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Pediatrics 2013;131;637; originally published online March 4, 2013;

DOI: 10.1542/peds.2012-2354

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American Academy of Pediatrics

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Mortality, ADHD, and Psychosocial Adversity in Adults With Childhood ADHD: A Prospective Study

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KEY WORDS

attention-deficit/hyperactivity disorder, mortality, persistence of ADHD, adult outcomes

ABBREVIATIONS

ADHD—attention-deficit/hyperactivity disorder

CI—confidence interval

DSM-IV TR—*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*

M.I.N.I.—Mini International Neuropsychiatric Interview

OR—odds ratio

SMR—standardized mortality ratio

Dr Barbaresi conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted; Dr Colligan participated in the conceptualization, design, and conduct of the final manuscript as submitted; Ms Weaver participated in the design of the study, carried out the initial analyses, revised and reviewed the manuscript, and approved the final manuscript as submitted; Dr Voigt participated in the design of the study, revised and reviewed the manuscript, and approved of the final manuscript as submitted; Ms Killian participated in the initial analyses, revised and reviewed the manuscript, and approved of the final manuscript as submitted; and Dr Katusic conceptualized and designed the study, revised and reviewed the manuscript, and approved of the final manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2012-2354

doi:10.1542/peds.2012-2354

Accepted for publication Nov 26, 2012

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by Public Health Service research grants MH076111, HD29745, and AG034676. Pilot work for the prospective portion of the project was funded by an investigator-initiated grant from McNeil Consumer and Specialty Pharmaceuticals.



WHAT'S KNOWN ON THIS SUBJECT: Attention-deficit/hyperactivity disorder (ADHD) has been viewed as a neurodevelopmental disorder, adversely affecting behavior and school performance, with studies suggesting increased risk for poor adult outcomes. However, no prospective studies have examined long-term outcomes of childhood ADHD in an epidemiologic sample.



WHAT THIS STUDY ADDS: Our epidemiologic study indicates that adults with childhood ADHD are at increased risk for death from suicide. ADHD persists into adulthood in 29.3% of childhood ADHD cases, and 56.9% have ≥ 1 psychiatric disorder other than ADHD.

abstract

FREE

OBJECTIVE: We examined long-term outcomes of attention-deficit/hyperactivity disorder (ADHD) in a population-based sample of childhood ADHD cases and controls, prospectively assessed as adults.

METHODS: Adults with childhood ADHD and non-ADHD controls from the same birth cohort ($N = 5718$) were invited to participate in a prospective outcome study. Vital status was determined for birth cohort members. Standardized mortality ratios (SMRs) were constructed to compare overall and cause-specific mortality between childhood ADHD cases and controls. Incarceration status was determined for childhood ADHD cases. A standardized neuropsychiatric interview was administered.

RESULTS: Vital status for 367 childhood ADHD cases was determined: 7 (1.9%) were deceased, and 10 (2.7%) were currently incarcerated. The SMR for overall survival of childhood ADHD cases versus controls was 1.88 (95% confidence interval [CI], 0.83–4.26; $P = .13$) and for accidents only was 1.70 (95% CI, 0.49–5.97; $P = .41$). However, the cause-specific mortality for suicide only was significantly higher among ADHD cases (SMR, 4.83; 95% CI, 1.14–20.46; $P = .032$). Among the childhood ADHD cases participating in the prospective assessment ($N = 232$; mean age, 27.0 years), ADHD persisted into adulthood for 29.3% (95% CI, 23.5–35.2). Participating childhood ADHD cases were more likely than controls ($N = 335$; mean age, 28.6 years) to have ≥ 1 other psychiatric disorder (56.9% vs 34.9%; odds ratio, 2.6; 95% CI, 1.8–3.8; $P < .01$).

CONCLUSIONS: Childhood ADHD is a chronic health problem, with significant risk for mortality, persistence of ADHD, and long-term morbidity in adulthood. *Pediatrics* 2013;131:637–644

Attention-deficit/hyperactivity disorder (ADHD) is the most common childhood neurodevelopmental disorder.^{1,2} Important questions about adult outcomes for childhood ADHD remain, including the rate of persistence of ADHD into adulthood, the psychiatric comorbidities of adult ADHD, and the risk of serious adverse outcomes, such as criminality and mortality. To understand the long-term impact of childhood ADHD, it is essential to answer these questions about the course of ADHD through the lifespan.

Although ADHD has been reported to affect 4.4% of adults, estimates of the persistence of ADHD from childhood to adulthood have varied widely, ranging from 6% to 66%.^{3–13} Previous, prospective studies have depended on outcomes for childhood ADHD cases referred to specialty treatment programs and therefore may not be representative of the entire population of individuals with ADHD.^{4–7,9,11} Other limitations of some previous studies include dependence on adult recall of childhood ADHD, studies limited to boys, small samples, and diagnostic criteria that do not account for differences in ADHD symptoms between children and adults.^{4–6,8–10,14}

Previous longitudinal studies of childhood ADHD and cross-sectional studies of adult ADHD have suggested high rates of comorbid psychiatric disorders in children and adults with ADHD.^{15–22} However, the largest cross-sectional study in adults was dependent on self-report of ADHD case status.¹⁶ The longitudinal studies of childhood ADHD used childhood ADHD cases referred to specialty treatment programs.^{4,6,7,9} Thus, high rates of comorbid psychiatric disorders may not be found in the entire population of adults with ADHD. Childhood ADHD may be a risk factor for later criminal behavior.^{5,23–26} Previous research also suggests that ADHD may be associated with in-

creased mortality, particularly from suicide or accidents.²³ We have previously described risk factors for ADHD, childhood comorbidities, treatment history, and educational outcomes through age 19 years for this cohort of ADHD cases.^{27–32} However, no study to date has reported mortality rates in a population-based cohort of childhood ADHD cases followed into adulthood.

In this paper, we describe a study of childhood ADHD cases and controls from the 1976 to 1982 Rochester, Minnesota, birth cohort, who participated in a prospective follow-up at a mean age of 27 years. We report the rates of overall mortality and mortality due to suicide and accidents, incarceration, persistence of ADHD into adulthood, and comorbid psychiatric conditions. This research provides a population-based perspective on the cumulative risk for adverse long-term outcomes associated with childhood ADHD.

METHODS

Study Setting

Rochester, Minnesota, is geographically isolated in southeastern Minnesota, and virtually all medical care for residents of Rochester is provided by the Mayo Clinic, Olmsted Medical Center, and their 3 affiliated hospitals. The resources of the Rochester Epidemiology Project provide infrastructure for population-based research.³³ All medical diagnoses and surgical procedures are recorded and indexed for computerized retrieval. For this ADHD study, all 41 public and private schools in Minnesota Independent School District 535 (city of Rochester school system) participated in a contractual research agreement that gave us permission to access their cumulative educational records for every child from the 1976 to 1982 Rochester, Minnesota, birth cohort. The study was approved by the

institutional review boards of the Mayo Clinic and Olmsted Medical Center. Written informed consent was obtained from all participants in the prospective portion of this study.

Subjects

Birth Cohort

This study used a birth cohort consisting of all children born between January 1, 1976, and December 31, 1982, to mothers residing in the townships comprising Minnesota Independent School District 535, who continued to live in Rochester until ≥ 5 years of age and who granted permission for use of their medical records for the study ($N = 5718$).

Identification of Childhood ADHD Cases and Controls in a Previous Retrospective Study

Details regarding our criteria and the multistep identification process of childhood ADHD cases in this birth cohort have been described elsewhere.³⁴ Subjects were defined as having research-identified childhood ADHD if their school and/or medical records included various combinations of the following 3 different categories of information: (1) documentation in medical and school records of behavioral symptoms consistent with the criteria for ADHD from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV TR)¹⁴; (2) positive ADHD questionnaire results; and (3) documented clinical diagnosis of ADHD. A total of 379 ADHD incident cases were identified. Research diagnostic criteria were met at a mean age of 10.4 years.

Non-ADHD controls were identified from the remaining members of the birth cohort who were in the community after 5 years of age and who had not fulfilled research criteria for childhood ADHD ($N = 4946$); subjects with severe intellectual disability ($N = 19$) or who

denied access to their medical records for research purposes ($N = 369$) were excluded from the study.

Recruitment for Prospective Study

Of the 379 subjects with research-identified childhood ADHD identified in our retrospective study, 362 who provided continued permission to access their medical records for research were invited to participate in the adult outcome study. Subject recruitment included mailings, with follow-up phone calls for subjects who did not respond to the letter. To ensure enrollment of sufficient non-ADHD controls, a random sample of 801 adults from the same birth cohort was also invited to participate. Five control subjects in the prospective study stated they had received a diagnosis of childhood ADHD. We reviewed records from these 5 subjects and determined that they had fulfilled our research criteria for childhood ADHD but had not been thus classified previously because they had moved from the community before receiving this diagnosis or because of the timing of the original data abstraction. These 5 subjects were therefore reclassified as childhood ADHD cases (total $N = 367$) for all analyses presented in this paper.

Determination of Vital Status

Vital status was determined at the time of recruitment for the prospective study. For each member of the birth cohort, duration of follow-up was calculated from the date they met research criteria for ADHD to their date of death, date of prospective study participation, or date last known to be alive, based on the date of their last documented medical visit in the Rochester Epidemiology Project records before 2009. We examined death certificates for all deceased members of the birth cohort to determine cause of death. We compared mortality between ADHD

cases and the remaining birth cohort members. We were specifically interested in both overall mortality and mortality attributable to suicide or accidents, given previous literature suggesting increased rates of suicide and accidents in persons with ADHD.²³ Overall survival (death from any cause) and cause-specific survival (death from suicide or accident, separately) were compared between cases and controls by fitting Cox proportional hazards regression models on the age scale and stratified by gender and year of birth. The estimated hazard ratio from the model is a comparison of each ADHD case with age- and gender-matched subjects from the remainder of the birth cohort, which is analogous to a standardized mortality ratio (SMR).

Incarceration Rates for Childhood ADHD Cases

We determined incarceration status for childhood ADHD cases at the time of recruitment on the basis of responses received during attempted mail and telephone contacts and monthly screening of web sites containing public data on criminal convictions (<https://cch.state.mn.us/>; <http://www.co.olmsted.mn.us>; <http://www.theinmatelocator.com/Minnesota.html>).

Adult ADHD Case Status and Presence of Other Psychiatric Disorders

All participants in the prospective study were administered the Mini International Neuropsychiatric Interview (M.I.N.I.), including the module for adult ADHD.^{35,36} The M.I.N.I. is a structured diagnostic interview for DSM-IV TR and *International Classification of Diseases, 10th Revision* psychiatric disorders. Because there are no agreed-on, norm-referenced diagnostic criteria for adult ADHD, we constructed a distribution of the number of symptoms of inattention and hyperactivity/

impulsivity endorsed by non-ADHD controls. A childhood ADHD incident case was classified as having persistent, adult ADHD if the number of symptoms exceeded 2 SDs above the mean number of current inattentive (ie, 4 symptoms) and/or hyperactive/impulsive symptoms (ie, 4 symptoms) endorsed by our non-ADHD controls. Our adult ADHD case definition also required endorsement of the M.I.N.I. statement that ADHD symptoms were having a significant adverse impact in 2 or more settings. Psychiatric disorders were determined by symptoms consistent with DSM-IV TR/*International Classification of Diseases, 10th Revision* as specified by the M.I.N.I.³⁶ The association between childhood ADHD status and presence of any psychiatric disorder was summarized by using an odds ratio (OR) estimated from a logistic regression model adjusted for age and gender.

RESULTS

Mortality

The SMR for overall survival of childhood ADHD cases versus controls was 1.88 (95% confidence interval [CI], 0.83–4.26; $P = .13$; Table 1). The cause-specific mortality for accidents only was similar for cases and controls (SMR, 1.70; 95% CI, 0.49–5.97; $P = .41$).

However, the cause-specific mortality for suicide only was significantly higher among ADHD cases than controls (SMR, 4.83; 95% CI, 1.14–20.46; $P = .032$).

Among the 7 ADHD cases who died, 5 had a previous history of both substance use disorder and ≥ 1 other psychiatric comorbidity.

Prospective Study Participants

Among the 367 eligible childhood ADHD cases, 232 (63.2%; 167 males, 65 females; mean age, 27.0 years) participated in the prospective study. Participating and nonparticipating adults with childhood

TABLE 1 Mortality Among ADHD Cases Versus Remainder of Members of the 1976 to 1982 Rochester, MN, Birth Cohort

	ADHD Cases (N = 367)	Remainder of Birth Cohort (N = 4946)
Total number of deaths ^a	7	37
Medically related	1	13
Suicide ^b	3	5
Homicide	0	2
Accident ^c	3	15
Unknown	0	2
Mean age of death (y)	21.9	19.9

^a Overall SMR, 1.88 (95% CI, 0.83–4.26; *P* = .13).

^b SMR for suicide only, 4.83 (95% CI, 1.14–20.46; *P* = .032).

^c SMR for accidents only, 1.70 (95% CI, 0.49–5.97; *P* = .41).

ADHD differed only on high school graduation rates (84.3% for participants vs 64.8% for nonparticipants; *P* < .01; Table 2). A total of 801 non-ADHD con-

trols from the same birth cohort were invited to participate, yielding 335 participants (210 males, 125 females; mean age, 28.6 years).

TABLE 2 Comparison of Participants and Nonparticipants in the Prospective Outcome Study Among Childhood ADHD Cases

	Nonparticipants (N = 152) ^a	Participants (N = 232)	<i>P</i>
Male, <i>n</i> (%)	121 (79.6)	167 (72.0)	0.09
Age on 12/31/2009			0.39
Mean (SD)	30.2 (1.9)	30.0 (1.9)	
Range	27.0–34.0	27.0–33.9	
White, <i>n</i> (%)	150 (98.7)	231 (99.6)	0.57
Address at last study contact:			
Unknown, <i>n</i>	17 ^b	0	0.06
Within 250 miles of Rochester, <i>n</i> (%)	112 (83.0)	208 (89.7)	
>250 miles from Rochester, <i>n</i> (%)	23 (17.0)	24 (10.3)	
Received stimulant treatment during childhood, <i>n</i> (%)	119 (78.3)	178 (76.7)	0.72
Psychiatric diagnosis before age 18			
Unknown, <i>n</i> ^b	17	22	0.62
No, <i>n</i> (%)	58 (43.0)	96 (45.7)	
Yes, <i>n</i> (%)	77 (57.0)	114 (54.3)	
Substance abuse before age 18, <i>n</i> (%)	33 (21.7)	51 (22.0)	0.95
Any learning disability before age 19, <i>n</i> (%)	109 (71.7)	161 (69.4)	0.63
High school graduation status ^c			
Unknown, <i>n</i>	13	3	<0.001
Moved, <i>n</i>	31	32	
Graduated, <i>n</i> (%)	70 (64.8)	166 (84.3)	
GED, <i>n</i> (%)	12 (11.1)	9 (4.6)	
Dropped, <i>n</i> (%)	26 (24.1)	22 (11.2)	
Sociodemographic factors at birth			
Maternal age at birth, mean (SD)	25.7 (5.0)	26.0 (4.6)	0.44
Maternal education			
Unknown, <i>n</i>	15	20	0.31
<High school, <i>n</i> (%)	16 (11.7)	13 (6.1)	
High school graduate, <i>n</i> (%)	52 (38.0)	88 (41.5)	
Some college, <i>n</i> (%)	44 (32.1)	74 (34.9)	
College graduate, <i>n</i> (%)	25 (18.3)	37 (17.5)	
Maternal marital status			
Married, <i>n</i> (%)	136 (89.5)	212 (91.4)	0.53
Not married, <i>n</i> (%)	16 (10.5)	20 (8.6)	

^a Nonparticipants included ADHD cases who were either deceased (*n* = 7), incarcerated at the time of recruitment (*n* = 10), denied permission for use of records for research at the time of the prospective study (*n* = 17), or who declined participation or did not respond to the recruitment letters (*n* = 118).

^b These subjects had previously denied access to their medical records for research purposes when these data were originally collected.

^c The graduation status is the subject's status as determined before their participation.

Incarceration

Childhood ADHD cases who were found to be incarcerated at the time of recruitment (*N* = 10) could not be invited to participate in the prospective study due to human subjects concerns.

Persistence of ADHD Into Adulthood

Among the 232 participating childhood ADHD cases, 68 (29.3%) fulfilled criteria for adult ADHD (95% CI, 23.5–35.2). Rates of persistent ADHD were similar for males (29.3%; 95% CI, 22.4–36.3) and females (29.2%; 95% CI, 18.2–40.3). If the M.I.N.I. requirement for self-report of adverse impact of ADHD symptoms were disregarded, the rate of persistent ADHD would increase to 38.8% (95% CI, 32.5–45.1).

Adult Psychiatric Disorders

Adults with research-identified childhood ADHD were significantly more likely than controls to have ≥1 comorbid psychiatric disorder besides adult ADHD (56.9% vs 34.9%; adjusted OR, 2.6; 95% CI, 1.8–3.8; *P* < .01). The most common adult psychiatric problems among childhood ADHD cases were alcohol dependence/abuse (26.3%), antisocial personality disorder (16.8%), other substance dependence/abuse (16.4%), current or past history of hypomanic episode (15.1%), generalized anxiety disorder (14.2%), and current major depressive episode (12.9%). Among the childhood ADHD cases, those with persistent ADHD were more likely to have ≥1 comorbid psychiatric disorder than those whose ADHD did not persist (80.9% vs 47.0%; adjusted OR, 4.8; 95% CI, 2.4–9.5; *P* < .001).

Cumulative Perspective on Adult Outcomes for Childhood ADHD

Among the 367 childhood ADHD cases, 7 (1.9%) were deceased at the time of recruitment and 10 (2.7%) were incarcerated (Fig 1). Among the 232 childhood ADHD cases who participated in the prospective study, 55 (23.7%) had persistent ADHD

with ≥ 1 comorbid psychiatric disorder; 13 (5.6%) had persistent ADHD only (without comorbid psychiatric disorders); and 77 (33.2%) had ≥ 1 other psychiatric disorder without persistent ADHD. Only 87 (37.5%) were free of these adverse outcomes.

DISCUSSION

Several important findings emerge from this population-based, epidemio-

logic study of ADHD across the lifespan. First, ADHD should no longer be viewed only as a disorder primarily affecting the behavior and learning of children, but also as a major health condition that confers increased risk for early death due to suicide. Second, although nearly one-third of children with ADHD will continue to fulfill norm-referenced criteria for ADHD as adults, the majority will have at least one mental

health problem in adulthood. Finally, the cumulative burden of ADHD through the lifespan is considerable, including mortality, social adversity in the form of criminal behavior, persistence of ADHD into adulthood, and increased rates of other mental health problems.

Previous research using clinic-referred samples suggests that adult ADHD may be associated with increased risk for early death.²³ Barkley et al²³ found

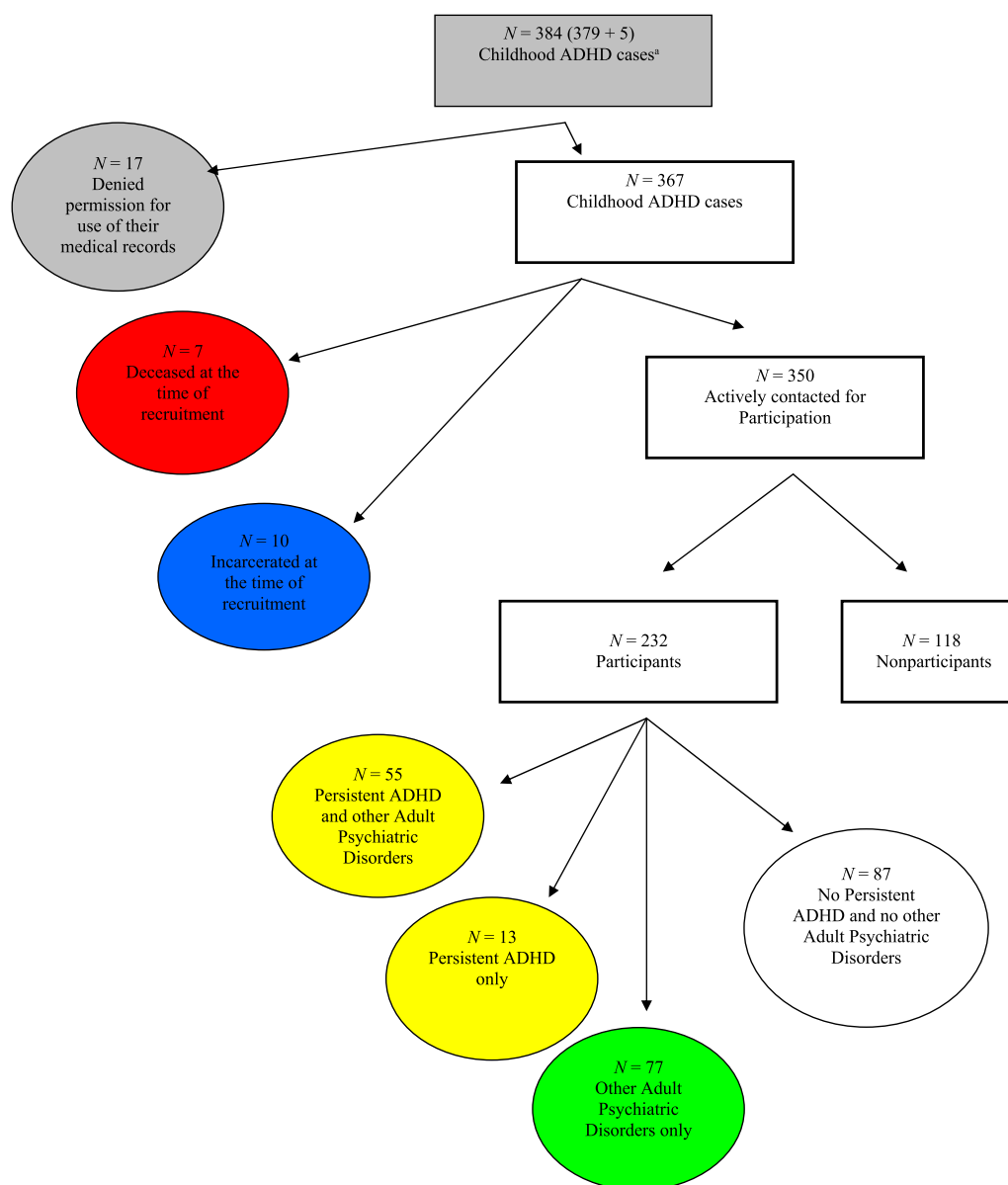


FIGURE 1

Mortality and psychosocial adversity among ADHD cases in the 1976 to 1982 Rochester, Minnesota, birth cohort. ^aIncludes 379 originally identified childhood ADHD cases and 5 controls identified with childhood ADHD as part of the current study.

adults with a history of childhood ADHD were more than twice as likely as controls to have considered or attempted suicide by age 21 years. By age 27, 5 of the 158 members of their original cohort had died: 2 by suicide, 1 in a car accident, and 1 from a drug overdose.²³ Our longitudinal, population-based study confirms that childhood ADHD is associated with significantly increased risk for early death from suicide. The majority of deaths among childhood ADHD cases were in individuals with comorbid substance use and psychiatric disorders (5 of 7). This finding suggests the psychiatric comorbidities associated with ADHD may place patients at risk for early death, although the relatively small number of cases precludes a statistical analysis.

Previous studies also suggest that childhood ADHD may be a risk factor for later criminal behavior. Barkley et al²³ found 73% of their subjects with persistent ADHD in their clinic-referred sample had been arrested, and 58% were incarcerated by age 27 years. In a prospective study of boys with ADHD referred to a psychiatric clinic, Mannuzza et al³⁷ found 47% had been arrested and 15% were incarcerated by age 25 years versus 24% and 1%, respectively, of the comparison sample. We found 2.7% of our nonreferred childhood ADHD cases were incarcerated at the time of recruitment for this prospective study. In a future report, we will examine the lifetime rates of incarceration and other legal problems for the ADHD cases and controls who participated in our prospective study.

Estimates of the rate of persistence of ADHD from childhood to adulthood have ranged from 6% to 66%.^{3–13} Previous prospective studies have depended on outcomes from childhood ADHD cases referred to specialty treatment programs.²³ The single epidemiologic study of persistence of ADHD into

adulthood depended on adult recall of childhood ADHD.⁸ Also, previous research has focused on boys.^{1,4,6,9,10} Sample sizes for prospective studies have been small, ranging from 50 to 147.^{4–6,9,26} Assessment procedures and research diagnostic criteria for ADHD have been variable. Also, DSM-IV TR criteria are based on childhood characteristics of ADHD.¹⁴ Therefore, the validity of the DSM-IV TR criteria to diagnose adult ADHD is questionable, because of the change in number and type of symptoms that characterize adult ADHD.³⁸ Only Barkley et al⁴ used adult ADHD diagnostic criteria based on a developmentally referenced standard and reported a persistence rate of 66% in a clinic-referred sample. In contrast, our 29.3% estimate of the rate of persistence of ADHD (similar for males and females) is based on a non-referred, population-based sample, using adult-specific, norm-referenced criteria.

Previous research has suggested that high rates of comorbid psychiatric disorders may be found among children and adults with ADHD. Barkley et al found increased rates of comorbid substance abuse disorder, anxiety disorder, mood disorder, personality disorders, and disruptive behavior disorders among adults with ADHD that had persisted from childhood into adulthood.²³ Adults whose childhood ADHD did not persist also had increased rates of psychiatric comorbidity, although lower than those with persistent ADHD (47.3% vs 84.3%).²³ Other smaller studies also report elevated rates of psychiatric comorbidity (65–89%) among adults with ADHD.^{15–22} However, these studies used non-representative samples of children referred to specialty treatment programs for ADHD. It is therefore particularly concerning that we found high rates of psychiatric comorbidity among our population-based sample of

adult subjects with a history of childhood ADHD, regardless of whether ADHD persisted into adulthood (80.9% and 47.0% comorbidity rates, respectively).

Several limitations should be considered when interpreting our findings. The initial retrospective identification of ADHD cases in the birth cohort may have been incomplete. However, comprehensive access to relevant information from school and medical records and use of rigorous research criteria suggest that it is unlikely that we missed a significant number of childhood ADHD cases.³⁴ The total number of deaths in the cohort was relatively small, potentially limiting our ability to detect differences in the rates of early death. However, the rate of death from suicide was significantly higher among ADHD cases than controls. Also, a larger, population-based, prospective study of this outcome would likely be impractical in other settings. We were not able to determine the rate of incarceration of all non-ADHD cases in the birth cohort, but reported this outcome for ADHD cases to describe their status at the time of recruitment for the prospective, adult study. Our prospective outcome study included 61% of the original cohort of childhood ADHD cases; however, participants and non-participants differed only on high school graduation rates. We ascertained adult ADHD and other psychiatric disorders on the basis of subject responses to a standardized, neuro-psychiatric interview. Barkley et al²³ found that self-report of ADHD symptoms is more accurate in mature adults than it is in children or adolescents. While the use of a normative cutoff of 2 SDs has not been empirically validated, this approach was used by Barkley et al,⁴ reflecting a common standard for identifying clinically significant symptom thresholds for neurodevelopmental disorders. Our use of

a 2-SD cutoff is also consistent with the finding that DSM-IV TR thresholds may not be appropriate to diagnose adult ADHD, because they are not developmentally referenced in adults.⁴ Finally, at the time of our original, retrospective study, Rochester, Minnesota, was primarily a white, middle class community, so inferences to other populations may be limited. Nevertheless, the residents of Rochester have excellent access to medical care and comprise a homogeneous population (95% white), thereby minimizing the confounding effects of so-

cioeconomic status, ethnicity, and race on the study questions. It is possible, if not likely, that the magnitude of the adverse outcomes in this cohort would be even greater in populations with additional challenges such as higher rates of poverty.

CONCLUSIONS

These findings have important implications for the effectiveness of care provided to children with ADHD and the system of care to meet the needs of individuals with ADHD across the life-

span. It is concerning that only a minority of children with ADHD reaches adulthood without suffering serious adverse outcomes, suggesting that the care of childhood ADHD is far from optimal. Our results also indicate that clinicians, insurers, and health care systems must be prepared to provide appropriate care for adults with ADHD.

ACKNOWLEDGMENTS

We thank study coordinators Candice Klein and Ann Van Oosten for their efforts in subject recruitment and conduct of the study assessments.

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Pediatrics 2013;131;637; originally published online March 4, 2013;

DOI: 10.1542/peds.2012-2354

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