



Published in final edited form as:

Psychol Med. 2014 June ; 44(8): 1779–1792. doi:10.1017/S0033291713002419.

The effects of temporally secondary co-morbid mental disorders on the associations of DSM-IV ADHD with adverse outcomes in the US National Comorbidity Survey Replication Adolescent Supplement (NCS-A)

R. C. Kessler^{1,*}, L. A. Adler², P. Berglund³, J. G. Green⁴, K. A. McLaughlin⁵, J. Fayyad⁶, L. J. Russo⁷, N. A. Sampson¹, V. Shahly¹, and A. M. Zaslavsky¹

¹Department of Health Care Policy, Harvard Medical School, Boston, MA, USA

²Departments of Psychiatry and Child and Adolescent Psychiatry, NYU School of Medicine and Psychiatry, NY VA Harbor Healthcare Service, New York, NY, USA

³University of Michigan, Institute for Social Research, Ann Arbor, MI, USA

⁴School of Education, Boston University, Boston, MA, USA

⁵Division of General Pediatrics, Children's Hospital Boston, Harvard Medical School, Boston, MA, USA

⁶Institute for Development Research, Advocacy, and Applied Care (IDRAAC), St George Hospital University Medical Center, Beirut, Lebanon

⁷Shire Development Inc., Wayne, PA, USA

Abstract

Background—Although DSM-IV attention deficit hyperactivity disorder (ADHD) is known to be associated with numerous adverse outcomes, uncertainties exist about how much these associations are mediated temporally by secondary co-morbid disorders.

Method—The US National Comorbidity Survey Replication Adolescent Supplement (NCS-A), a national survey of adolescents aged 13–17 years ($n = 6483$ adolescent–parent pairs), assessed DSM-IV disorders with the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). Statistical decomposition was used to compare direct effects of ADHD with indirect effects of ADHD through temporally secondary mental disorders (anxiety, mood, disruptive behavior, substance disorders) in predicting poor educational performance (suspension, repeating a grade, below-average grades), suicidality (ideation, plans, attempts) and parent perceptions of adolescent functioning (physical and mental health, interference with role functioning and distress due to emotional problems).

© Cambridge University Press 2013

*Address for correspondence: R. C. Kessler, Ph.D., Department of Health Care Policy, Harvard Medical School, 180 Longwood Avenue, Boston, MA 02115, USA. kessler@hcp.med.harvard.edu.

Supplementary material: For supplementary material accompanying this paper visit <http://dx.doi.org/10.1017/S0033291713002419>.

Results—ADHD had significant gross associations with all outcomes. Direct effects of ADHD explained most (51.9–67.6%) of these associations with repeating a grade in school, perceived physical and mental health (only girls), interference with role functioning and distress, and significant components (34.5–44.6%) of the associations with school suspension and perceived mental health (only boys). Indirect effects of ADHD on educational outcomes were predominantly through disruptive behavior disorders (26.9–52.5%) whereas indirect effects on suicidality were predominantly through mood disorders (42.8–59.1%). Indirect effects on most other outcomes were through both mood (19.8–31.2%) and disruptive behavior (20.1–24.5%) disorders, with anxiety and substance disorders less consistently important. Most associations were comparable for girls and boys.

Conclusions—Interventions aimed at reducing the adverse effects of ADHD might profitably target prevention or treatment of temporally secondary co-morbid disorders.

Keywords

Adolescence; attention deficit hyperactivity disorder (ADHD); co-morbidity; DSM-IV; epidemiology; National Comorbidity Survey Replication Adolescent Supplement (NCS-A); prevalence

Introduction

Attention deficit hyperactivity disorder (ADHD) is a common condition involving inattention, hyperactivity and impulsivity. The prevalence of DSM-IV ADHD among US adolescents has been estimated as 5.9–7.1% (Willcutt, 2012). Although a rich literature describes associations of ADHD with academic underachievement (Frazier *et al.* 2007; Pingault *et al.* 2011; Klein *et al.* 2012), suicidality (James *et al.* 2004; Sourander *et al.* 2009; Chronis-Tuscano *et al.* 2010; Impey & Heun, 2012) and psychosocial role impairment (Kadesjo & Gillberg, 2001; Strine *et al.* 2006; Larson *et al.* 2011), much ambiguity surrounds the risk pathways involved in these adverse effects owing to the very high co-morbidities of ADHD with other psychiatric disorders (Pliszka, 2000; Kadesjo & Gillberg, 2001; Gillberg *et al.* 2004; Steinhausen *et al.* 2006), most of which post-date ADHD in onset (Taurines *et al.* 2010; Kessler *et al.* 2012b).

Despite some concern that high ADHD co-morbidity might represent an artifact of shared diagnostic criteria or informant bias, expert consensus holds that co-morbidity is a real and distinctive clinical feature of ADHD (Angold *et al.* 1999; Daviss, 2008). However, as many of the disorders co-morbid with ADHD have been independently linked to the same adverse outcomes as ADHD (Szatmari *et al.* 1989; Lollar *et al.* 2012), it is plausible to think that they might mediate the observed associations of ADHD with those outcomes. Although clinic-based research has begun exploring this possibility to optimize ADHD treatment and refine secondary prevention strategies (Lahey *et al.* 2002; Biederman *et al.* 2008; Molina *et al.* 2012), comparatively little is known about the mediating effects of co-morbidities in the general population. One large US epidemiological survey of youth (aged 6–17 years) with parent-reported ADHD documented that numerous indicators of functioning declined as the number of co-morbid disorders increased (Larson *et al.* 2011), but failed to investigate the mediating effects of specific co-morbidities. Two smaller prospective studies examined this

attenuation but their estimates were biased by controls including only childhood-onset (i.e. not adolescent-onset) co-morbid disorders (Hinshaw *et al.* 2012), leading to an underestimation of the extent to which co-morbid disorders mediate the effects of ADHD. One of these two studies also included controls for intercurrent ADHD symptom profiles (Latimer *et al.* 2003), leading to an overestimation of the mediating effects of co-morbid disorders.

Elaborating the complex interconnections between ADHD and co-morbid conditions in leading to adverse outcomes of ADHD might help to identify promising areas for targeted preventive and treatment interventions. The current report presents data of this sort based on the US National Comorbidity Survey Replication Adolescent Supplement (NCS-A), a national survey of common adolescent DSM-IV disorders. We first examined the prevalence and associations of DSM-IV ADHD with temporally secondary co-morbid disorders and diverse measures of adverse outcomes. Statistical decomposition methods were then used to trace out the extent to which the gross (uncontrolled) associations of ADHD with the outcomes are due to direct effects of ADHD *versus* indirect effects of ADHD through temporally secondary anxiety, mood, disruptive behavior and substance disorders.

Method

Sample

The NCS-A is a well-characterized community epidemiological study of the presence and correlates of adolescent DSM-IV disorders. Previous reports have described study design, field procedures and overall disorder prevalence (Kessler *et al.* 2009a, b, 2012a; Merikangas *et al.* 2009). In brief, adolescents (aged 13–17 years) selected from a dual-frame household–school sample were interviewed at home between February 2001 and January 2004 in separate household and school samples. Adolescents were administered face-to-face interviews and one parent or surrogate (hereafter referred to as the parent) for each participating adolescent completed a self-administered questionnaire. The conditional adolescent response rate was 86.8% and 82.6% for household and school samples respectively. Parent data were only available for a subset of adolescent respondents; this was taken into consideration by weighting data in complete pairs to adjust for differences with incomplete pairs (Kessler *et al.* 2009a, b). This report focuses on the 6483 adolescent–parent pairs having complete data. Each participant was paid US\$50 for participation. Recruitment and consent procedures were approved by the Human Subjects Committees of Harvard Medical School and the University of Michigan. Data were weighted to adjust for discrepancies between the sample and the US Census population distributions of a wide range of sociodemographic and geographic variables (Kessler *et al.* 2009a, b).

Measures

DSM-IV disorders—All adolescents completed the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI), a fully structured diagnostic interview (Kessler & Üstün, 2004), to assess lifetime and recent prevalence of common DSM-IV disorders. Diagnoses included two mood, six anxiety, five disruptive behavior and two substance disorders. Age of onset (AOO) of each lifetime disorder was assessed

retrospectively using probes shown experimentally to maximize recall accuracy (Knäuper *et al.* 1999). Adolescent self-reports were obtained for all 15 disorders. Parent informant reports were obtained for four disorders shown in prior research to benefit most from inclusion of informant reports (Grills & Ollendick, 2002; De Los Reyes & Kazdin, 2005). ADHD was one of those disorders along with major depression/dysthymia, conduct disorder and oppositional defiant disorder. A clinical reappraisal study documented good concordance of all diagnoses with independent clinical assessments based on the Schedule for Affective Disorders and Schizophrenia for School Age Children, Present and Lifetime Version (K-SADS-PL; Kaufman *et al.* 1997), with adolescent and parent reports combined using an ‘or’ rule. In the case of ADHD, however, maximum concordance with K-SADS diagnoses was obtained by using only parent reports of Criteria A (at least six of nine symptoms of inattention and/or hyperactivity-impulsivity), B (some impairing symptoms before age 7), C (clinically significant impairment in at least two settings) and D (clinically significant impairment in social, academic or occupational functioning) (Frazier *et al.* 2007), yielding area under the receiver operating characteristic curve (AUC) of 0.78, sensitivity (SN) of 0.58 and specificity (SP) of 0.96. The positive likelihood ratio [LR+; (SN)/(1-SP)] was 18.7, a value well above the minimum LR+ value of 10.0 generally considered definitive for ruling in diagnoses (Haynes *et al.* 2006). As a result, parent-only reports are used here to define ADHD. Concordance (AUC) of diagnoses based on the CIDI with diagnoses based on the K-SADS for other disorders was in the range 0.79–0.94 for anxiety and mood disorders, 0.85–0.98 for disruptive behavior disorders other than ADHD and 0.92–0.98 for substance abuse.

Adverse outcomes—Three domains of adverse adolescent outcomes are considered here: educational performance, suicidal behaviors and parent perceptions of adolescent health and functioning.

Educational performance: Parents were asked about lifetime occurrence and AOO of their adolescent being suspended from school and having to repeat a grade in school. Adolescents rated their grades over the most recent school year on a seven-point scale from ‘below average’ to ‘above average’. As only a small proportion of adolescents rated their grades below average, responses were collapsed into a single yes-no measure of below-average grades.

Suicidal behaviors: Adolescents were asked about their lifetime history of suicidal behaviors with a modified version of the Suicidal Behavior Module of the CIDI (Nock *et al.* 2009). These questions assessed lifetime occurrence and AOO of suicide ideation, plans and attempts.

Parent perceptions of adolescent health and functioning: Parents were asked to rate their adolescent's overall physical and mental health on a 0 to 10 scale, where 0 represents ‘the worst possible health’ and 10 represents ‘the best possible health.’ Responses were standardized to a mean of 0 and a variance of 1 to facilitate interpretation. Parents also completed the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997), a 25-item screening instrument that includes parent ratings of the extent to which adolescent

difficulties with ‘emotions, concentration, behavior, or being able to get along with other people’ interfere with the adolescent's everyday life in the areas of ‘home life, friendships, learning and leisure activities’ and cause ‘upset or distress’. Response categories for interference and distress were ‘a great deal’, ‘quite a lot’, ‘only a little’ or ‘not at all’ (coded 3-0 respectively) (Goodman, 2001; Becker *et al.* 2006). Again, responses were standardized to a mean of 0 and a variance of 1 to facilitate interpretation.

Sociodemographics—Sociodemographics considered here include sex, race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic, Other), parental education [less than high school graduation, high school or General Educational Development (GED), some post-secondary education, college degree], number of biological parents residing with the adolescent (0, 1, 2), and urbanicity of residence (major metropolitan area, other urbanized area, rural area). Survey information was collected to date transitions in the number of biological parents residing with the adolescent, allowing us to define that variable as a time-varying predictor of disorder onset and role impairments. Urbanicity was assessed only for time of interview.

Analysis methods

Logistic regression analysis (Hosmer & Lemeshow, 2001) examined sociodemographic correlates of ADHD. Discrete-time survival analysis (Willett & Singer, 1993) with person-year the unit of analysis and a logistic link function estimated associations of temporally primary ADHD with subsequent first onset of other DSM-IV/CIDI disorders controlling sociodemographics. Survival coefficients and their standard errors were exponentiated and are reported as odds ratios (ORs) with 95% confidence intervals (CIs).

The gross (i.e. without controls for co-morbidities) associations of lifetime ADHD with the adverse outcomes were estimated using either discrete-time survival analysis to predict dated lifetime outcomes (suspension, grade retention, suicidality), logistic regression to predict below-average school performance, or ordinary least-squares regression analysis (Draper & Smith, 1998) to predict continuous outcomes (parent perceptions of adolescent health, functioning and distress), all controlling sociodemographics. We then examined parallel models for net (i.e. controlling co-morbidities) associations between lifetime ADHD and the same outcomes. Given that ADHD pre-dates the overwhelming majority of co-morbid disorders (Taurines *et al.* 2010), differences between gross and net associations are largely due to indirect effects of ADHD through secondary disorders: that is, the product of the associations of ADHD with secondary disorders and of secondary disorders with the outcomes. It is important to note that these indirect effects indicate the existence of temporal mediation of the gross associations of ADHD with later outcomes, but that temporal mediation does not necessarily represent causal mediation because of the possible existence of unmeasured common causes. Formal statistical decomposition methods exist to trace out these temporally indirect effects by comparing coefficients for ADHD in models with and without controls for mediators (Karlson & Holm, 2011). We used these methods to calculate the extent to which the associations of ADHD with the outcomes were mediated through intervening mood, anxiety, disruptive behavior and substance disorders. Estimates of direct effects (i.e. coefficients for ADHD in models controlling co-morbid disorders) and indirect

effects (i.e. effects of ADHD mediated through each of the four sets of secondary disorders) were then divided by estimates of gross associations of ADHD with the outcomes to describe the proportions of gross associations due to each component.

Standard errors of prevalence estimates and regression coefficients were estimated using the Taylor series method (Wolter, 1985) implemented in SAS (SAS Institute, 2008) to account for NCS-A sample weights and clustering. Simulation was used to estimate standard errors of proportional direct and indirect effect estimates using the jackknife repeated replications pseudo-replication method (Wolter, 1985) implemented in a SAS macro. Significance of predictor sets was evaluated using Wald χ^2 tests based on Taylor series coefficient variance-covariance matrices. Statistical significance was consistently evaluated using 0.05-level two-sided tests.

Results

Prevalence

Lifetime and 12-month prevalence of DSM-IV/CIDI ADHD (standard errors in parentheses) is 8.1% (0.6) and 6.3% (0.5) respectively. Prevalence is significantly higher among boys than girls [12.1% (0.9) *v.* 3.9% (0.5) lifetime, $\chi_1^2=66.2, p<0.001$; 9.6% (0.9) *v.* 2.8% (0.5) 12-month, $\chi_1^2=45.8, p<0.001$].

Sociodemographic correlates

Lifetime DSM-IV/CIDI ADHD is significantly more common among adolescents living with neither or only one biological parent than with both biological parents (OR 2.4–2.1; $\chi_2^2=22.6, p<0.001$) (Table 1). This association is found among both boys (OR 2.9–2.2) and girls (OR 1.8–1.9). However, ADHD is unrelated to race/ethnicity ($\chi_2^2=0.3, p=0.86$), parent education ($\chi_3^2=7.1, p=0.07$) or urbanicity ($\chi_2^2=0.7, p=0.69$).

Associations of ADHD with temporally secondary DSM-IV/CIDI disorders

Lifetime DSM-IV/CIDI ADHD is associated with elevated odds of all 14 temporally secondary DSM-IV/CIDI disorders considered here (Table 2). The range of ORs is 1.3–6.8. Eleven ORs are significant: both mood disorders (2.5–3.7), three anxiety disorders (1.5–2.4), all four disruptive behavior disorders (2.2–6.8) and both substance disorders (2.2–2.4). By far the highest ORs are with conduct disorder (4.5) and oppositional defiant disorder (6.8). ORs differ significantly by sex of respondent only for one disorder: eating disorders (OR 4.9 for boys, 1.2 for girls, $\chi_1^2=8.4, p=0.004$).

Associations of ADHD with functional outcomes

Lifetime ADHD is significantly associated with all the measures of functioning considered here (Table 3). The ORs for ADHD predicting the three dichotomous measures of poor educational performance (suspension, repeating a grade, below-average grades) are in the range 2.8–4.3 and are equivalent for boys and girls ($\chi_1^2=0.0 - 2.8, p=0.10-0.99$). The ORs for ADHD predicting suicide ideation and plans are 3.1 and 4.2 respectively, and are

equivalent for boys and girls ($\chi^2=0.6 - 1.9, p=0.17-0.42$), whereas the OR for ADHD predicting suicide attempts is significantly higher among boys (12.3) than girls (2.4; $\chi^2=3.9, p=0.049$).

ADHD is associated with significantly reduced perceived (by parents) physical (12% of a S.D.) and mental (56% of a S.D.) health. These associations are equivalent for boys and girls ($t=0.2-1.0, p=0.38-0.85$). ADHD is associated with significantly increased interference with activities due to psychological problems (S.D.=1.49) and significantly increased distress due to psychological problems (S.D.=1.37). These associations are equivalent for boys and girls ($t=0.2-1.1, p=0.29-0.80$).

Direct effects of ADHD and indirect effects through secondary DSM-IV/CIDI disorders

The extent to which the gross associations of ADHD with the outcomes considered here are mediated by temporally secondary DSM-IV/CIDI disorders varies substantially across outcomes (Table 4). Direct effects of ADHD explain more than 50% of the gross associations of ADHD with repeating a grade in school (71.6% among boys and 65.6% among girls), perceived physical (67.6% among girls) and mental (51.9% among girls) health, interference with role functioning (57.1% among boys and 56.2% among girls) and distress (53.5% among boys and 56.4% among girls), and smaller but nonetheless statistically significant components of the gross associations of ADHD with school suspension (37.7% among boys and 34.5% among girls), below-average grades (39.8%, only boys), suicidal ideation and plans (19.3% and 24.2% respectively, only boys) and perceived mental health (44.6%, only boys). Direct effects of ADHD are statistically insignificant, in comparison, in predicting below-average grades (only girls), suicidal ideation and plans (only girls), and parent perceptions of adolescent physical health (only boys).

Indirect effects of ADHD on educational outcomes are predominantly through temporally secondary disruptive behavior disorders (26.9–52.5%) whereas indirect effects on suicidality are predominantly through temporally secondary mood disorders (42.8–59.1%). Indirect effects of ADHD on most other outcomes, in comparison, are through a mix of both temporally secondary mood (19.8–31.2%) and disruptive behavior (20.1–24.5%) disorders. Indirect effects of ADHD through temporally secondary anxiety disorders are consistently insignificant among boys but are statistically significant, albeit relatively modest in substantive terms, among girls in predicting repeating a grade in school, below-average grades and suicide ideation and plans (13.1, 10.9, 12.2 and 11.3% respectively). Finally, indirect effects of ADHD through temporally secondary substance disorders are statistically significant among boys only in predicting school suspension, suicide ideation and plans (25.0, 19.8 and 23.5% respectively) and among girls only in predicting suicide ideation (14.6%).

Discussion

The basic patterns of ADHD prevalence and socio-demographic distribution in the NCS-A are consistent with previous US studies, establishing broad comparability between the NCS-

A and existing literature. In brief, the NCS-A lifetime ADHD prevalence estimate (8.1%) is within the range of previous US national surveys (Dey *et al.* 2004; CDC, 2005, 2010; Pastor & Reuben, 2008; Bloom *et al.* 2010; Schieve *et al.* 2012). The same is true of the NCS-A 12-month prevalence estimate (6.3%) (Polanczyk *et al.* 2007; Willcutt, 2012) other than for a considerably higher 12-month prevalence estimate (8.6%) in another US national survey (Froehlich *et al.* 2007; Merikangas *et al.* 2010) that was subsequently shown to use an ADHD measure that was upwardly biased (Lewczyk *et al.* 2003). The significantly higher prevalence of ADHD among girls than boys in the NCS-A is perhaps the most consistently documented sociodemographic difference in ADHD prevalence in both clinical (Novik *et al.* 2006) and epidemiological (Froehlich *et al.* 2007) studies. The finding that ADHD is associated with non-intact family structure is also consistent with other community surveys (Hurtig *et al.* 2007) and with prospective studies that find child–adolescent ADHD to be a risk factor for parent marital conflict and dissolution (Wymbs *et al.* 2008; Schermerhorn *et al.* 2012). Our failure to find significant associations of ADHD with race/ethnicity, urbanicity and parental education is largely consistent with previous community studies (Froehlich *et al.* 2007; Bussing *et al.* 2010), although regional studies, which tend to use convenience samples, yield more mixed results (Wolraich *et al.* 1996; Gaub & Carlson, 1997; Angold *et al.* 2002).

The NCS-A finding that ADHD is significantly associated with numerous temporally secondary co-morbid mental disorders is consistent with other cross-sectional surveys (Pliszka, 2000; Kadesjo & Gillberg, 2001; Steinhausen *et al.* 2006) and also with most (Costello *et al.* 2003; Molina & Pelham, 2003; Bussing *et al.* 2010; Chronis-Tuscano *et al.* 2010), but not all (Copeland *et al.* 2009), longitudinal community surveys. The finding that the strongest of such associations are with conduct disorder and oppositional defiant disorder is also consistent with previous studies (Pliszka, 2000; Connor *et al.* 2010), as is the finding that these associations are largely comparable for boys and girls (Fergusson *et al.* 1993a).

As noted in the introduction, an extensive literature documents that ADHD is significantly associated with numerous adverse outcomes similar to those in the NCS-A (e.g. Kadesjo & Gillberg, 2001; James *et al.* 2004; Strine *et al.* 2006; Frazier *et al.* 2007; Sourander *et al.* 2009; Chronis-Tuscano *et al.* 2010; Larson *et al.* 2011; Pingault *et al.* 2011; Impey & Heun, 2012; Klein *et al.* 2012). However, we also noted that much ambiguity surrounds the risk pathways in these associations due to the high co-morbidity of ADHD with numerous temporally secondary mental disorders. Although several previous studies addressed this issue by showing that statistical adjustments for co-morbidity reduce the associations of ADHD with various indicators of impairment (Fergusson *et al.* 1993b; Flory & Lynam, 2003; Bauermeister *et al.* 2007; Arias *et al.* 2008; Torok *et al.* 2012), the most convincing studies of this sort focused on the cross-classification of ADHD only with other externalizing disorders (typically conduct disorder and/or oppositional defiant disorder) in school samples and examined effects only on measures of school performance (Daley & Birchwood, 2010). The NCS-A analysis is, to our knowledge, the first attempt to carry out a formal decomposition of indirect effects through a wider range of temporally secondary

mental disorders in explaining the gross associations of ADHD with a more diverse set of outcomes in a community epidemiological survey.

Our finding that the direct effect of ADHD is a key component of the gross associations of ADHD with educational outcomes is consistent with several other community studies of childhood ADHD and adolescent school performance, although, as noted in the previous paragraph, the latter studies typically controlled only for other disruptive behavior disorders (Fergusson *et al.* 1997; Rapport *et al.* 1999). Questions can be raised about the ADHD subtypes that account for these effects (i.e. inattentive, hyperactive-impulsive, combined) and about the component mechanisms that mediate these effects (e.g. working memory, behavioral inhibition, sluggish cognitive tempo) (Raiker *et al.* 2012; Barkley, 2013), but these questions extend beyond the limits of the NCS-A because of the unreliability of the NCS-A distinction between AD and HD subtypes and the absence of information on ADHD component mechanisms.

The NCS-A finding that temporally secondary disruptive behavior disorders and, to a lesser extent, substance disorders (for school suspension among boys) account statistically (although not necessarily causally) for significant components of the gross associations of ADHD with the measures of poor educational performance considered here are less consistent with previous research, which has typically, although not always (Monuteaux *et al.* 2007), found that the significant associations of disruptive behavior disorders with adolescent school performance disappear when ADHD is controlled (Fergusson *et al.* 1997; Rapport *et al.* 1999). However, it is important to note that the NCS-A measures of educational performance are broader than the objective academic test measures typically used as outcomes in studies of the effects of ADHD on school performance. Disruptive behavior disorders have been found to be more important in predicting outcomes indicative of broader failures in role performance in the domains of occupational and marital functioning (Fergusson *et al.* 2010), and later antisocial behaviors (Gunter *et al.* 2006; Elkins *et al.* 2007; Pardini & Fite, 2010). The NCS-A results are broadly consistent with those other studies in finding significant indirect effects of ADHD through temporally secondary disruptive behavior disorders not only on the educational outcomes considered here but also on perceived mental health, interference with role functioning and distress due to emotional problems. The fact that these indirect effects were found to be comparable for boys and girls is consistent with the small amount of previous literature on this issue (Fergusson *et al.* 2010; Rucklidge, 2010; Hasson & Fine, 2012). We are unaware of any previous research, in comparison, that speaks to the NCS-A findings that the indirect effects of ADHD through temporally secondary anxiety and substance disorders are weaker, less consistent and more differentiated by adolescent sex (i.e. effects through anxiety disorders only on repeating a grade, below-average grades, and suicidality and only among girls; and effects through substance disorders only on suspension from school and suicidality and only among boys) than are the indirect effects of ADHD through temporally secondary mood or disruptive behavior disorders.

Our results should be interpreted in light of several limitations. First, DSM-IV disorders were assessed with a fully structured diagnostic interview rather than a clinical interview, although this limitation is tempered somewhat by the good concordance between survey

diagnoses and blinded clinical diagnoses (Kessler *et al.* 2009c). Second, the outcome measures were limited in scope and not validated, leading to an incomplete assessment of the adverse effects of ADHD. Given the focus on adolescents, we were also unable to consider adverse effects of ADHD on adult impairments in employment, finances, marriage and parenting (Fayyad & Kessler, in press). Third, the use of cross-sectional data to assess lifetime disorders and AOO and to make inferences about dynamic associations presumably led to underestimation of lifetime prevalence, imprecision in AOO reports that resulted in uncertainties in the estimates of temporal priorities between ADHD and the disorders characterized here as temporally secondary. Fourth, the non-experimental nature of the NCS-A makes it impossible to reject the hypothesis that unmeasured common causes of ADHD, secondary disorders and the outcomes considered here accounted for the associations we found. This means that, even though we were able to document that temporally secondary disorders account statistically for substantial components of the gross associations between ADHD and the outcomes considered here, there is no guarantee that these are causal effects.

Despite these limitations, our results demonstrate clearly that temporally secondary co-morbid disorders figure prominently in the associations of ADHD with most of the outcomes considered here. Such findings raise the possibility that interventions aimed either at preventing secondary disorders from occurring or at detecting and treating these disorders when they do occur might help to reduce the adverse effects of ADHD even when the ADHD itself is refractive. Little is known about this possibility, as controlled studies have not evaluated the effects of such intervention. However, this seems a potentially fruitful line of investigation given that co-morbidity with temporally secondary disorders is the norm among patients with ADHD (Taurines *et al.* 2010), that this co-morbidity complicates ADHD treatment (Ollendick *et al.* 2008), and that at least some treatments have shown effectiveness in reducing core symptoms of both ADHD and its co-morbidities (Connor *et al.* 2010).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Preparation of the current report was sponsored by Shire Pharmaceuticals. The NCS-A is supported by the National Institute of Mental Health [NIMH; U01-MH60220, R01-MH66627 (A.M.Z.) and U01MH060220-09S1] with supplemental support from the National Institute on Drug Abuse (NIDA), the Substance Abuse and Mental Health Services Administration (SAMHSA), the Robert Wood Johnson Foundation (RWJF; Grant 044780), and the John W. Alden Trust. A complete list of NCS-A publications can be found at www.hcp.med.harvard.edu/ncs. A public use version of the NCS-A dataset is available for secondary analysis. Instructions for accessing the dataset can be found at www.hcp.med.harvard.edu/ncs/index.php. The NCS-A is carried out in conjunction with the WHO World Mental Health (WMH) Survey Initiative. We thank the staff of the WMH Data Collection and Data Analysis Coordination Centers for assistance with instrumentation, fieldwork and consultation on data analysis. The WMH Data Coordination Centers have received support from NIMH (R01-MH070884, R13-MH066849, R01-MH069864, R01-MH077883), NIDA (R01-DA016558), the Fogarty International Center of the National Institutes of Health (FIRCA R03-TW006481), the John D. and Catherine T. MacArthur Foundation, the Pfizer Foundation, and the Pan American Health Organization. The WMH Data Coordination Centers have also received unrestricted educational grants from Astra Zeneca, BristolMyersSquibb, Eli Lilly and Company, GlaxoSmithKline, Ortho-McNeil, Pfizer, Sanofi-Aventis, and Wyeth. A complete list of WMH publications can be found at www.hcp.med.harvard.edu/wmh/.

Declaration of Interest: In the past 3 years Dr Kessler has been a consultant for Integrated Benefits Institute, Janssen Scientific Affairs, Sanofi-Aventis Groupe, Shire US Inc., and Transcept Pharmaceuticals. During the same time period Dr Adler has received grant/research support from Abbott Laboratories, Bristol-Myers Squibb, Merck & Co., Shire, Eli Lilly, Cephalon, National Institute of Drug Abuse, Chelsea Therapeutics, Organon, and Theravance. He has served on advisory boards and as a consultant to Abbott Laboratories, Novartis Pharmaceuticals, Shire, Eli Lilly, Ortho McNeil/Janssen/Johnson and Johnson, Merck, Organon, Sanofi-Aventis Pharmaceuticals, Psychogenics, Mindsite-uncompensated, AstraZeneca, Major League Baseball, i3 Research, Alcobra Pharmaceuticals, Otsuka, and Theravance. He has served as a consultant to EPI-Q, INC Research, United Biosource, Otsuka, and Major League Baseball Players Association. He has an options grant with Alcobra Pharmaceuticals. Dr Russo is a full-time employee and shareholder of Shire Pharmaceuticals.

References

- Angold A, Costello EJ, Erkanli A. Comorbidity. *Journal of Child Psychology and Psychiatry*. 1999; 40:57–87. [PubMed: 10102726]
- Angold A, Erkanli A, Farmer EM, Fairbank JA, Burns BJ, Keeler G, Costello EJ. Psychiatric disorder, impairment, and service use in rural African American and white youth. *Archives of General Psychiatry*. 2002; 59:893–901. [PubMed: 12365876]
- Arias AJ, Gelernter J, Chan G, Weiss RD, Brady KT, Farrer L, Kranzler HR. Correlates of co-occurring ADHD in drug-dependent subjects: prevalence and features of substance dependence and psychiatric disorders. *Addictive Behaviors*. 2008; 33:1199–1207. [PubMed: 18558465]
- Barkley RA. Distinguishing sluggish cognitive tempo from ADHD in children and adolescents: executive functioning, impairment, and comorbidity. *Journal of Clinical Child and Adolescent Psychology*. 2013; 42:161–173. [PubMed: 23094604]
- Bauermeister JJ, Shrout PE, Ramirez R, Bravo M, Alegria M, Martinez-Taboas A, Chavez L, Rubio-Stipec M, Garcia P, Ribera JC, Canino G. ADHD correlates, comorbidity, and impairment in community and treated samples of children and adolescents. *Journal of Abnormal Child Psychology*. 2007; 35:883–898. [PubMed: 17505876]
- Becker A, Steinhausen HC, Baldurosson G, Dalsgaard S, Lorenzo MJ, Ralston SJ, Dopfner M, Rothenberger A. Psychopathological screening of children with ADHD: Strengths and Difficulties Questionnaire in a pan-European study. *European Child and Adolescent Psychiatry*. 2006; 15(Suppl. 1):I56–I62. [PubMed: 17177017]
- Biederman J, Petty CR, Dolan C, Hughes S, Mick E, Monuteaux MC, Faraone SV. The long-term longitudinal course of oppositional defiant disorder and conduct disorder in ADHD boys: findings from a controlled 10-year prospective longitudinal follow-up study. *Psychological Medicine*. 2008; 38:1027–1036. [PubMed: 18205967]
- Bloom B, Cohen RA, Freeman G. Summary health statistics for U.S. children: National Health Interview Survey, 2009. *Vital and Health Statistics Series*. 2010; Series 10(No. 250):1–82.
- Bussing R, Mason DM, Bell L, Porter P, Garvan C. Adolescent outcomes of childhood attention-deficit/hyperactivity disorder in a diverse community sample. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2010; 49:595–605. [PubMed: 20494269]
- CDC. Mental health in the United States. Prevalence of diagnosis and medication treatment for attention-deficit/hyperactivity disorder – United States, 2003. Centers for Disease Control and Prevention. *Morbidity and Mortality Weekly Report*. 2005; 54:842–847. [PubMed: 16138075]
- CDC. Increasing prevalence of parent-reported attention-deficit/hyperactivity disorder among children – United States, 2003 and 2007. Centers for Disease Control and Prevention. *Morbidity and Mortality Weekly Report*. 2010; 59:1439–1443. [PubMed: 21063274]
- Chronis-Tuscano A, Molina BS, Pelham WE, Applegate B, Dahlke A, Overmyer M, Lahey BB. Very early predictors of adolescent depression and suicide attempts in children with attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*. 2010; 67:1044–1051. [PubMed: 20921120]
- Connor DF, Steeber J, McBurnett K. A review of attention-deficit/hyperactivity disorder complicated by symptoms of oppositional defiant disorder or conduct disorder. *Journal of Developmental and Behavioral Pediatrics*. 2010; 31:427–440. [PubMed: 20535081]

- Copeland WE, Shanahan L, Costello EJ, Angold A. Childhood and adolescent psychiatric disorders as predictors of young adult disorders. *Archives of General Psychiatry*. 2009; 66:764–772. [PubMed: 19581568]
- Costello EJ, Mustillo S, Erkanli A, Keeler G, Angold A. Prevalence and development of psychiatric disorders in childhood and adolescence. *Archives of General Psychiatry*. 2003; 60:837–844. [PubMed: 12912767]
- Daley D, Birchwood J. ADHD and academic performance: why does ADHD impact on academic performance and what can be done to support ADHD children in the classroom? *Child: Care, Health and Development*. 2010; 36:455–464.
- Daviss WB. A review of co-morbid depression in pediatric ADHD: etiology, phenomenology, and treatment. *Journal of Child and Adolescent Psychopharmacology*. 2008; 18:565–571. [PubMed: 19108661]
- De Los Reyes A, Kazdin AE. Informant discrepancies in the assessment of childhood psychopathology: a critical review, theoretical framework, and recommendations for further study. *Psychological Bulletin*. 2005; 131:483–509. [PubMed: 16060799]
- Dey AN, Schiller JS, Tai DA. Summary health statistics for U.S children: National Health Interview Survey, 2002. *Vital and Health Statistics*. 2004; Series 10(No. 221):1–78. [PubMed: 15791897]
- Draper, NR.; Smith, H. *Applied Regression Analysis*. 3rd. John Wiley and Sons; New York: 1998.
- Elkins IJ, McGue M, Iacono WG. Prospective effects of attention-deficit/hyperactivity disorder, conduct disorder, and sex on adolescent substance use and abuse. *Archives of General Psychiatry*. 2007; 64:1145–1152. [PubMed: 17909126]
- Fayyad, J.; Kessler, RC. The epidemiology and societal burden of ADHD. In: Adler, L.; Spencer, T.; Wilens, TE., editors. *Attention-Deficit Hyperactivity Disorder in Adults and Children*. Cambridge University Press; New York: in press
- Fergusson DM, Boden JM, Horwood LJ. Classification of behavior disorders in adolescence: scaling methods, predictive validity, and gender differences. *Journal of Abnormal Psychology*. 2010; 119:699–712. [PubMed: 20853914]
- Fergusson DM, Horwood LJ, Lynskey MT. Prevalence and comorbidity of DSM-III-R diagnoses in a birth cohort of 15 year olds. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1993a; 32:1127–1134. [PubMed: 8282656]
- Fergusson DM, Lynskey MT, Horwood LJ. Conduct problems and attention deficit behaviour in middle childhood and cannabis use by age 15. *Australian and New Zealand Journal of Psychiatry*. 1993b; 27:673–682. [PubMed: 8135692]
- Fergusson DM, Lynskey MT, Horwood LJ. Attentional difficulties in middle childhood and psychosocial outcomes in young adulthood. *Journal of Child Psychology and Psychiatry and Allied Disciplines*. 1997; 38:633–644.
- Flory K, Lynam DR. The relation between attention deficit hyperactivity disorder and substance abuse: what role does conduct disorder play? *Clinical Child and Family Psychology Review*. 2003; 6:1–16. [PubMed: 12659448]
- Frazier TW, Youngstrom EA, Glutting JJ, Watkins MW. ADHD and achievement: meta-analysis of the child, adolescent, and adult literatures and a concomitant study with college students. *Journal of Learning Disabilities*. 2007; 40:49–65.
- Froehlich TE, Lanphear BP, Epstein JN, Barbaresi WJ, Katusic SK, Kahn RS. Prevalence, recognition, and treatment of attention-deficit/hyperactivity disorder in a national sample of US children. *Archives of Pediatric and Adolescent Medicine*. 2007; 161:857–864.
- Gaub M, Carlson CL. Behavioral characteristics of DSM-IV ADHD subtypes in a school-based population. *Journal of Abnormal Child Psychology*. 1997; 25:103–111. [PubMed: 9109027]
- Gillberg C, Gillberg IC, Rasmussen P, Kadesjo B, Soderstrom H, Rastam M, Johnson M, Rothenberger A, Niklasson L. Co-existing disorders in ADHD – implications for diagnosis and intervention. *European Child and Adolescent Psychiatry*. 2004; 13(Suppl. 1):I80–I92. [PubMed: 15322959]
- Goodman R. The Strengths and Difficulties Questionnaire: a research note. *Journal of Child Psychology and Psychiatry*. 1997; 38:581–586. [PubMed: 9255702]

- Goodman R. Psychometric properties of the Strengths and Difficulties Questionnaire. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2001; 40:1337–1345. [PubMed: 11699809]
- Grills AE, Ollendick TH. Issues in parent-child agreement: the case of structured diagnostic interviews. *Clinical Child and Family Psychology Review*. 2002; 5:57–83. [PubMed: 11993545]
- Gunter TD, Arndt S, Riggins-Caspers K, Wenman G, Cadoret RJ. Adult outcomes of attention deficit hyperactivity disorder and conduct disorder: are the risks independent or additive? *Annals of Clinical Psychiatry*. 2006; 18:233–237. [PubMed: 17162622]
- Hasson R, Fine JG. Gender differences among children with ADHD on continuous performance tests: a meta-analytic review. *Journal of Attention Disorders*. 2012; 16:190–198. [PubMed: 22290696]
- Haynes, RB.; Sackett, DL.; Guyatt, GH.; Tugwell, P. *Clinical Epidemiology: How to Do Clinical Practice Research*. 3rd. Lippincott Williams & Wilkins; Philadelphia: 2006.
- Hinshaw SP, Owens EB, Zalecki C, Huggins SP, Montenegro-Nevado AJ, Schrodek E, Swanson EN. Prospective follow-up of girls with attention-deficit/hyperactivity disorder into early adulthood: continuing impairment includes elevated risk for suicide attempts and self-injury. *Journal of Consulting and Clinical Psychology*. 2012; 80:1041–1051. [PubMed: 22889337]
- Hosmer, DW.; Lemeshow, S. *Applied Logistic Regression*. 2nd. Wiley; New York: 2001.
- Hurtig T, Ebeling H, Taanila A, Miettunen J, Smalley S, McGough J, Loo S, Jarvelin MR, Moilanen I. ADHD and comorbid disorders in relation to family environment and symptom severity. *European Child and Adolescent Psychiatry*. 2007; 16:362–369. [PubMed: 17401612]
- Impey M, Heun R. Completed suicide, ideation and attempt in attention deficit hyperactivity disorder. *Acta Psychiatrica Scandinavica*. 2012; 125:93–102. [PubMed: 22118301]
- James A, Lai FH, Dahl C. Attention deficit hyperactivity disorder and suicide: a review of possible associations. *Acta Psychiatrica Scandinavica*. 2004; 110:408–415. [PubMed: 15521824]
- Kadesjo B, Gillberg C. The comorbidity of ADHD in the general population of Swedish school-age children. *Journal of Child Psychology and Psychiatry*. 2001; 42:487–492. [PubMed: 11383964]
- Karlson KB, Holm A. Decomposing primary and secondary effects: a new decomposition method. *Research in Social Stratification and Mobility*. 2011; 29:221–237.
- Kaufman J, Birmaher B, Brent DA, Rao U, Ryan ND. Schedule for Affective Disorders and Schizophrenia for School Age Children, Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1997; 36:980–988. [PubMed: 9204677]
- Kessler RC, Avenevoli S, Costello EJ, Georgiades K, Green JG, Gruber MJ, He JP, Koretz D, McLaughlin KA, Petukhova M, Sampson NA, Zaslavsky AM, Merikangas KR. Prevalence, persistence, and sociodemographic correlates of DSM-IV disorders in the National Comorbidity Survey Replication Adolescent Supplement. *Archives of General Psychiatry*. 2012a; 69:372–380. [PubMed: 22147808]
- Kessler RC, Avenevoli S, Costello EJ, Green JG, Gruber MJ, Heeringa S, Merikangas KR, Pennell BE, Sampson NA, Zaslavsky AM. Design and field procedures in the US National Comorbidity Survey Replication Adolescent Supplement (NCS-A). *International Journal of Methods in Psychiatric Research*. 2009a; 18:69–83. [PubMed: 19507169]
- Kessler RC, Avenevoli S, Costello EJ, Green JG, Gruber MJ, Heeringa S, Merikangas KR, Pennell BE, Sampson NA, Zaslavsky AM. National Comorbidity Survey Replication Adolescent Supplement (NCS-A): II. Overview and design. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2009b; 48:380–385. [PubMed: 19242381]
- Kessler RC, Avenevoli S, Green J, Gruber MJ, Guyer M, He Y, Jin R, Kaufman J, Sampson NA, Zaslavsky AM. National Comorbidity Survey Replication Adolescent Supplement (NCS-A): III. Concordance of DSM-IV/CIDI diagnoses with clinical reassessments. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2009c; 48:386–399. [PubMed: 19252450]
- Kessler RC, Avenevoli S, McLaughlin KA, Green JG, Lakoma MD, Petukhova M, Pine DS, Sampson NA, Zaslavsky AM, Merikangas KR. Lifetime co-morbidity of DSM-IV disorders in the US National Comorbidity Survey Replication Adolescent Supplement (NCS-A). *Psychological Medicine*. 2012b; 42:1997–2010. [PubMed: 22273480]

- Kessler RC, Üstün TB. The World Mental Health (WMH) Survey Initiative Version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). *International Journal of Methods in Psychiatric Research*. 2004; 13:93–121. [PubMed: 15297906]
- Klein RG, Mannuzza S, Olazagasti MA, Roizen E, Hutchison JA, Lashua EC, Castellanos FX. Clinical and functional outcome of childhood attention-deficit/hyperactivity disorder 33 years later. *Archives of General Psychiatry*. 2012; 69:1295–1303. [PubMed: 23070149]
- Knäuper B, Cannell CF, Schwarz N, Bruce ML, Kessler RC. Improving accuracy of major depression age-of-onset reports in the US National Comorbidity Survey. *International Journal of Methods in Psychiatric Research*. 1999; 8:39–48.
- Lahey BB, Loeber R, Burke J, Rathouz PJ, McBurnett K. Waxing and waning in concert: dynamic comorbidity of conduct disorder with other disruptive and emotional problems over 7 years among clinic-referred boys. *Journal of Abnormal Psychology*. 2002; 111:556–567. [PubMed: 12428769]
- Larson K, Russ SA, Kahn RS, Halfon N. Patterns of comorbidity, functioning, and service use for US children with ADHD, 2007. *Pediatrics*. 2011; 127:462–470. [PubMed: 21300675]
- Latimer WW, August GJ, Newcomb MD, Realmuto GM, Hektner JM, Mathy RM. Child and familial pathways to academic achievement and behavioral adjustment: a prospective six-year study of children with and without ADHD. *Journal of Attention Disorders*. 2003; 7:101–116. [PubMed: 15018359]
- Lewczyk CM, Garland AF, Hurlburt MS, Gearity J, Hough RL. Comparing DISC-IV and clinician diagnoses among youths receiving public mental health services. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2003; 42:349–356. [PubMed: 12595789]
- Lollar DJ, Hartzell MS, Evans MA. Functional difficulties and health conditions among children with special health needs. *Pediatrics*. 2012; 129:e714–e722. [PubMed: 22371461]
- Merikangas K, Avenevoli S, Costello J, Koretz D, Kessler RC. National Comorbidity Survey Replication Adolescent Supplement (NCS-A): I. Background and measures. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2009; 48:367–369. [PubMed: 19242382]
- Merikangas KR, He JP, Brody D, Fisher PW, Bourdon K, Koretz DS. Prevalence and treatment of mental disorders among US children in the 2001–2004 NHANES. *Pediatrics*. 2010; 125:75–81. [PubMed: 20008426]
- Molina BS, Pelham WE Jr. Childhood predictors of adolescent substance use in a longitudinal study of children with ADHD. *Journal of Abnormal Psychology*. 2003; 112:497–507. [PubMed: 12943028]
- Molina BS, Pelham WE Jr, Cheong J, Marshal MP, Gnagy EM, Curran PJ. Childhood attention-deficit/hyperactivity disorder (ADHD) and growth in adolescent alcohol use: the roles of functional impairments, ADHD symptom persistence, and parental knowledge. *Journal of Abnormal Psychology*. 2012; 121:922–935. [PubMed: 22845650]
- Monuteaux MC, Faraone SV, Gross LM, Biederman J. Predictors, clinical characteristics, and outcome of conduct disorder in girls with attention-deficit/hyperactivity disorder: a longitudinal study. *Psychological Medicine*. 2007; 37:1731–1741. [PubMed: 17451627]
- Nock MK, Hwang I, Sampson N, Kessler RC, Angermeyer M, Beautrais A, Borges G, Bromet E, Bruffaerts R, de Girolamo G, de Graaf R, Florescu S, Gureje O, Haro JM, Hu C, Huang Y, Karam EG, Kawakami N, Kovess V, Levinson D, Posada-Villa J, Sagar R, Tomov T, Viana MC, Williams DR. Cross-national analysis of the associations among mental disorders and suicidal behavior: findings from the WHO World Mental Health Surveys. *PLoS Medicine*. 2009; 6:e1000123. [PubMed: 19668361]
- Novik TS, Hervas A, Ralston SJ, Dalsgaard S, Rodrigues Pereira R, Lorenzo MJ. ADORE Study Group. Influence of gender on attention-deficit/hyperactivity disorder in Europe – ADORE. *European Child and Adolescent Psychiatry*. 2006; 15(Suppl. 1):I15–I24. [PubMed: 17177011]
- Ollendick TH, Jarrett MA, Grills-Taquechel AE, Hovey LD, Wolff JC. Comorbidity as a predictor and moderator of treatment outcome in youth with anxiety, affective, attention deficit/hyperactivity disorder, and oppositional/conduct disorders. *Clinical Psychology Review*. 2008; 28:1447–1471. [PubMed: 18973971]
- Pardini DA, Fite PJ. Symptoms of conduct disorder, oppositional defiant disorder, attention-deficit/hyperactivity disorder, and callous-unemotional traits as unique predictors of psychosocial

- maladjustment in boys: advancing an evidence base for DSM-V. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2010; 49:1134–1144. [PubMed: 20970701]
- Pastor PN, Reuben CA. Diagnosed ADHD and learning disability, United States, 2004–2006 data from the National Health Interview Survey. *Vital and Health Statistics*. 2008; Series 10(No. 237):1–14. [PubMed: 18998276]
- Pingault JB, Tremblay RE, Vitaro F, Carbonneau R, Genolini C, Falissard B, Cote SM. Childhood trajectories of inattention and hyperactivity and prediction of educational attainment in early adulthood: a 16-year longitudinal population-based study. *American Journal of Psychiatry*. 2011; 168:1164–1170. [PubMed: 21799065]
- Pliszka SR. Patterns of psychiatric comorbidity with attention-deficit/hyperactivity disorder. *Child and Adolescent Psychiatric Clinics of North America*. 2000; 9:525–540. [PubMed: 10944655]
- Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and meta-regression analysis. *American Journal of Psychiatry*. 2007; 164:942–948. [PubMed: 17541055]
- Raiker JS, Rapport MD, Kofler MJ, Sarver DE. Objectively-measured impulsivity and attention-deficit/hyperactivity disorder (ADHD): testing competing predictions from the working memory and behavioral inhibition models of ADHD. *Journal of Abnormal Child Psychology*. 2012; 40:699–713. [PubMed: 22271141]
- Rappaport MD, Scanlan SW, Denney CB. Attention-deficit/hyperactivity disorder and scholastic achievement: a model of dual developmental pathways. *Journal of Child Psychology and Psychiatry and Allied Disciplines*. 1999; 40:1169–1183.
- Rucklidge JJ. Gender differences in attention-deficit/hyperactivity disorder. *Psychiatric Clinics of North America*. 2010; 33:357–373. [PubMed: 20385342]
- SAS Institute. SAS/STAT[®] Software, Version 9.2 for Unix. SAS Institute Inc.; Cary, NC: 2008.
- Schermerhorn AC, D'Onofrio BM, Slutske WS, Emery RE, Turkheimer E, Harden KP, Heath AC, Martin NG. Offspring ADHD as a risk factor for parental marital problems: controls for genetic and environmental confounds. *Twin Research and Human Genetics*. 2012; 15:700–713. [PubMed: 22958575]
- Schieve LA, Gonzalez V, Boulet SL, Visser SN, Rice CE, Braun KV, Boyle CA. Concurrent medical conditions and health care use and needs among children with learning and behavioral developmental disabilities, National Health Interview Survey, 2006–2010. *Research in Developmental Disabilities*. 2012; 33:467–476. [PubMed: 22119694]
- Sourander A, Klomek AB, Niemela S, Haavisto A, Gyllenberg D, Helenius H, Sillanmaki L, Ristkari T, Kumpulainen K, Tamminen T, Moilanen I, Piha J, Almqvist F, Gould MS. Childhood predictors of completed and severe suicide attempts: findings from the Finnish 1981 Birth Cohort Study. *Archives of General Psychiatry*. 2009; 66:398–406. [PubMed: 19349309]
- Steinhausen HC, Novik TS, Baldursson G, Curatolo P, Lorenzo MJ, Rodrigues Pereira R, Ralston SJ, Rothenberger A. ADORE Study Group. Co-existing psychiatric problems in ADHD in the ADORE cohort. *European Child and Adolescent Psychiatry*. 2006; 15(Suppl. 1):I25–I29. [PubMed: 17177012]
- Strine TW, Lesesne CA, Okoro CA, McGuire LC, Chapman DP, Balluz LS, Mokdad AH. Emotional and behavioral difficulties and impairments in everyday functioning among children with a history of attention-deficit/hyperactivity disorder. *Preventing Chronic Disease*. 2006; 3:A52. [PubMed: 16539793]
- Szatmari P, Boyle M, Offord DR. ADDH and conduct disorder: degree of diagnostic overlap and differences among correlates. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1989; 28:865–872. [PubMed: 2478519]
- Taurines R, Schmitt J, Renner T, Conner AC, Warnke A, Romanos M. Developmental comorbidity in attention-deficit/hyperactivity disorder. *Attention Deficit Hyperactivity Disorder*. 2010; 2:267–289.
- Torok M, Darke S, Kaye S. Attention deficit hyperactivity disorder and severity of substance use: the role of comorbid psychopathology. *Psychology of Addictive Behaviors*. 2012; 26:974–979. [PubMed: 22486329]

- Willcutt EG. The prevalence of DSM-IV attention-deficit/hyperactivity disorder: a meta-analytic review. *Neurotherapeutics*. 2012; 9:490–499. [PubMed: 22976615]
- Willett JB, Singer JD. Investigating onset, cessation, relapse, and recovery: why you should, and how you can, use discrete-time survival analysis to examine event occurrence. *Journal of Consulting and Clinical Psychology*. 1993; 61:952–965. [PubMed: 8113496]
- Wolraich ML, Hannah JN, Pinnock TY, Baumgaertel A, Brown J. Comparison of diagnostic criteria for attention-deficit hyperactivity disorder in a county-wide sample. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1996; 35:319–324. [PubMed: 8714320]
- Wolter, KM. *Introduction to Variance Estimation*. Springer-Verlag; New York: 1985.
- Wymbs BT, Pelham WE Jr, Molina BS, Gnagy EM, Wilson TK, Greenhouse JB. Rate and predictors of divorce among parents of youths with ADHD. *Journal of Consulting and Clinical Psychology*. 2008; 76:735–744. [PubMed: 18837591]

Table 1
Sociodemographic correlates of lifetime DSM-IV/CIDI ADHD (*n*=6483)^a

	Total		Boys		Girls		χ^2 ^b
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	
Sex							
Male	3.4*	(2.5–4.6)	–	–	–	–	–
Female	1.0	–	–	–	–	–	–
χ^2_1	66.6*	–	–	–	–	–	–
Race/ethnicity							
Non-Hispanic black	1.1	(0.8–1.6)	1.3	(0.7–2.3)	0.8	(0.3–1.8)	–
Hispanic	1.1	(0.7–1.8)	1.0	(0.6–1.6)	1.6	(0.99–2.5)	–
Other	1.0	–	1.0	–	1.0	–	3.7
χ^2_2	0.3	–	0.7	–	4.8	–	–
Parents' education							
Less than high school	1.7*	(1.1–2.6)	1.7*	(1.03–2.9)	1.6	(0.7–3.5)	–
High school	1.2	(0.8–1.9)	1.2	(0.7–2.0)	1.5	(0.7–3.1)	–
Some college	1.3	(0.8–2.1)	1.6	(0.9–2.6)	0.8	(0.4–1.4)	–
College graduate	1.0	–	1.0	–	1.0	–	5.5
χ^2_3	7.1	–	6.1	–	2.3	–	–
Number of biological parents living with the adolescent							
None	2.4*	(1.6–3.6)	2.9*	(1.8–4.5)	1.8	(0.8–4.0)	–
One	2.1*	(1.4–3.0)	2.2*	(1.4–3.6)	1.9*	(1.1–3.1)	–
Both	1.0	–	1.0	–	1.0	–	–
χ^2_2	22.6*	–	23.5*	–	5.7	–	1.0
Urbanicity							
Major metro	0.8	(0.6–1.3)	0.9	(0.6–1.4)	0.6	(0.3–1.3)	–
Other urban	0.8	(0.6–1.3)	0.8	(0.5–1.2)	0.7	(0.3–1.4)	–

	Total		Boys		Girls		χ^2 ^b
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	
Rural	1.0	-	1.0	-	1.0	-	1.8
χ^2	0.7		1.1		1.9		

CIDI, Composite International Diagnostic Interview; ADHD, attention deficit hyperactivity disorder; OR, odds ratio; CI, confidence interval.

^aBased on a series of bivariate logistic regression equations, one for each of the sociodemographic predictors. The equations in the first column predicted lifetime ADHD in the total sample ($n=6483$), those in the second and third columns predicted lifetime ADHD separately among boys and girls.

^bThe χ^2 tests evaluate the significance of sex differences in ORs.

* Significant at the 0.05 level, two-sided test.

Table 2
Associations between lifetime DSM-IV/CIDI ADHD and the subsequent lifetime onset of other lifetime DSM-IV/CIDI disorders (n=6483)^a

	Lifetime prevalence of co-morbid disorder		Proportion of co-morbid cases in which ADHD is temporal primary			χ^2_{df}
	%	(S.E.)	%	(S.E.)	OR (95% CI)	
I. Mood disorders						
MDD/dysthymia	40.5	(3.8)	87.4	(3.1)	3.7* (2.9-4.8)	3.3
Bipolar disorder	13.1	(2.1)	89.6	(4.2)	2.5* (1.6-3.9)	0.0
Any	47.5	(4.0)	87.7	(2.9)	3.6* (2.8-4.7)	2.9
II. Anxiety disorders						
Specific phobia	24.8	(1.9)	39.2	(5.5)	1.5* (1.2-1.9)	0.0
Social phobia	9.1	(1.8)	64.2	(6.7)	1.3 (0.9-1.9)	1.5
Panic disorder	2.8	(1.0)	62.6	(14.8)	1.3 (0.6-2.6)	1.1
Separation anxiety disorder	8.8	(1.7)	67.4	(6.0)	1.4 (0.9-2.2)	1.3
Post-traumatic stress disorder	6.9	(1.7)	86.4	(4.5)	2.3* (1.4-4.0)	0.6
Generalized anxiety disorder	1.6	(0.4)	82.2	(15.6)	2.4* (1.2-5.1)	0.2
Any	35.1	(3.0)	45.2	(5.1)	1.4* (1.1-1.8)	0.0
III. Disruptive behavior disorders						
Conduct disorder	22.4	(3.3)	83.1	(3.7)	4.5* (3.2-6.5)	1.2
Oppositional defiant disorder	46.5	(3.3)	70.5	(3.8)	6.8* (5.3-8.7)	0.5
Intermittent explosive disorder	23.6	(2.3)	79.8	(4.2)	2.2* (1.7-3.0)	0.2
Eating disorders	12.5	(3.0)	98.7	(0.2)	3.2* (2.0-5.2)	8.4* ^c
Any	64.7	(2.8)	70.5	(3.5)	4.4* (3.8-5.2)	1.7
IV. Substance disorders						
Alcohol abuse	13.1	(3.1)	99.8	(0.0)	2.4* (1.4-4.1)	0.6
Drug abuse	17.4	(2.8)	100.0	-	2.2* (1.6-3.2)	0.0
Any	22.7	(3.3)	99.9	(0.0)	2.4* (1.6-3.4)	0.5
V. Any disorder	79.2	(2.4)	55.4	(3.7)	2.5* (2.1-2.9)	5.6* ^c

CIDI, Composite International Diagnostic Interview; MDD, major depressive disorder; S.E., standard error; OR, odds ratio; CI, confidence interval.

^d Discrete-time survival models with person-year as the unit of analysis were used to predict first onset of each outcome disorder. ADHD was treated as time varying (i.e. turned on only at age of onset) and controls were used for the sociodemographic variables in Table 1. Person-year was coded as a series of year-specific dummy predictor variables. The models were estimated using a logistic link function. Results for boys and girls are combined. Comparable results separated by sex of respondents are available on request.

^b The χ^2 tests evaluate the significance of sex differences in ORs.

^c The OR (95% CI) of ADHD is 4.9 (3.0–8.2) with eating disorders among boys and 1.2 (0.6–2.7) among girls, and 2.8 (2.4–3.2) with any disorder among boys and 1.8 (1.4–2.5) among girls.

* Significant at the 0.05 level, two-sided test.

Table 3
Gross (i.e. without controls for secondary co-morbid disorders) associations between DSM-IV/CIDI ADHD and adverse outcomes (n=6483)^a

	Total		Boys		Girls		χ^2/t^c
	Est ^b	(95% CI)	Est ^b	(95% CI)	Est ^b	(95% CI)	
I. Poor educational performance							
Suspension	4.3*	(3.2 to 5.7)	4.6*	(3.2 to 6.7)	3.5*	(2.2 to 5.3)	0.7
Repeated a grade	3.1*	(2.3 to 4.3)	3.3*	(2.3 to 4.8)	1.8	(0.9 to 3.6)	2.8
Below-average grades	2.8*	(1.7 to 4.6)	2.8*	(1.6 to 4.8)	2.7*	(1.1 to 6.7)	0.0
II. Suicidality							
Ideation	3.1*	(1.9 to 5.1)	3.5*	(1.8 to 6.9)	2.5*	(1.5 to 4.1)	0.7
Plan	4.2*	(2.0 to 8.7)	5.3*	(1.9 to 14.9)	2.5*	(1.5 to 4.2)	1.9
Attempt	5.5*	(2.1 to 14.5)	12.3*	(2.8 to 54.2)	2.4*	(1.1 to 5.4)	3.9*
III. Parent perceptions of adolescent health and functioning							
Physical health	-0.1*	(-0.2 to -0.02)	-0.1	(-0.2 to 0.1)	-0.2	(-0.5 to 0.00)	1.0
Mental health	-0.6*	(-0.7 to -0.4)	-0.6	(-0.7 to -0.4)	-0.6*	(-0.7 to -0.4)	0.2
Interference	1.5*	(1.4 to 1.6)	1.5	(1.3 to 1.6)	1.5*	(1.2 to 1.9)	0.3
Distress	1.4*	(1.3 to 1.5)	1.3	(1.2 to 1.5)	1.5*	(1.2 to 1.7)	1.1

CIDI, Composite International Diagnostic Interview; ADHD, attention deficit hyperactivity disorder; CI, confidence interval.

^a A multiple regression model was used to predict each outcome. The predictors were lifetime ADHD and controls for the sociodemographic variables in Table 1. The models for below-average grades and the parent perceptions were estimated at the person level and referred to current functioning at the time of interview. The model for below-average grades used a logistic link function to predict a dichotomous outcome whereas the models for parent perceptions used a linear link function to predict continuous (standardized to a mean of 0 and variance of 1 in the total sample) outcomes. The models for the other outcomes were estimated at the person-year level to predict lifetime outcomes in a discrete-time survival framework using a logistic link function. The predictors in the survival models were treated as time varying (i.e. turned on only at age of onset). Person-year was coded as a series of year-specific dummy predictor variables in the survival models.

^b The coefficients in Parts I and II are odds ratios predicting dichotomous outcomes, those in Part III are linear regression coefficients predicting standardized (mean of 0, variance of 1) continuous outcomes.

^c The χ^2/t tests evaluate the significance of sex differences in effects of ADHD. χ^2 tests are used for dichotomous outcomes and *t* tests for continuous outcomes.

* Significant at the 0.05 level, two-sided test.

Table 4
Decomposition of gross associations between DSM-IV/CIDI ADHD and adverse outcomes into direct effects of ADHD and indirect effects of ADHD through secondary DSM-IV/CIDI disorders (n=6483)^a

	Indirect effect of ADHD through secondary DSM-IV/CIDI disorders									
	Direct effect of ADHD		Mood disorders		Anxiety disorders		Disruptive behavior disorders		Substance abuse	
	%	(S.E.)	%	(S.E.)	%	(S.E.)	%	(S.E.)	%	(S.E.)
I. Poor educational performance										
Suspension										
Total	36.1*	(4.6)	6.3	(3.4)	0.5	(0.9)	36.8*	(4.8)	20.2*	(3.6)
Boys	37.7*	(5.4)	4.2	(5.2)	-1.1	(1.3)	34.2*	(6.1)	25.0*	(4.9)
Girls	34.5*	(8.9)	8.5	(5.4)	5.3	(2.9)	41.8*	(9.5)	10.0	(4.6)
Repeated a grade										
Total	68.2*	(8.3)	-11.7*	(9.1)	3.7	(2.4)	33.9*	(9.0)	5.8	(4.6)
Boys	71.6*	(11.3)	-11.8	(12.2)	1.5	(2.1)	38.3*	(11.0)	0.5	(9.5)
Girls	65.6	(15.0)	-15.2*	(13.5)	13.1*	(6.4)	26.9	(15.0)	9.6	(7.6)
Below-average grades										
Total	21.9	(13.2)	6.4	(6.2)	3.5	(1.6)	48.8*	(8.2)	19.3	(10.6)
Boys	39.8*	(17.6)	-9.5	(12.9)	1.1	(1.9)	52.5*	(13.0)	16.1	(16.3)
Girls	11.7	(21.7)	17.5*	(8.7)	10.9*	(4.7)	48.2*	(15.0)	11.7	(21.7)
II. Suicidality^b										
Ideation										
Total	12.0	(7.0)	42.8*	(5.1)	3.9	(2.0)	20.8*	(6.0)	20.5*	(5.4)
Boys	19.3*	(6.7)	46.0*	(7.1)	0.7	(1.4)	14.2	(7.2)	19.8*	(7.2)
Girls	-2.3	(16.9)	46.5*	(7.3)	12.2*	(4.2)	29.0	(11.4)	14.7*	(5.9)
Plan										
Total	9.8	(10.2)	48.0*	(8.2)	2.5	(2.2)	23.7*	(11.4)	16.0*	(6.0)
Boys	24.2*	(9.6)	44.2*	(13.7)	-1.1	(3.7)	9.2	(14.4)	23.5*	(7.7)
Girls	-14.0	(16.0)	59.1*	(9.8)	11.3*	(5.4)	36.9*	(16.6)	6.7	(6.3)

	Indirect effect of ADHD through secondary DSM-IV/CIDI disorders									
	Direct effect of ADHD		Mood disorders		Anxiety disorders		Disruptive behavior disorders		Substance abuse	
	%	(S.E.)	%	(S.E.)	%	(S.E.)	%	(S.E.)	%	(S.E.)
III. Parent perceptions of adolescent health and functioning										
Physical health										
Total	43.3	(26.9)	51.3*	(19.6)	15.9*	(9.6)	8.6*	(22.0)	-19.1*	(17.3)
Boys	14.0	(36.3)	69.7*	(31.4)	12.6	(10.5)	14.6	(25.8)	-10.8	(32.6)
Girls	67.6*	(23.6)	22.1	(19.8)	15.4	(8.2)	3.0	(23.0)	-8.1	(8.0)
Mental health										
Total	48.8*	(5.9)	27.7*	(5.5)	2.7	(1.4)	24.1*	(5.5)	-3.3*	(3.3)
Boys	44.6*	(6.2)	31.2*	(6.3)	1.8	(1.5)	24.5*	(5.8)	-2.0	(5.5)
Girls	51.9*	(7.9)	23.6*	(6.8)	5.2	(2.7)	22.0*	(7.7)	-2.6	(3.2)
Interference with role functioning										
Total	54.3*	(3.1)	21.3*	(2.7)	0.5	(0.4)	22.7*	(2.9)	1.1	(1.8)
Boys	57.1*	(4.1)	20.8*	(2.9)	0.4	(0.6)	23.2*	(3.2)	-1.4	(2.3)
Girls	56.2*	(5.1)	19.9*	(3.6)	0.8	(0.7)	21.3*	(4.8)	1.9	(1.5)
Distress										
Total	52.0*	(3.8)	21.9*	(2.9)	0.8	(0.6)	23.0*	(2.6)	2.2	(1.7)
Boys	51.8*	(4.9)	21.4*	(2.2)	0.7	(0.5)	23.2*	(2.6)	2.9	(7.2)
Girls	56.4*	(5.8)	19.8*	(3.8)	0.9	(0.8)	20.1*	(4.2)	2.8	(1.7)

CIDI, Composite International Diagnostic Interview; ADHD, attention deficit hyperactivity disorder; s.e., standard error.

^aThe decompositions are of the associations between total ADHD and the outcomes in Table 3. The coefficients in each row are standardized to sum to 100%, which represents the total effect of ADHD as reported in the first column of Table 3.

^bNo results are reported for attempted suicides because the number of attempted suicides was too small for reliable analysis; that is, none of the component coefficients in the decomposition was statistically significant even though the total effect in Table 3 was significant.

* Significant at the 0.05 level, two-sided test.