (93.4–95.3)
Race/ethnicity		
White		
Type 1	93.1 (92.8–93.3)	99.4 (99.4–99.4)
Type 2	92.2 (91–93.4)	97 (96.5–97.5)
Black		
Type 1	96.6 (96.3–97)	99.7 (99.7–99.8)
Type 2	96.5 (95.9–97)	98.8 (98.5–99)
Hispanic		
Type 1	91.9 (90.9–92.8)	98.9 (98.8–99)
Type 2	82.8 (77.8–87.7)	90 (88–92)
Other[a]		
Type 1	85.8 (83.8–87.9)	99.2 (99–99.3)
Type 2	91 (87.7–94.4)	94.4 (92.5–96.3)

[a]Other includes Asian/Pacific Islanders, American Indian, and other race/ethnicity.

Table 4

Proportion of Incident Cases Meeting Etiological Criteria in the 2 Time Periods (2002 and 2008) Closest to the Prevalence Years, Overall and by Demographic Subgroups[a]

	Clinical Diabetes Type 1			Clinical Diabetes Type 2		
	2002, No. (%)	2008, No. (%)[b]	*P* Value	2002, No. (%)	2008, No. (%)	*P* Value
Age, y						
0-≤4	23 (92.0)	68 (82.9)	.27			
5-≤9	113 (89.0)	192 (87.7)	.72			
10-≤14	138 (80.2)	204 (84.6)	.24	22 (81.5)	34 (89.5)	.36
15-≤19	67 (82.7)	100 (86.2)	.50	33 (82.5)	52 (88.1)	.43
10-≤19				55 (82.1)	86 (88.7)	.23
0-≤19	341 (84.2)	564 (85.7)	.50			
Race/ethnicity						
White	267 (84.5)	413 (88.1)	.15	10 (55.6)	20 (90.9)	.01
Black	34 (86.5)	86 (75.8)	.19	16 (91.3)	26 (90.6)	.93
Hispanic	32 (87.2)	50 (79.6)	.30	21 (94.1)	29 (83.9)	.30
Asian Pacific Islander	7 (87.5)	11 (100.0)	.23	1 (100.0)	1 (100.0)	NA
American Indian	1 (33.3)	1 (100.0)	NA	7 (87.5)	10 (90.9)	.81
Sex						
Female	157 (84.4)	266 (86.9)	.44	36 (90.0)	53 (93.0)	.60
Male	184 (84.0)	298 (84.7)	.84	19 (70.4)	33 (82.5)	.24

[a] Etiological criteria for type 1 diabetes: presence of 1 or more diabetes autoantibodies (glutamic acid decarboxylase or insulinoma associated antibody); and for type 2 diabetes: no evidence of diabetes autoimmunity and presence of insulin resistance.[20]

[b] Three case patients missing race/ethnicity not shown.

Table 5

Comparison of the Demographics of the Populations Under Surveillance (2001 and 2009) With the US Census (2000 and 2010)

	No. (%)			
	US Census 2000	SEARCH 2001 Prevalence Population[a]	US Census 2010	SEARCH 2009 Prevalence Population[b]
Race/ethnicity[c]				
White	194 552 774 (69.1)	7 638 429 (64.9)	196 817 552 (63.8)	7 689 947 (61.0)
Black	33 947 837 (12.1)	977 677 (8.3)	37 685 848 (12.2)	1 051 643 (8.3)
Hispanic	35 305 818 (12.6)	1 916 968 (16.3)	50 477 594 (16.4)	2 340 785 (18.6)
American Indian	2 068 883 (0.7)	248 343 (2.1)	2 247 098 (0.7)	238 507 (1.9)
Asian Pacific Islander	10 476 678 (3.7)	701 027 (6.0)	14 946 700 (4.8)	934 989 (7.4)
Non-Hispanic: some other race	467 770 (0.2)	20 885 (0.2)	604 265 (0.2)	23 256 (0.2)
Non-Hispanic: ≥2 races	4 602 146 (1.6)	263 063 (2.2)	5 966 481 (1.9)	336 406 (2.7)
Age, y[c]				
0-≤4	19 175 798 (6.8)	837 430 (7.1)	20 201 362 (6.5)	852 042 (5.3)
5-≤9	20 549 505 (7.3)	895 283 (7.6)	20 348 657 (6.6)	847 743 (5.3)
10-≤14	20 528 072 (7.3)	880 014 (7.5)	20 677 194 (6.7)	849 263 (5.3)
15-≤19	20 219 890 (7.2)	842 557 (7.2)	22 040 343 (7.1)	891 970 (5.6)
Education, for adults ≥25 y[d]				
<High school graduate	(19.6)	(16.9)	(14.9)	(13.0)
High school graduate	(28.6)	(23.6)	(29.0)	(23.9)
Some college	(27.4)	(30.2)	(28.1)	(29.7)
≥Bachelor's degree	(24.4)	(29.3)	(27.9)	(33.4)
Median household income, US $[d]	41 994	43 649	51 914	60 129

[a] Data are from 2000, but the prevalence areas were defined by SEARCH in 2001.

[b] Data are from 2010, but the prevalence areas were defined by SEARCH in 2009.

[c] Data are from Summary File 1 from the 2000 and 2010 Census.

[d] Data are from Summary File 3 from the 2000 Census and data are based on 5-y estimates from 2010 American Community Survey. SEARCH prevalence population numbers do not include American Indian subsite information for Education and Income.

EXHIBIT 118

Economic Costs of Diabetes in the U.S. in 2017

American Diabetes Association

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OBJECTIVE

This study updates previous estimates of the economic burden of diagnosed diabetes and quantifies the increased health resource use and lost productivity associated with diabetes in 2017.

RESEARCH DESIGN AND METHODS

We use a prevalence-based approach that combines the demographics of the U.S. population in 2017 with diabetes prevalence, epidemiological data, health care cost, and economic data into a Cost of Diabetes Model. Health resource use and associated medical costs are analyzed by age, sex, race/ethnicity, insurance coverage, medical condition, and health service category. Data sources include national surveys, Medicare standard analytical files, and one of the largest claims databases for the commercially insured population in the U.S.

RESULTS

The total estimated cost of diagnosed diabetes in 2017 is $327 billion, including $237 billion in direct medical costs and $90 billion in reduced productivity. For the cost categories analyzed, care for people with diagnosed diabetes accounts for 1 in 4 health care dollars in the U.S., and more than half of that expenditure is directly attributable to diabetes. People with diagnosed diabetes incur average medical expenditures of ~$16,750 per year, of which ~$9,600 is attributed to diabetes. People with diagnosed diabetes, on average, have medical expenditures ~2.3 times higher than what expenditures would be in the absence of diabetes. Indirect costs include increased absenteeism ($3.3 billion) and reduced productivity while at work ($26.9 billion) for the employed population, reduced productivity for those not in the labor force ($2.3 billion), inability to work because of disease-related disability ($37.5 billion), and lost productivity due to 277,000 premature deaths attributed to diabetes ($19.9 billion).

CONCLUSIONS

After adjusting for inflation, economic costs of diabetes increased by 26% from 2012 to 2017 due to the increased prevalence of diabetes and the increased cost per person with diabetes. The growth in diabetes prevalence and medical costs is primarily among the population aged 65 years and older, contributing to a growing economic cost to the Medicare program. The estimates in this article highlight the substantial financial burden that diabetes imposes on society, in addition to intangible costs from pain and suffering, resources from care provided by nonpaid caregivers, and costs associated with undiagnosed diabetes.

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See accompanying articles, pp. 929, 933, 940, 949, 956, 963, 971, 979, 985, and e72.

Diabetes imposes a substantial burden on society in the form of higher medical costs, lost productivity, premature mortality, and intangible costs in the form of reduced quality of life. The estimated economic burden associated with diagnosed diabetes in the U.S. in 2012 was $245 billion in the form of higher medical costs ($176 billion) and reduced productivity ($69 billion) (1). The population diagnosed with diabetes has continued to grow, by ~700,000 people annually between 2012 and 2015, with prevalence projected to continue rising over time as the population grows and ages (2,3). Furthermore, there continue to be changes in the demographics of the population with diabetes, health care use and delivery patterns, technology, medical costs, insurance coverage, and economic conditions that affect the economic burden associated with diabetes. This study updates previous estimates, with the goal to quantify the economic burden of diabetes at the national and state levels in 2017. Such information can help inform and motivate strategies to reduce diabetes prevalence and burden.

RESEARCH DESIGN AND METHODS

The methodology used is similar to that of previous diabetes burden studies sponsored by the American Diabetes Association (1,4), with updated data sources and modifications to refine the analyses where appropriate. Although the primary focus of this analysis is the national economic burden of disease, the national estimates are calculated by summing the state-level estimates that reflect variation across states in demographics, health risk factors and lifestyle choices, prices, and economic outcomes. (State-level estimates of diabetes prevalence and costs are provided in Supplementary Table A-16.) All cost and utilization estimates are extrapolated to the U.S. population in 2017, with cost estimates calculated in 2017 dollars using the hospital services, physician services, and prescription drug components of the medical consumer price index or total consumer price index (5).

Inputs to the study include both state-level and national-level data. Sources for state-level data include the American Community Survey (ACS), Behavioral Risk Factor Surveillance System (BRFSS), Medicare Current Beneficiary Survey (MCBS), and Long Term Care Minimum Data Set (MDS). Sources for national data (which are extrapolated to the state level) include the Current Population Survey (CPS), OptumInsight de-identified Normative Health Information (dNHI) database, Medical Expenditure Panel Survey (MEPS), National Ambulatory Medical Care Survey (NAMCS), National Hospital Ambulatory Medical Care Survey (NHAMCS), National Home and Hospice Care Survey (NHHCS), National Health Interview Survey (NHIS), National (Nationwide) Inpatient Sample (NIS), and Medicare 5% sample Standard Analytical Files (SAFs). We use the most recent year's data available for each of these data sources, though for certain analyses we combine multiple years of data to increase sample size. Supplementary Table A-1 describes how these data sources are used along with their respective strengths and limitations as pertinent to this study.

Estimating the Size of the Population With Diabetes

For each of the 50 states and the District of Columbia, we estimate the prevalence of diagnosed diabetes for 480 population strata defined by age-group (<18, 18–34, 35–44, 45–54, 55–59, 60–64, 65–69, and ≥70 years), sex, race/ethnicity (non-Hispanic white, non-Hispanic black, non-Hispanic other, and Hispanic), insurance status (commercial; government, including Medicare, Medicaid, Children's Health Insurance Program, Veterans Health Administration, and other government-sponsored coverage; and uninsured), and whether residing in the community, a residential care facility, or a nursing home. (Government employees and military personnel and dependents with insurance are counted under private insurance.) The reason for modeling the large number of strata reflects differences in diabetes prevalence and costs across these strata and that different data sources are used to estimate diabetes prevalence for people residing in the community, in a residential care facility, or in a nursing home.

The population database starts with the 2016 ACS, which contains state-level population estimates by age, sex, race/ethnicity, whether the person has medical insurance, and whether the person resides in a group setting. We use random sampling with replacement to statistically match each person in the 2016 ACS with a similar person in a file containing patient health information and risk factors. ACS individuals residing in the community are matched to a similar individual in the 2015–2016 BRFSS of the same age, sex, race/ethnicity, state, family income level, and insurance type. ACS individuals residing in residential care facilities and nursing homes are matched to a person of similar age, sex, race/ethnicity, and state from the 2015 MDS and 2013 MCBS, respectively.

Diabetes status in the MDS and MCBS is based on clinical diagnosis, whereas diabetes status in the BRFSS is based on respondents answering "yes" to the question, "Have you EVER been told by a doctor or health professional that you have diabetes or sugar diabetes?" The prevalence estimates exclude gestational diabetes mellitus. These sources do not contain diabetes status for children. Therefore, we combined the 2014–2016 NHIS files to estimate national diabetes prevalence rates for children—based on self-report (6) like the BRFSS information—which we then extrapolated to the state population files by age (6–12 and 13–17 years), sex, and race/ethnicity.

To estimate diabetes prevalence in 2017, we scaled the state estimates based on population growth between 2016 and 2017 by demographic group. For validation, when we apply prevalence rates for each strata (demographic, insurance, state) to the 2015 population, our national estimate of diagnosed diabetes is slightly higher than that reported by the Centers for Disease Control and Prevention (CDC) (23.4 million vs. 23.0 million). Our higher estimate possibly reflects that our analysis incorporates data from residential care and nursing facilities, whereas the CDC estimate is based on a representative sample of the noninstitutionalized population.

Estimating the Direct Medical Cost Attributed to Diabetes

We estimate health resource use among the population with diabetes in excess of resource use that would be expected in the absence of diabetes. Diabetes increases the risk of developing neurological, peripheral vascular, cardiovascular, renal, endocrine/metabolic, ophthalmic, and other complications (see Supplementary Appendix 2 for a more comprehensive list of medical conditions and ICD-9 and ICD-10 codes). Diabetes also increases the cost of treating general conditions that are not directly related to diabetes. Therefore, only the relevant portion of health care expenditures for these medical conditions is attributed to diabetes.

The approach used to quantify the excess health resource use associated with diabetes was influenced by four data limitations: *1*) absence of a single data source for all estimates, *2*) small sample size in some data sources, *3*) correlation of both diabetes and its comorbidities with other factors such as age and obesity, and *4*) underreporting of diabetes and its comorbidities in certain data sources such as the NIS, NAMCS, and NHAMCS. Because of these limitations, we estimate diabetes-attributed costs using one of two approaches for each cost component.

For cost components estimated solely from MEPS (ambulance services, home health, podiatry, diabetes supplies, and other equipment and supplies), we use a comparison of annual per capita health resource use for people with and without diabetes controlling for age, sex, and race/ethnicity. For nursing/residential facility use (which is not captured by MEPS) and for cost components that rely on analysis of medical encounter data (hospital inpatient, emergency care, and ambulatory visits), we employ an attributed risk methodology often used in disease burden studies that relies on population etiological fractions (7). Etiological fractions estimate the excess use of health care services among the diabetes population relative to a similar population that does not have diabetes. Both approaches used in this study are equivalent under a reasonable set of assumptions. However, the first approach cannot be used with some national data sources analyzed—e.g., visit/hospital discharge–level files such as NIS, NAMCS, and NHAMCS, which may not identify the patient as having diabetes even if the patient does indeed have diabetes.

The attributable fraction approach combines etiological fractions (ε) with total projected U.S. health service use (U) in 2017 for each age-group (a), sex (s), medical condition (c), and care delivery setting (H), which includes hospital inpatient, emergency department, and ambulatory service (physician office visits and hospital outpatient/clinic visits):

$$\text{Attributed health resource use}_H = \sum_{age}\sum_{sex}\sum_{\substack{medical\\condition}} \varepsilon_{H,a,s,c} \times U_{H,a,s,c}$$

The etiological fraction is calculated using the diagnosed diabetes prevalence (P) and the relative rate ratio (R):

$$\varepsilon_{H,a,s,c} = \frac{P_{a,s} \times (R_{H,a,s,c} - 1)}{P_{a,s} \times (R_{H,a,s,c} - 1) + 1}$$

The rate ratio for hospital inpatient days, emergency visits, and ambulatory visits represents how annual per capita health service use for the population with diabetes compares to the population without diabetes:

$$R_{H,a,s,c} = \frac{\text{annual per capita use for people with diabetes}_{a,s,c}}{\text{annual per capita use for people without diabetes}_{a,s,c}}$$

Diabetes and its comorbidities are correlated with other patient characteristics such as demographics and body weight. To mitigate bias caused by correlation, we estimate age/sex/setting–specific etiological fractions for each medical condition. The primary data sources for calculating etiological fractions are the 2015 OptumInsight dNHI data and the 2014 Medicare 5% sample SAF. The dNHI data contain a complete set of medical claims for more than 31 million commercially insured beneficiaries in 2015 and allows patient records to be linked during the year and across health delivery settings. This allows us to identify people with a diabetes ICD-9 (250.xx) or ICD-10 diagnosis code in at least one of their inpatient medical claims or in two or more separate noninpatient claims during the year. The Medicare 5% sample SAF contains claims data filed on behalf of Medicare beneficiaries under both Part A and Part B, and as with the dNHI data, we identify people with diabetes based on diabetes ICD-9 diagnosis codes. The large size of these two claims databases enables the generation of age/sex/setting–specific rate ratios for each medical condition that are more stable than the rates estimated using MEPS.

Unlike the MEPS data, the dNHI data and Medicare 5% claims data do not contain race/ethnicity and select patient characteristics that could affect both patient health status and health-seeking behaviors. For the 10 medical conditions that are the largest contributors to the overall cost of diabetes—general medical condition, other chronic ischemic heart disease, myocardial infarction, heart failure, hypertension, conduction disorders and cardiac dysrhythmias, cellulitis, occlusion of cerebral arteries, end-stage renal disease (ESRD), and renal failure and its sequelae—we estimate two multivariate Poisson regressions, using data from 2011–2015 MEPS, to determine the extent to which controlling only for age and sex might bias the rate ratios. First, we estimate a naive model that produces diabetes-related rate ratios for hospital inpatient days, emergency visits, and ambulatory visits controlling for age and sex only. Then, we estimate a full model that includes diabetes status as the main explanatory variable and various known predictors of health service utilization including age, sex, education level, income, marital status, medical insurance status, and race/ethnicity as covariates.

For the full model, our focus is not on the relationship between health care use and the covariates (other than diabetes); instead, these covariates are included to control for patient characteristics not available in medical claims data that could be correlated with both medical conditions and health-seeking behavior. The full model omits indicators for presence of coexisting conditions or complications of diabetes (e.g., hypertension), since including such variables could downward bias the estimated relationship between diabetes and health care use for each of the 10 medical conditions. The rate ratio coefficients for the diabetes flag variable in the naive and full models are then compared. The findings suggest statistically significant overestimates of the rate ratios for eight condition categories for both emergency visits and impatient days when using the naive model. For ambulatory visits, we find significant overestimates in the rate ratios for five condition categories from the MEPS-based naive model compared with the full model.

To remedy the relative risk overestimation for these condition categories, we scaled the rate ratios estimated from dNHI and Medicare 5% sample SAFs using the regression results from the MEPS analysis by applying a scalar (with the scalar calculated as the full model rate ratio divided by the naive model rate ratio). For emergency department visits, claims-based rate ratios are scaled down for other chronic ischemic heart disease (scale = 0.89), myocardial infarction (0.89), heart failure (0.86), hypertension (0.63), cellulitis (0.89), occlusion of cerebral arteries (0.94), chronic renal failure–ESRD (0.73), and renal failure and its sequelae (0.77). For inpatient days, claims-based rate ratios are scaled down for other

chronic ischemic heart disease (0.99), myocardial infarction (0.92), heart failure (0.81), hypertension (0.69), cellulitis (0.85), occlusion of cerebral arteries (0.98), chronic renal failure–ESRD (0.72), and renal failure and its sequelae (0.64). Physician office visits are scaled down for myocardial infarction (0.98), heart failure (0.76), hypertension (0.87), occlusion of cerebral arteries (0.93), and renal failure and its sequelae (0.25). We did not find a significant overestimate of the rate ratios for general medical conditions for any of the three health service delivery settings comparing the MEPS-based naive model and the full model. However, a comparison of the claims-based rate ratios with the rate ratios calculated from the MEPS-based naive model finds that the claims-based rate ratios for general conditions are significantly higher than the MEPS-based rate ratios for emergency department visits and inpatient days. Therefore, to be conservative in our cost estimates, we downward adjusted claims-based rate ratios for emergency department visits (0.52) and inpatient days (0.50) for the general condition group by applying a scalar calculated as the MEPS-based naive model rate ratio divided by the claims-based rate ratio.

Estimates of health resource use attributed to diabetes are combined with estimates of the average medical cost per unit of health care utilization, in 2017 dollars, to compute total medical costs attributed to diabetes. For hospital inpatient days, office visits, emergency visits, and outpatient visits, we use the average cost per visit/day specific to the medical conditions modeled. We pooled the 2011–2015 MEPS files to estimate average cost per unit of health care utilized. Although MEPS contains both inpatient facility and professional expenditures and NIS contains only facility charges (which are converted to costs using hospital-specific cost-to-charge ratios), the NIS has a much larger sample (n = ~7 million discharges in 2014) and also contains five-digit diagnosis codes. Therefore, we use the 2014 NIS data to estimate inpatient facility costs and use the pooled 2011–2015 MEPS files to estimate the cost for professional services. Average costs per event or day by medical condition are shown in Supplementary Table A-3.

Utilization of prescription medication (excluding insulin and other antidiabetes agents) for each medical condition is estimated from medications prescribed during physician office, emergency department, and outpatient visits attributed to diabetes. Average number of medications prescribed during a physician office visit for each age/sex/race stratum is estimated using data from the 2013–2015 NAMCS along with 2012–2014 NHAMCS for emergency department visits and 2009–2011 NHAMCS for outpatient visits. We calculate the total number of people with diabetes who use insulin and other antidiabetes agents by combining diabetes prevalence and the rate of use for these antidiabetes agents obtained from the 2013–2015 NHIS. Average cost per prescription filled, yearly average cost per insulin user, and yearly average cost per oral agent and other antidiabetes agent user are obtained from the 2013–2015 MEPS. We combined the utilization of these medications with the average cost per prescription to estimate the cost by age, sex, race/ethnicity, and insurance status. Average per capita cost for diabetes supplies by age/sex/race stratum is calculated from MEPS (excluding over-the-counter medications owing to lack of data on whether diabetes increases use of such medications).

The 2012 cost study estimated prevalence of diagnosed diabetes among the population in nursing homes by demographic using the 2004 National Nursing Home Survey (NNHS) data but scaled the diabetes prevalence estimates to be consistent with an estimated 32.8% prevalence among nursing home residents obtained from the existing literature (8). In this iteration of the study, we use the 2015 Centers for Medicare & Medicaid Services (CMS) MDS data to estimate diabetes prevalence among this population and find that the estimated prevalence of diagnosed diabetes is 25% among the nursing home population in 2017.

Nursing/residential facility use attributed to diabetes is estimated using an attributable risk approach where the prevalence of diabetes among residents is compared with the prevalence of diabetes among the overall population in the same age/sex stratum. The analysis is conducted separately for long-stay and residential facility residents to estimate total days of care. Unlike the 2012 study, due to data unavailability there is no separate analysis done for short stays at nursing/residential facilities. Similar to the previous studies, cost per day per resident is obtained from a geographically representative cost of care survey for 2017 (9).

Hospice days attributed to diabetes represent a combination of length of stay and diabetes prevalence among hospice residents. The 2007 NHHCS is used to calculate the number of hospice residents with diabetes and those that have a primary diagnosis of diabetes along with the average length of stay for each age/sex/race stratum. Based on more recent estimates available from the National Hospice and Palliative Care Organization (NHPCO) on diabetes prevalence among hospice residents (10), the 2007 NHHCS-based prevalence estimates for the various strata are adjusted and updated to impute the 2017 diabetes prevalence. Cost per hospice resident per day is based on the 2017 report from NHPCO (11) and is combined with hospice days attributed to diabetes to estimate total cost of hospice care attributed to diabetes.

The 2011–2015 MEPS files are pooled to increase sample size to analyze use of home health, podiatry, ambulance services, and other equipment and supplies. These cost components are estimated by comparing annual per capita cost for people with and without diabetes, controlling for age. Due to small sample size, sex and race/ethnicity are not included as a stratum when calculating costs per capita.

Estimating the Indirect Cost Attributed to Diabetes

The indirect costs associated with diabetes include work days missed due to health conditions (absenteeism), reduced work productivity while working due to health conditions (presenteeism), reduced workforce participation due to disability, household productivity losses, and lost productivity due to premature mortality (12). The approach mirrors that used in the 2012 study but with more recent data.

- **Absenteeism** is defined as the number of work days missed due to poor health among employed individuals, and prior research finds that people with diabetes have higher rates of absenteeism than the population without diabetes. Estimates from the literature range from no statistically significant diabetes effect on absenteeism to studies reporting 1–6 extra missed work days (and odds ratios of more absences ranging

from 1.5 to 3.3) (12–14). Analyzing 2014–2016 NHIS data and using a negative binomial regression to control for overdispersion in self-reported missed work days, we estimate that people with diabetes have statistically higher missed work days—ranging from 1.0 to 4.2 additional days missed per year by demographic group, or 1.7 days on average—after controlling for age-group, sex, race/ethnicity, diagnosed hypertension status (yes/no), and body weight status (normal, overweight, obese, unknown). Diabetes is entered as a dichotomous variable (diagnosed diabetes = 1; otherwise 0) as well as an interaction term with age-group. Controlling for hypertension and body weight produces more conservative estimates of the diabetes impact on absenteeism, as comorbidities of diabetes are correlated with body weight status and a portion of hypertension is attributed to diabetes.

- **Presenteeism** is defined as reduced productivity while at work among employed individuals and is generally measured through worker responses to surveys. These surveys rely on the self-reported inputs on the number of reduced productivity hours incurred over a given time frame. Multiple recent studies report that individuals with diabetes display higher rates of presenteeism than their peers without diabetes (12,15–17). We model productivity loss associated with diabetes-attributed presenteeism using the estimate (6.6%) from the 2012 study—which is toward the lower end of the 1.8–38% range reported in the literature.
- **Inability to work** associated with diabetes is estimated using a conservative approach that focuses on unemployment related to long-term disability. Logistic regression with 2014–2016 NHIS data suggests that people aged 18–65 years with diabetes are significantly less likely to be in the workforce than people without diabetes. It is unclear to what extent people with diabetes voluntarily leave the workforce or do so because of diabetes. Therefore, we use a conservative approach (which likely underestimates the cost associated with inability to work) to estimate the economic burden associated with reduced labor force participation. Using logistic regression, we estimate the relationship between diabetes and receipt of Supplemental Security Income (SSI) payments for disability—controlling for age-group, sex, race/ethnicity, hypertension status, and body weight status (normal, overweight, obese). Diabetes status is included in the regression both as a separate variable and interacted with age-group to provide age-specific impacts. Study results suggest that people with diabetes have a 3.1 percentage point higher rate of being out of the workforce and receiving disability payments compared with their peers without diabetes. The diabetes effect increases with age and varies by demographic—ranging from 2.1 percentage points for non-Hispanic white males aged 60–64 years to 10.6 percentage points for non-Hispanic black females aged 55–59 years. The average daily earnings estimated from the CPS for those in the workforce are used as a proxy for the economic impact of reduced employment due to chronic disability. SSI payments are considered transfer payments and therefore are not included in the cost estimates.
- **Reduced productivity for those not in the workforce** is included in our estimate of the national burden. This population includes all adults aged <65 years who are not employed (including those voluntarily or involuntarily not in the workforce). The contribution of people not in the workforce to national productivity includes time spent providing child care, household activities, and other activities such as volunteering in the community. We use per capita absenteeism estimates for the working population as a proxy for reduced productivity days among the nonemployed population in a similar demographic. Whereas each work day lost due to absenteeism is based on estimated average daily earnings, there is no readily available measure of the value of a day lost for those not in the workforce. Some studies use minimum wage as a proxy for the value of time lost, but this may underestimate the value of time. Using average earnings for their employed counterparts will overestimate the value of time. Similar to the 2012 study, we use 75% of the average earnings for people in the workforce as a productivity proxy for those aged <65 years not in the labor force (which is close to the midpoint between minimum wage and average hourly wage earned by a demographic

Table 1—Health resource use in the U.S., by diabetes status and type of service, 2017 (in millions of units)

	Population with diabetes					
	Attributed to diabetes		Incurred by people with diabetes		Incurred by population	
Health resource	Units	% of U.S. total	Units	% of U.S. total	without diabetes	U.S. total*
Institutional care						
Hospital inpatient days	22.6	13.9	40.3	24.8	122.2	162
Nursing/residential facility days	57.3	7.5	200.0	26.1	567.3	767
Hospice days	0.3	0.3	14.2	12.7	97.8	112
Outpatient care						
Physician office visits	121.6	12.5	208.6	21.5	760.4	969
Emergency department visits	7.2	5.2	16.8	12.2	121.1	138
Hospital outpatient visits	13.5	11.7	22.2	19.2	93.0	115
Home health visits	10.1	5.0	43.0	21.2	159.9	203
Medication prescriptions	664.4	16.6	1,092.8	27.4	2,898.0	3,991

Data sources: NIS (2014), CMS MDS (2013), NAMCS (2013–2015), NHAMCS (2012–2014), MEPS (2011–2015), and NHHCS (2007), OptumInsight dNHI (2015), and Medicare 5% SAFs (2014). *Numbers do not necessarily sum to totals because of rounding.

Exhibit 118

Table 2—Health care expenditures in the U.S., by diabetes status and type of service, 2017 (in millions of dollars)

	Population with diabetes					
	Attributed to diabetes		Total incurred by people with diabetes		Population	
Cost component	Dollars	% of U.S. total	Dollars	% of U.S. total	without diabetes	Total*
Institutional care						
Hospital inpatient	69,661	14	122,729	25	362,855	485,584
Nursing/residential facility	6,439	7	24,484	25	71,934	96,419
Hospice	64	0.3	3,180	13	21,933	25,114
Outpatient care						
Physician office	29,990	12	51,882	21	190,024	241,906
Emergency department	7,990	5	18,651	12	133,894	152,545
Ambulance services	332	8	700	17	3,356	4,056
Hospital outpatient	12,049	10	21,012	18	98,872	119,884
Home health	3,388	5	14,479	21	53,824	68,303
Podiatry	252	10	607	25	1,835	2,442
Outpatient medications and supplies						
Insulin	14,981	100	14,981	100	0	14,981
Diabetes supplies	3,723	100	3,723	100	0	3,723
Other antidiabetes agents†	15,855	100	15,855	100	0	15,855
Prescription medications	71,235	17	117,160	27	310,697	427,856
Other equipment and supplies‡	1,310	4	4,564	16	24,796	29,360
Total	237,269	14	414,427	24	1,277,908	1,692,335

Data sources: NIS (2014), CMS MDS (2013), NAMCS (2013–2015), NHAMCS (2012–2014), MEPS (2011–2015), NHHCS (2007), NHIS (2014–2016), OptumInsight dNHI (2015), and Medicare 5% SAFs (2014). *Numbers do not necessarily sum to totals because of rounding. †Includes oral medications and noninsulin injectable antidiabetes agents such as exenatide and pramlintide. ‡Includes but is not limited to eyewear, orthopedic items, hearing devices, prosthesis, bathroom aids, medical equipment, and disposable supplies.

similar to the unemployed aged <65 years).

- **Premature mortality** associated with diabetes reduces future productivity (and not just the current year productivity). Ideally, to model the value of lost productivity in 2017 associated with premature mortality, one would calculate the number and characteristics of all people who would have been alive in 2017 but who died prior to 2017 because of diabetes. Data limitations prevent using this approach. Instead, we estimate the number of premature deaths associated with diabetes in 2017 and calculate the present value of their expected future earnings. To estimate the total

Table 3—Health care expenditures attributed to diabetes in the U.S., by age-group and type of service, 2017 (in millions of dollars, with percentages in parentheses)

	Age (years)		
Cost component	<65 (N = 13.7 million)	≥65 (N = 11.0 million)	Total* (N = 24.7 million)
Institutional care			
Hospital inpatient	24,835 (36)	44,826 (64)	69,661
Nursing/residential facility	2,568 (40)	3,871 (60)	6,439
Hospice	6 (9)	58 (91)	64
Outpatient care			
Physician office	9,591 (32)	20,399 (68)	29,990
Emergency department	4,258 (53)	3,732 (47)	7,990
Ambulance services	105 (32)	227 (68)	332
Hospital outpatient	5,322 (44)	6,728 (56)	12,049
Home health	2,588 (76)	801 (24)	3,388
Podiatry	94 (37)	158 (63)	252
Outpatient medications and supplies			
Insulin	8,850 (59)	6,132 (41)	14,981
Diabetes supplies	2,272 (61)	1,452 (39)	3,723
Other antidiabetes agents†	8,456 (53)	7,399 (47)	15,855
Prescription medications	21,702 (30)	49,534 (70)	71,235
Other equipment and supplies‡	783 (60)	527 (40)	1,310
Total*	91,428 (39)	145,841 (61)	237,269
Average cost per person with diabetes (actual dollars)	6,675	13,239	9,601

Data sources: NIS (2014), CMS MDS (2013), NAMCS (2013–2015), NHAMCS (2012–2014), MEPS (2011–2015), NHHCS (2007), NHIS (2014–2016), OptumInsight dNHI (2015), and Medicare 5% SAFs (2014). *Numbers do not necessarily sum to totals because of rounding. †Includes oral medications and noninsulin injectable antidiabetes agents. ‡Includes but is not limited to eyewear, orthopedic items, hearing devices, prosthesis, bathroom aids, medical equipment, and disposable supplies.

Table 4—Health care expenditures attributed to diabetes in the U.S., by demographic

Characteristics	Diabetes prevalence	Total direct cost ($, millions)	Average cost per person with diabetes ($, actual)
Age (years)			
<18	110,000	860	7,510
18–34	1,020,000	6,850	6,740
35–44	1,920,000	10,510	5,480
45–54	4,060,000	26,140	6,440
55–59	3,050,000	22,600	7,400
60–64	3,530,000	24,460	6,920
65–69	3,590,000	46,710	13,030
≥70	7,430,000	99,140	13,340
Sex			
Male	12,810,000	128,830	10,060
Female	11,900,000	108,450	9,110
Race/ethnicity			
White, non-Hispanic	15,080,000	150,260	9,800
Black, non-Hispanic	4,030,000	42,240	10,470
Other, non-Hispanic	1,890,000	14,880	7,890
Hispanic	3,710,000	29,900	8,050

Data sources: NIS (2014), CMS MDS (2013), NAMCS (2013–2015), NHAMCS (2012–2014), MEPS (2011–2015), NHHCS (2007), NHIS (2014–2016), OptumInsight dNHI (2015), and Medicare 5% SAFs (2014).

number of deaths attributable to diabetes, we analyzed the CDC's 2015 Mortality Multiple Cause File to obtain mortality data by age, sex, and race/ethnicity for cardiovascular disease, cerebrovascular disease, renal failure, and diabetes. We use the same estimates as our previous study: ~16% of cardiovascular disease (excluding cerebrovascular disease) deaths can be attributed to diabetes, and ~28% of deaths listing cerebrovascular disease as the primary cause and ~55% of deaths listing renal failure as the primary cause can be attributed to diabetes. To generate 2017 estimates, we grow the 2015 CDC mortality data using the annual population growth rate from 2015 to 2017 for each age, sex, and race/ethnicity group.

Productivity loss associated with early mortality is calculated by taking the net present value of future productivity (PVFP) for men and women by age and race/ethnicity using the same discount rate (3%), assumptions, and equation outlined in the 2008 American Diabetes Association report (4). We combined average annual earnings from the CPS, expected mortality rates from the CDC, and employment rates from the CPS by age, sex, and race/ethnicity to calculate the net present value of future earnings of a person who dies prematurely.

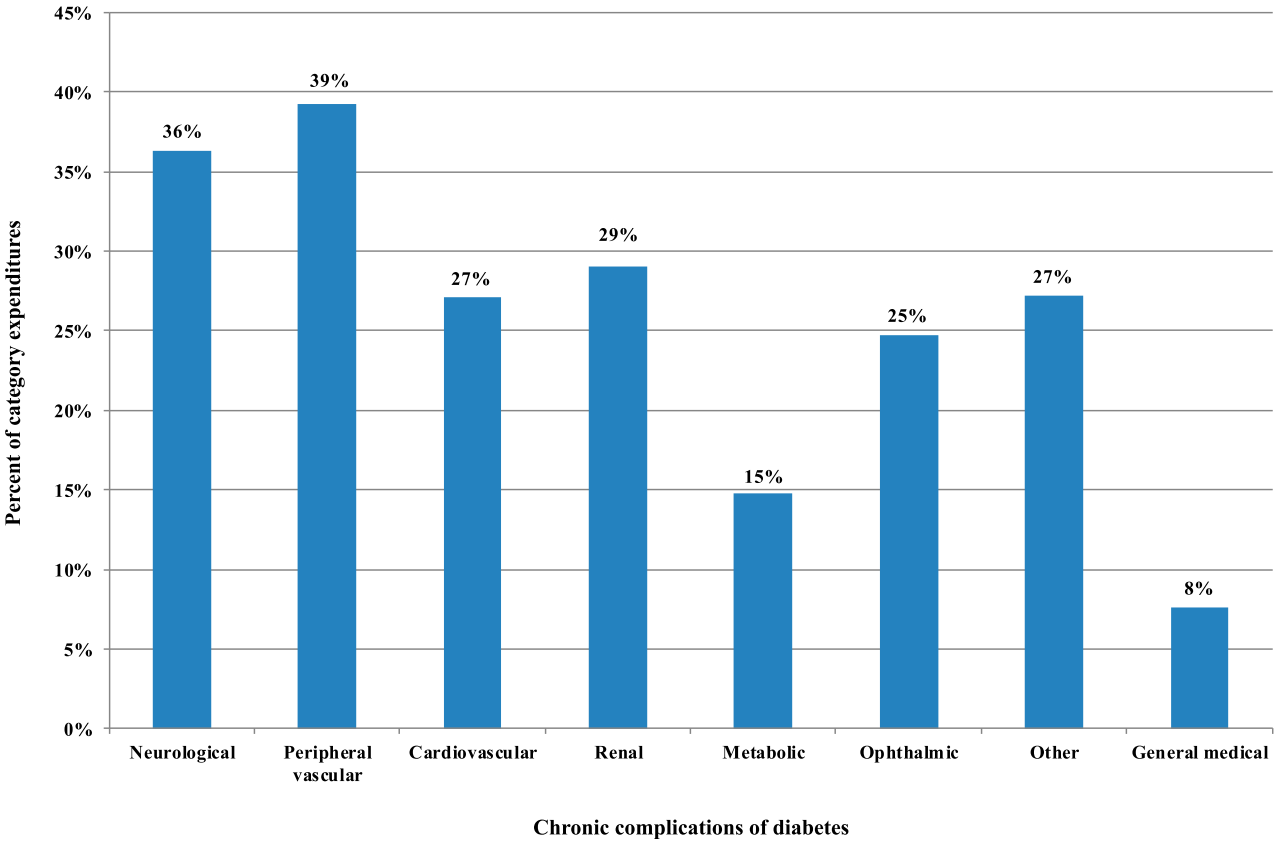

Figure 1—Percent of medical condition-specific expenditures associated with diabetes. Data sources: NIS (2014), CMS MDS (2013), NAMCS (2013–2015), NHAMCS (2012–2014), MEPS (2011–2015), NHHCS (2007), NHIS (2014–2016), OptumInsight dNHI (2015), and Medicare 5% SAFs (2014). See Supplementary Appendix 2 for diagnosis codes for each category of medical condition.

Exhibit 118

Employment rates for 2015 are used to calculate PVFP.

We do not count productivity loss for the population aged <18 years. While children constitute a small proportion of the population with diabetes, omitting productivity loss associated with diabetes among children could bias low the cost estimates. For example, the economic cost associated with parents who take time off from work to take their children to the doctor for diabetes-related visits is omitted from these cost estimates.

RESULTS

In 2017, an estimated 24.7 million people in the U.S. are diagnosed with diabetes, representing ~7.6% of the total population (and 9.7% of the adult population). The estimated national cost of diabetes in 2017 is $327 billion, of which $237 billion (73%) represents direct health care expenditures attributed to diabetes and $90 billion (27%) represents lost productivity from work-related absenteeism, reduced productivity at work and at home, unemployment from chronic disability, and premature mortality. Particularly noteworthy is that excess costs associated with medications constitute 43% of the total direct medical burden. This includes nearly $15 billion for insulin, $15.9 billion for other antidiabetes agents, and $71.2 billion in excess use of other prescription medications attributed to higher disease prevalence associated with diabetes.

Health Resource Use Attributed to Diabetes

Table 1 shows estimates of health resource utilization attributed to diabetes and incurred by people with diabetes as a percentage of total national utilization. For example, of the projected 162 million hospital inpatient days in the U.S. in 2017, an estimated 40.3 million days (24.8%) are incurred by people with diabetes, of which 22.6 million days are attributed to diabetes. About one-fourth of all nursing/residential facility days are incurred by people with diabetes. About half of all physician office visits, emergency department visits, hospital outpatient visits, and medication prescriptions (excluding insulin and other antidiabetes agents) incurred by people with diabetes are attributed to their diabetes.

Health Care Expenditures Attributed to Diabetes

Health care expenditures attributed to diabetes reflect the additional expenditures the nation incurs because of diabetes. This equates to the total health care expenditures for people with diabetes minus the projected level of expenditures that would have occurred for those people in the absence of diabetes. Table 2 summarizes national expenditure for the cost components included, accounting for nearly $1.7 trillion in projected expenditure for 2017. Approximately $414 billion of the total is incurred by people with diabetes, reflecting 1 in 4 (24%) of all health care dollars. Costs attributed to diabetes exceed $237 billion, or 57% of total medical costs incurred by people with diabetes. For the cost components included, 1 in every 7 health care dollars (14%) is attributed to diabetes.

National health-related expenditures are projected to exceed $3.5 trillion in 2017 (18), but slightly less than half of these expenditures are included in our analysis. These cost estimates omit national expenditures (and any portion of such expenditures that might be attributable to diabetes) for administering government health and private insurance programs, investment in research and infrastructure, over-the-counter medications, disease management and wellness programs, and office visits to nonphysician providers other than podiatrists (e.g., dentists and optometrists).

The largest contributors to the cost of diabetes are higher use of prescription

Table 5—Annual per capita health care expenditures in the U.S., by diabetes status, 2017 (in actual dollars)

		Unadjusted		Adjusted for age and sex		
Cost component	With diabetes ($)	Without diabetes ($)	Ratio with to without diabetes	Without diabetes ($)	Ratio with to without diabetes	Attributed to diabetes ($)*
Institutional care						
Hospital inpatient	4,966	1,202	4.1	2,147	2.3	2,819
Nursing/residential facility	991	238	4.2	730	1.4	261
Hospice	129	73	1.8	126	1.0	3
Outpatient care						
Physician office	2,099	629	3.3	886	2.4	1,213
Emergency	755	443	1.7	431	1.7	323
Ambulance services	28	11	2.5	15	1.9	13
Hospital outpatient and freestanding ambulatory surgical center	850	327	2.6	363	2.3	488
Home health	586	178	3.3	449	1.3	137
Podiatry	25	6	4.0	14	1.7	10
Outpatient medications and supplies						
Insulin	606	NA	NA	NA	NA	606
Diabetes supplies	151	NA	NA	NA	NA	151
Other antidiabetes agents†	642	NA	NA	NA	NA	641
Prescription medications	4,741	1,029	4.6	1,858	2.6	2,882
Other equipment and supplies‡	185	82	2.2	132	1.4	53
Total*	16,752	4,220	4.0	7,151	2.3	9,601

Data sources: NIS (2014), CMS MDS (2013), NAMCS (2013–2015), NHAMCS (2012–2014), MEPS (2011–2015), NHHCS (2007), NHIS (2014–2016), OptumInsight dNHI (2015), Medicare 5% SAFs (2014), and U.S. Census Bureau (2017). NA, not applicable. *Numbers do not necessarily sum to totals because of rounding. †Includes antidiabetes agents such as exenatide and pramlintide. ‡Includes but is not limited to eyewear, orthopedic items, hearing devices, prosthesis, bathroom aids, medical equipment, and disposable supplies.

Table 6—Indirect burden of diabetes in the U.S., 2017 (in billions of dollars)

Cost component	Productivity loss	Total cost attributable to diabetes ($)	Proportion of indirect costs*
Work days absent	14 million days	3.3	3.7%
Reduced performance at work	114 million days	26.9	29.7%
Reduced productivity days for those not in labor force	14 million days	2.3	2.6%
Reduced labor force participation due to disability	182 million days	37.5	41.7%
Mortality	277,000 deaths	19.9	22.1%
Total		89.9	100%

Data source: analysis of the NHIS (2014–2016), CPS (2016), CDC mortality data, and U.S. Census Bureau population estimates for 2016 and 2017. *Numbers do not necessarily sum to totals because of rounding.

medications beyond antihyperglycemic medications ($71.2 billion), higher use of hospital inpatient services ($69.7 billion), medications and supplies to directly treat diabetes ($34.6 billion), and more office visits to physicians and other health providers ($30.0 billion).

Approximately 61% of all health care expenditures attributed to diabetes are for health resources used by the population aged ≥65 years, much of which is borne by the Medicare program (Table 3). Dividing total attributed health care expenditures by the number of people with diabetes, we estimate the average annual excess expenditures for the population aged <65 years and ≥65 years, respectively, at $6,675 and $13,239. Health care expenditures attributed to diabetes generally increase with age, although among younger people, average costs are slightly higher likely due to a higher proportion of these cases being type 1 versus type 2 diabetes, are slightly higher for men (mainly due to men having higher attributable fractions on several key measures), and are highest for the non-Hispanic black population due to a higher use of emergency care and hospital outpatient care (Table 4).

Figure 1 summarizes the proportion of medical expenditures attributed to diabetes for each chronic complication over total U.S. health care expenditure, combining expenditures for hospital inpatient, hospital outpatient, emergency department, and physician and other provider office visits as well as prescription medications. For patients with diabetes who receive care for peripheral vascular conditions, 39% of these expenditures are attributed to diabetes. For the general medical conditions category (which includes all care not included in the other categories), 8% of expenditures incurred by people with diabetes are attributed to their diabetes.

The population with diabetes is older and sicker than the population without diabetes, and consequently annual medical expenditures are much higher (on average) than for people without diabetes (Table 5). When we compare expenditures for people with diabetes to expenditures for a population of similar age and sex, people with diabetes have health care expenditures that are 2.3 times higher ($16,752 vs. $7,151) than expenditures would be expected for this same population in the absence of diabetes. This suggests that diabetes is responsible for an estimated $9,601 in excess expenditures per year per person with diabetes. This 2.3 multiple is unchanged from the 2007 and 2012 studies.

After adjusting for inflation, the total cost of insulin and other medications to control blood glucose increased by 45% from 2012 to 2017, to a total of $31 billion. The inflation-adjusted cost of insulin increased by 110% during the same period. These increases are attributable to both an increase in the number of people using these medications and the cost of the medications themselves.

Indirect Costs Attributed to Diabetes

The total indirect cost of diabetes is estimated at $89.9 billion (Table 6). Major contributors to this burden are reduced employment ($37.5 billion), presenteeism ($26.9 billion), and premature mortality ($19.9 billion). Work days absent ($3.3 billion) and reduced productivity for those not in the workforce ($2.3 billion) represent a relatively small portion of the total burden.

Of the estimated 24.7 million people with diagnosed diabetes, analysis of NHIS data suggests that ~8.1 million are in the workforce. If people with diabetes participated in the labor force at rates similar to their peers without diabetes, there would be ~2 million additional people aged 18–64 years in the workforce. However, using a more conservative approach (described previously) where reduced labor force participation is associated with receiving disability payments, we estimate 756,000 fewer working-age adults in the workforce in 2017—equivalent to 182 million lost

Table 7—Mortality costs attributed to diabetes, 2017

Primary cause of death	Total U.S. deaths (thousands)*	Deaths attributed to diabetes		
		Deaths (thousands)	% of U.S. deaths in category	Value of lost productivity ($, billions)
Diabetes	85	85	100	8.5
Renal disease	72	39	54	1.9
Cerebrovascular disease	150	42	28	1.9
Cardiovascular disease	689	111	16	7.6
Total	NA	277	NA	19.9

*Data source: CDC National Vital Statistics Reports for total deaths in 2015 by primary cause of death, scaled to 2017 using the annual diabetes population growth rate from 2015 to 2017 for each age, sex, and race/ethnicity group. NA, not applicable.

work days. While disability payments themselves are a cost to the government, from a societal perspective they are considered transfer payments and thus not included in the burden estimates.

The cost of missed work days due to absenteeism is estimated at $3.3 billion, representing 14 million days. If people not in the workforce had similar rates of days where they are unable to work due to poor health as their employed peers, this would equate to 14 million excess sick days with estimated productivity loss valued at $2.3 billion.

Reduced performance at work (presenteeism) accounted for 30% of the indirect cost of diabetes. The estimate of a 6.6% annual decline in productivity attributed to diabetes equates to 114 million lost work days per year.

The estimated number of deaths in 2017 attributable to diabetes is 277,000 (Table 7); for 85,000 deaths, diabetes is listed as the primary cause. Of the 689,000 deaths where cardiovascular disease is listed as the primary cause, ~111,000 (16%) are attributable to diabetes. Approximately 42,000 cases where cerebrovascular disease is listed as the primary cause of death are attributable to diabetes, and 39,000 cases where renal disease is listed as the primary cause of death are attributable to diabetes. The average cost per premature death declines with age (reflecting fewer remaining expected working years), and across all premature deaths, cost averaged ~$71,700 per case.

Trends in Diabetes Costs, 2007–2017

Between 2012 and 2017, we estimate that medical costs associated with diabetes increased by 26% (from $188 billion to $237.3 billion) when adjusted for general inflation (Fig. 2). Adjusting for both inflation and growth in diabetes prevalence, the excess medical cost per person with diabetes grew by 14% (from $8,417 to $9,601 in 2017 dollars) (Fig. 5).

The indirect costs of diabetes grew by 23% when adjusted for general inflation (Fig. 3), which on a per capita basis reflects 11% growth (from $3,283 to $3,640 per person in 2017 dollars) (Fig. 5).

Combined, the inflation adjusted total economic burden of diabetes increased from ~$261 billion in 2012 to $327.3 billion in 2017 (or 25% growth) (Fig. 4). Adjusted for inflation and growth in diabetes prevalence, the average economic cost associated with diabetes increased from $11,700 to $13,247 (in 2017 dollars), or 13% growth (Fig. 5).

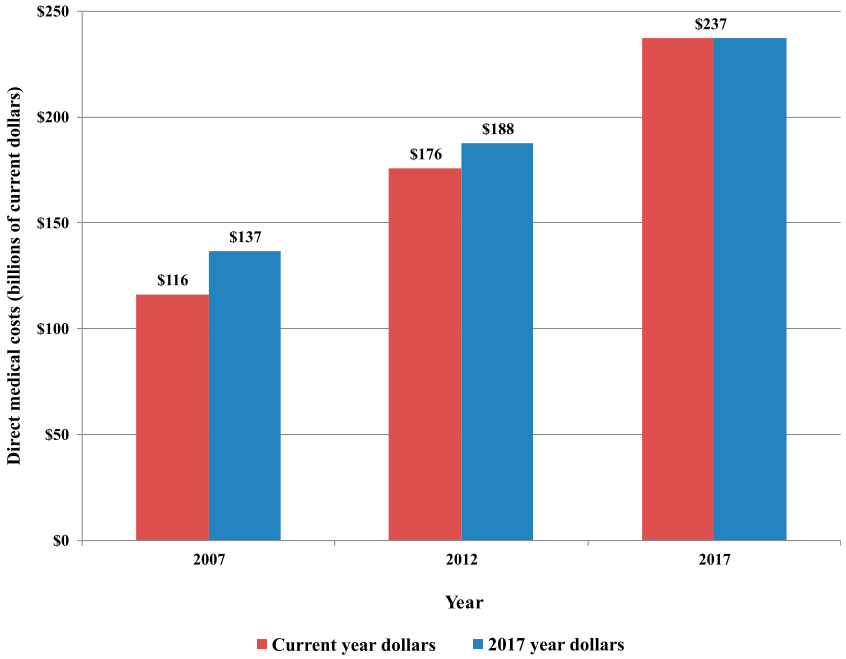

Figure 2—Total direct costs of diabetes, 2007–2017.

CONCLUSIONS

This study estimates ~24.7 million people (~9.7% of adults) had diagnosed diabetes in the U.S. in 2017. Diabetes costs the nation ~$327 billion, which includes $237 billion in direct medical cost and $90 billion in lost productivity. Similar to estimates in 2007 and 2012, after adjusting for age and sex, annual per capita health care expenditure is 2.3 times higher for people with diabetes compared with those without diabetes. A large portion of medical costs associated with diabetes costs is for comorbidities.

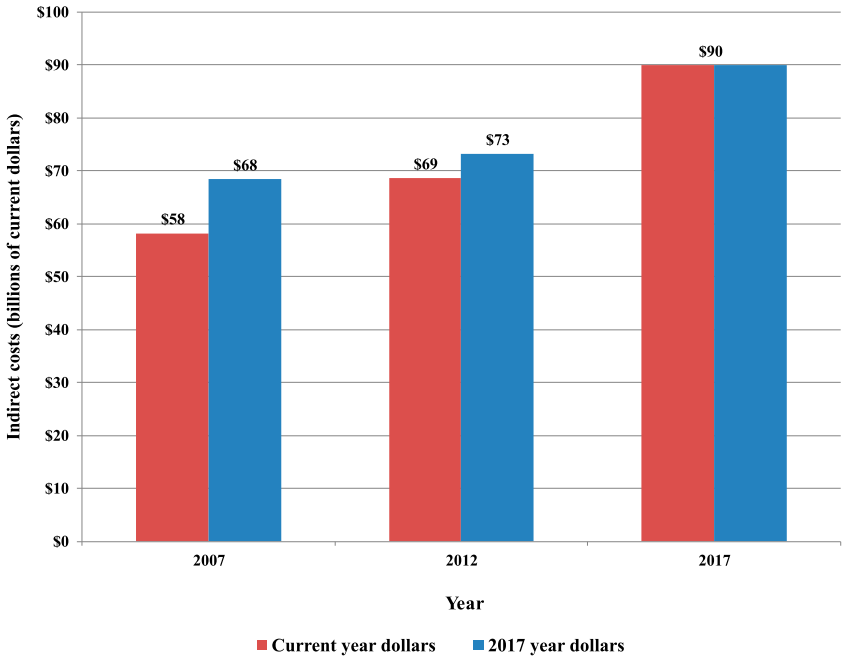

Figure 3—Total indirect costs of diabetes, 2007–2017.

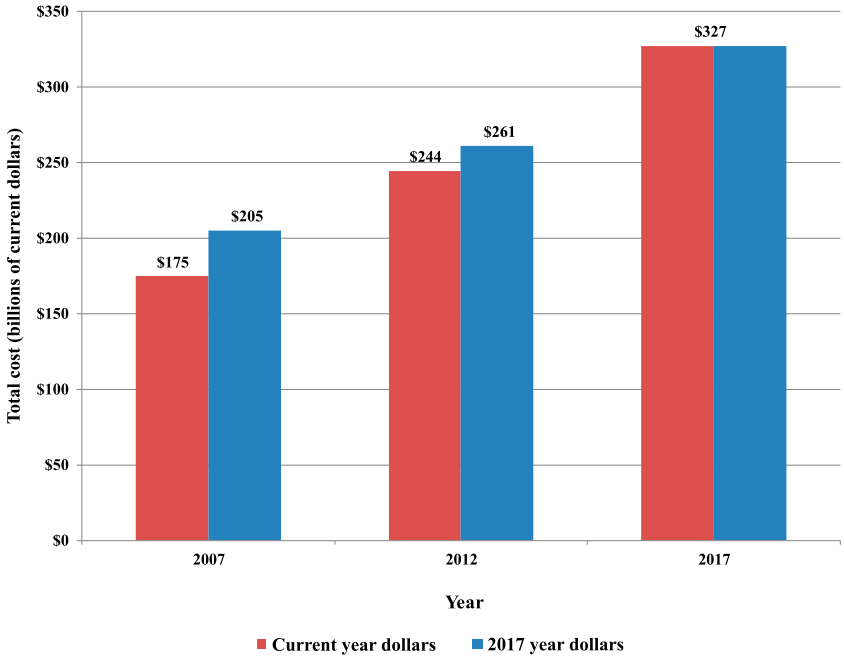

Figure 4—Total economic cost of diabetes, 2007–2017.

For costs that include hospital and office-based services as well as prescription medications and supplies, the costs to directly treat diabetes are estimated at $29.3 billion. An estimated $37.3 billion in cardiovascular-related spending is associated with diabetes (with the presence of diabetes contributing to higher medical expenditures among patients seeking cardiovascular-related care). Outside of the chronic complication categories modeled, the presence of diabetes is associated with greater use of health care services in general—including longer stays in the hospital regardless of primary reason for hospitalization. This underscores that simply aggregating all costs associated only with diabetes diagnosis codes grossly underestimates the medical costs directly attributable to diabetes.

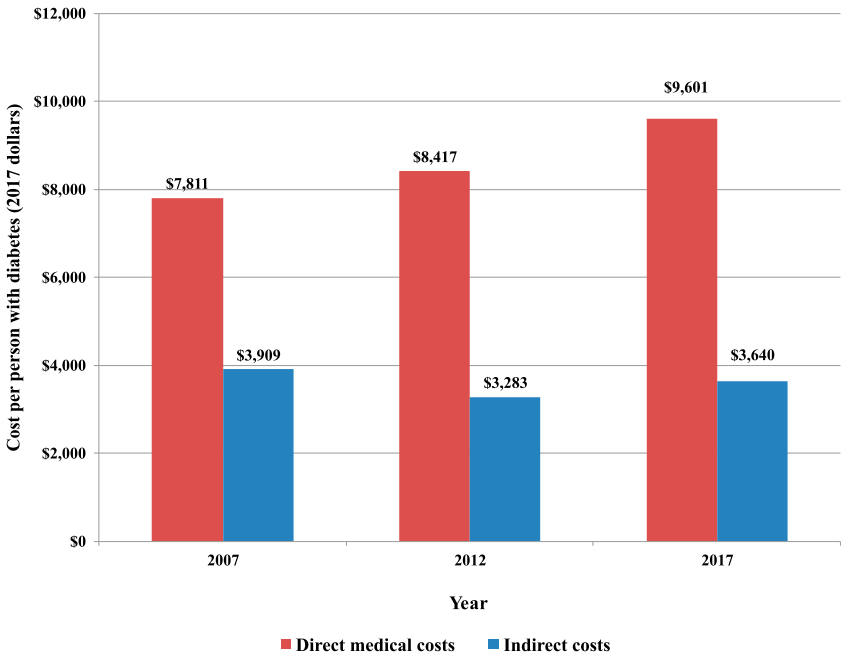

Figure 5—Average cost of diabetes, 2007–2017 (in 2017 dollars).

While much of the cost of diabetes appears to fall on insurers (especially Medicare) and employers (in the form of reduced productivity at work, missed work days, and higher employer expenditures for health care), in reality such costs are passed along to all of society in the form of higher insurance premiums and taxes, reduced earnings, and reduced standard of living.

Comparing the 2017 estimates with those produced for 2012, the overall cost of diabetes appears to have increased by ~25% after adjusting for inflation, reflecting an 11% increase in national prevalence of diagnosed diabetes and a 13% increase in the average annual diabetes-attributed cost per person with diabetes.

Study limitations include the following:

- Due to data limitations, we omitted from this analysis potential increase in the use of over-the-counter medications and optometry and dental services. Diabetes increases the risk of periodontal disease, so one would expect dental costs to be higher for people with diabetes. Small sample size in MEPS data prevented meaningful analysis of these cost components. We also omitted expenditures for prevention programs targeted to people with diabetes, research activities, and health administration costs. These omissions underestimate the full medical costs associated with diabetes.
- The study omits lost productivity associated with care for diabetes of family members (e.g., time off from work to care for a child or an elderly parent with diabetes). The value of informal care and personal aides is excluded from our cost estimate. Time and costs associated with traveling to doctor visits and other medical emergencies are omitted. These omissions underestimate the indirect costs associated with diabetes.
- Also omitted from the cost estimates are the intangible costs of diabetes such as pain, suffering, and reduced quality of life.
- A complicating factor in estimating costs attributed to diabetes is that health behavior that affects both the presence of diabetes and the presence of other comorbidities, unless controlled for, could result in an overestimate of the link between diabetes and use of health resources. Controlling for demographics helps to control for this correlation. In addition, for the top 10 cost drivers we conducted

additional analysis controlling for other important explanatory variables using MEPS data, and based on the results we reduced the etiological fractions for several diabetes complications and for the general medical conditions group—depending on care delivery setting. This potential limitation also applies to the estimates of indirect costs attributed to diabetes, especially the estimated productivity loss due to presenteeism, potentially biasing these estimates high.

- Other study limitations discussed previously include small sample size for some data sources used, the use of a data source (dNHI) that overrepresents the commercially insured population for the population younger than age 65 years, and the need to use different approaches to model different cost components because of data limitations. Another limitation common to claims-based analysis is the possibility of inaccurate diagnosis codes. Claims data tend to be less accurate than medical records in identifying patients with specific conditions due to reasons such as rule-out diagnosis, coding error, etc. The direction of such bias on our risk ratio calculations is unknown, although it is anticipated to be small as there is no reason to believe that the coding of comorbidities would be significantly different for people with and without diabetes.

Using a methodology that is largely consistent with our previous studies conducted in 2007 and 2012, with updated national survey and claims data from previous data sources, we estimate the total burden of diabetes in 2017. The estimates presented here show that diabetes places an enormous burden on society and has increased over time—both in the economic terms presented here and in reduced quality of life.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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EXHIBIT 119

Type 1 diabetes

Overview

Type 1 diabetes, once known as juvenile diabetes or insulin-dependent diabetes, is a chronic condition in which the pancreas produces little or no insulin. Insulin is a hormone needed to allow sugar (glucose) to enter cells to produce energy.

Different factors, including genetics and some viruses, may contribute to type 1 diabetes. Although type 1 diabetes usually appears during childhood or adolescence, it can develop in adults.

Despite active research, type 1 diabetes has no cure. Treatment focuses on managing blood sugar levels with insulin, diet and lifestyle to prevent complications.

Symptoms

Type 1 diabetes signs and symptoms can appear relatively suddenly and may include:

- Increased thirst
- Frequent urination
- Bed-wetting in children who previously didn't wet the bed during the night
- Extreme hunger
- Unintended weight loss
- Irritability and other mood changes
- Fatigue and weakness
- Blurred vision

When to see a doctor

Consult your doctor if you notice any of the above signs and symptoms in you or your child.

Request an Appointment at Mayo Clinic

Causes

The exact cause of type 1 diabetes is unknown. Usually, the body's own immune system — which normally fights harmful bacteria and viruses — mistakenly destroys the insulin-producing (islet, or islets of Langerhans) cells in the pancreas. Other possible causes include:

- Genetics
- Exposure to viruses and other environmental factors

The role of insulin

Once a significant number of islet cells are destroyed, you'll produce little or no insulin. Insulin is a hormone that comes from a gland situated behind and below the stomach (pancreas).

- The pancreas secretes insulin into the bloodstream.
- Insulin circulates, allowing sugar to enter your cells.
- Insulin lowers the amount of sugar in your bloodstream.
- As your blood sugar level drops, so does the secretion of insulin from your pancreas.

The role of glucose

Glucose — a sugar — is a main source of energy for the cells that make up muscles and other tissues.

- Glucose comes from two major sources: food and your liver.
- Sugar is absorbed into the bloodstream, where it enters cells with the help of insulin.
- Your liver stores glucose as glycogen.
- When your glucose levels are low, such as when you haven't eaten in a while, the liver breaks down the stored glycogen into glucose to keep your glucose levels within a normal range.

In type 1 diabetes, there's no insulin to let glucose into the cells, so sugar builds up in your bloodstream. This can cause life-threatening complications.

Risk factors

Some known risk factors for type 1 diabetes include:

- **Family history.** Anyone with a parent or sibling with type 1 diabetes has a slightly increased risk of developing the condition.
- **Genetics.** The presence of certain genes indicates an increased risk

of developing type 1 diabetes.

- **Geography.** The incidence of type 1 diabetes tends to increase as you travel away from the equator.
- **Age.** Although type 1 diabetes can appear at any age, it appears at two noticeable peaks. The first peak occurs in children between 4 and 7 years old, and the second is in children between 10 and 14 years old.

Complications

Over time, type 1 diabetes complications can affect major organs in your body, including heart, blood vessels, nerves, eyes and kidneys. Maintaining a normal blood sugar level can dramatically reduce the risk of many complications.

Eventually, diabetes complications may be disabling or even life-threatening.

- **Heart and blood vessel disease.** Diabetes dramatically increases your risk of various cardiovascular problems, including coronary artery disease with chest pain (angina), heart attack, stroke, narrowing of the arteries (atherosclerosis) and high blood pressure.
- **Nerve damage (neuropathy).** Excess sugar can injure the walls of the tiny blood vessels (capillaries) that nourish your nerves, especially in the legs. This can cause tingling, numbness, burning or pain that usually begins at the tips of the toes or fingers and gradually spreads upward. Poorly controlled blood sugar could cause you to eventually lose all sense of feeling in the affected limbs.

  Damage to the nerves that affect the gastrointestinal tract can cause problems with nausea, vomiting, diarrhea or constipation. For men, erectile dysfunction may be an issue.
- **Kidney damage (nephropathy).** The kidneys contain millions of tiny blood vessel clusters that filter waste from your blood. Diabetes can damage this delicate filtering system. Severe damage can lead to kidney failure or irreversible end-stage kidney disease, which requires dialysis or a kidney transplant.
- **Eye damage.** Diabetes can damage the blood vessels of the retina

(diabetic retinopathy), potentially causing blindness. Diabetes also increases the risk of other serious vision conditions, such as cataracts and glaucoma.

- **Foot damage.** Nerve damage in the feet or poor blood flow to the feet increases the risk of various foot complications. Left untreated, cuts and blisters can become serious infections that may ultimately require toe, foot or leg amputation.
- **Skin and mouth conditions.** Diabetes may leave you more susceptible to infections of the skin and mouth, including bacterial and fungal infections. Gum disease and dry mouth also are more likely.
- **Pregnancy complications.** High blood sugar levels can be dangerous for both the mother and the baby. The risk of miscarriage, stillbirth and birth defects increases when diabetes isn't well-controlled. For the mother, diabetes increases the risk of diabetic ketoacidosis, diabetic eye problems (retinopathy), pregnancy-induced high blood pressure and preeclampsia.

Prevention

There's no known way to prevent type 1 diabetes. But researchers are working on preventing the disease or further destruction of the islet cells in people who are newly diagnosed.

Ask your doctor if you might be eligible for one of these clinical trials, but carefully weigh the risks and benefits of any treatment available in a trial.

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By Mayo Clinic Staff

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