

Estimation of Prevalence of DSM-IV and Latent Class-Defined ADHD Subtypes in a Population-Based Sample of Child and Adolescent Twins

Rosalind J. Neuman,^{1,2} Nantawat Sitdhiraksa,³ Wendy Reich,¹ Ted H.-C. Ji,¹ Cynthia A. Joyner,¹ Ling-Wei Sun,¹ and Richard D. Todd,^{1,2}

¹Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri, United States of America

²Department of Genetics, Washington University School of Medicine, St. Louis, Missouri, United States of America

³Mahidol University, Faculty of Medicine, Siriraj Hospital, Salaya, Phuttamonthon District, Nakhon Pathom, Thailand

The goal of this study is to determine the prevalence and age of onset of *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; DSM-IV; American Psychiatric Association, 1994) and latent class-derived attention deficit/hyperactivity disorder (ADHD) subtypes in a population-based twin sample of boys and girls. Missouri birth records identified families with a twin pair 7 to 18 years of age. Telephone screening interviews for ADHD symptoms were completed for 5007 families. Diagnostic assessments were administered to 564 families with at least one twin meeting screening criteria, plus 183 control families. Prevalence and age of onset for both ADHD nosologies were calculated by sex and zygosity from parent report data. The prevalence of any DSM-IV ADHD was 6.2% overall, 7.4% in boys and 3.9% in girls. The inattentive subtype was most common in boys; the combined subtype was most common in girls. The mean age of onset of symptoms in children with any DSM-IV ADHD was 3.5 years, with no significant differences between boys and girls. Prevalences of latent class defined ADHD subtypes also varied by sex with the severe inattentive and combined classes more common in boys than girls. The age of onset of symptoms did not differ between boys and girls but were higher than in the DSM-IV subtypes. Findings in this twin sample showed that clinically significant ADHD, defined by either DSM-IV or latent class criterion, has an early age of onset and is more common in boys than girls. As clinical samples are most commonly composed of male combined subtypes, the inattentive subtype of both sexes in the general population is an under-treated segment of the general population.

Attention deficit/hyperactivity disorder (ADHD) is a common, highly heritable, psychiatric syndrome with onset in early childhood. As defined in *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; DSM-IV; American Psychiatric Association, 1994),

there are three subtypes of ADHD (predominantly inattentive, predominantly hyperactive/impulsive and combined) based on the presence or absence of six or more inattentive and/or six or more hyperactive/impulsive symptoms in addition to impairment and age-of-onset criteria. Accurate population prevalence rates of any disorder or phenotype of interest are important parameters for conducting proper genetic studies in addition to their importance for community health care planning (Burd et al., 2003). Since ADHD and ADHD subtypes appear to be a highly heritable syndrome or group of syndromes and are the focus of many ongoing genetic linkage and disequilibrium studies (for a summary see Faraone et al., 2005), it is important to have accurate information about the prevalence of ADHD subtypes (Todd, 2000a, 2000b). Furthermore, to minimize sampling biases, prevalence estimates should be determined using a random sample of the population rather than school- or clinic-based estimates which are likely to be biased.

Though a variety of studies using earlier DSM-III (3rd ed.; American Psychiatric Association, 1980) or DSM-III-R (3rd ed., rev.; American Psychiatric Association, 1984) diagnostic criteria had estimated the prevalence of ADHD to be between 3% and 10% (Szatmari, 1982), little research has been published on the population prevalence of individual DSM-IV ADHD subtypes. Among those that have been published, prevalence rates have ranged between 8% and 20%, a much larger variance than is given by the 3% to 5% prevalence reported in the DSM-IV manual (Baumgaertel et al., 1995; Gaub & Carlson, 1997; Graetz et al., 2001; Rohde et al., 1999; Wolraich et al., 1996). Moreover, many of these studies did not use

Received 29 March, 2005; accepted 29 April, 2005.

Address for correspondence: Rosalind J. Neuman, Department of Psychiatry, Washington University School of Medicine, Campus Box 8134, 660 South Euclid Avenue, St. Louis, MO 63110-1093, USA. E-mail: roz@gretta.wustl.edu

parent report data about their children, or did not report subtype prevalences. In addition, few of these reports included sex specific age of onset data of DSM-IV ADHD subtypes.

To avoid the diagnostic uncertainty that arises when using the strict cut-off approach of the DSM, some investigators have proposed alternative definitions of ADHD hoping to produce more etiologically homogeneous ADHD subtypes which might better discriminate between genetic and nongenetic subtypes (Carlson & Mann, 2002; McBurnett et al., 2001; Milberger et al., 1996; Todd et al., 2004). In particular, we have demonstrated that the application of latent class analysis (LCA) to parent reports of the 18 DSM-IV symptoms in population-based samples results in the generation of reliable ADHD subtypes (Hudziak et al., 1998; Rasmussen et al., 2002) that predict school failure (Todd et al., 2002), have family/genetic specificity (Neuman et al., 1999; Rasmussen et al., 2004; Todd et al., 2001) and consistent patterns of comorbidity (Neuman et al., 2001) and Volk (in review). We have also shown that the latent class-derived ADHD phenotypes can be consistently reproduced across various studies of ADHD, are highly heritable, and may be more appropriate than DSM-IV subtypes for molecular genetic studies. Overall, the latent class nosology produces ADHD subtypes that are not concordant with DSM-IV ADHD subtypes and often include individuals that do not have a DSM-IV ADHD diagnosis (Hudziak et al., 1998; Neuman et al., 2001; Rasmussen et al., 2002; Todd et al., 2002).

Given the inconsistent prevalence rates reported from DSM-IV studies of ADHD and the scarcity of reports on the prevalence of alternative ADHD phenotypes, additional population-based studies of the prevalence rates for both DSM-IV and alternative nosologies of ADHD need to be conducted. Our goal in this report is to present population prevalence data for DSM-IV and latent class-defined ADHD subtypes obtained from a birth records-based twin study of ADHD in the state of Missouri. We also report age of onset and prevalence of ADHD subtypes by gender.

Methods and Materials

Overview of the Study Design and Diagnostic Interview

For this study we employed a two-stage sampling design in which a best informant parent or guardian (usually the mother) completed a screening interview by telephone about their twin offspring and completed the Achenbach Child Behavior Checklist (CBCL). Families in which one or both twins passed the screening interview were invited to participate in a comprehensive diagnostic evaluation. The brief screening interview confirmed that the correct family had been located, asked about the presence of three past or present inattentive symptoms and three past or present hyperactive/impulsive symptoms for each twin, as well as a series of standard zygosity questions. Twin zygosity

was determined using responses to zygosity questions in the latent class approach described by Heath et al. (2003). At the time this study was initiated, it was widely believed that hyperactive/impulsive subtype ADHD reflected a preschool form of combined subtype (reviewed in Barkley, 1997) and did not really exist. Since the study would be interviewing children over 6 years of age to ensure the inattentive and combined subtype forms of ADHD were captured, a criterion of endorsement of three or more present or past inattentive symptoms were used as a cut-off score for referral to the second stage of the study.

Parents and twins completed a modified DSM-IV version of the Diagnostic Interview for Children and Adolescents (DICA; Carlson & Mann, 2002; Reich, 2000) called the Missouri Assessment for Genetics Interview for Children (MAGIC) that queries present and past existence of all DSM-IV symptoms of ADHD and related diagnoses. As with previous versions of the DICA the interview was developed with versions for child and adolescent self-report (7 to 12 years, MAGIC-C; 13 to 19 years, MAGIC-A), and parent (MAGIC-P) report about their offspring. A companion manual and a 6-week training course were established for all three MAGIC interviews. All interviewers had a college degree in psychology or related background. Different interviewers interviewed each child or adolescent twin about themselves and the parent or best informant (mother 95.6% of the time) about each twin.

For children aged 7 to 12 years, these diagnostic interviews were always completed in person, either at home or in our office. For adolescents aged 13 to 19 years, interviews were completed either in person or by phone with equal frequency. Parent interviews on each twin were also conducted either in person or by phone. In addition to the diagnostic interview, twins seen in person completed the block design and vocabulary sub-sections of the Wechsler Intelligence Scale for Children (WISC-III) and the Wide Range Achievement Test (WRAT-3). Adolescents interviewed by phone completed only the vocabulary section of the WISC-III (Todd et al., 2002). The study protocol was reviewed and approved by the Washington University School of Medicine Human Studies Committee prior to contacting any subjects. Verbal informed consent was obtained from parent or guardian before completion of telephone screening interviews. Written informed consent (or assent for individuals under the age of 18 years) was obtained from each participant (or legal guardian where appropriate) prior to participation.

Reliability and prospective stability studies were completed on the MAGIC. With respect to a DSM-IV diagnosis of ADHD, interrater reliability for the child, adolescent and parent versions was excellent, with kappas greater than .9 for DSM-IV and latent class-defined ADHD subtype diagnoses as well as for endorsement of the 18 individual criterion A ADHD symptoms (Todd et al., 2003).

Ascertainment of Twin Families

All twin births in the state of Missouri between 1979 and 1991 were identified by a computerized search of birth records. Pairs were excluded where one or both twins were known to be deceased or mentally retarded and twin pairs who had been adopted were excluded because of lack of access to records under Missouri State law. We also excluded some female–female twin pairs born between the years of 1979 and 1986 as these were actively involved in another ongoing twin study (Hudziak et al., 1998). Thus, 70.7% ($n = 7681$ pairs) of all twins born between 1979 and 1991 were eligible to be contacted. Of the 7681 eligible families, 5412 could be contacted and screening interviews were successfully completed in 5007 families (65.2% of the total eligible sample and 92.5% of the contacted sample). Of these, 1211 families (24.4%) had at least one twin who passed the screener and was therefore eligible for the diagnostic evaluation phase. The CBCL forms for both twins were returned by 59.8% of the families completing the screener. In addition to the families meeting the ADHD screening criteria for diagnostic interviews, 281 families were randomly selected across birth years ($M = 21.6$ families per year, $SD = 6.1$) for completion of diagnostic interviews. This random control group was included to allow unbiased estimates of the ADHD population prevalences. In addition, families in which a child had a CBCL anxious/withdrawn subscale score of greater than the 95 percentile ($n = 104$) were chosen for possible diagnostic interviews. The high anxious/withdrawn subscale scoring group on the CBCL was included as a possible depressed group to maintain the ‘blindness’ of interviewers conducting diagnostic interviews.

Of the potential 1596 families (1211 screener positive, 281 random, 104 CBCL anxious/withdrawn), 1324 were approached for participation, using approximately equal numbers of families for each birth year. Three hundred and thirty-seven families (25.4%) refused to participate in the diagnostic interview phase of the study. The current study is based on 747 families that completed the diagnostic interview section of the study. This includes 564 families identified through positive ADHD screener scores and 183 randomly selected families. The depression families, ascertained to eliminated interview bias, were not included in this analysis. Results in the current report include complete data on 1472 individual twins from either the random controls ($n = 365$) or ADHD screener positive families ($n = 1107$). We shall refer to this data set as the MOTWINS.

Representativeness of the Sample

To test for participation biases families who participated in this study were contrasted with those who refused using a variety of demographic data including the twins’ age, sex, zygosity, self-identified race, and on zip code–based 1990 United States Federal Census data. From the census data median income and average racial composition were extracted by zip code.

Data Analysis

Data analyses included parent responses about current symptoms for twins from the MAGIC-P interview only. Diagnoses of DSM-IV ADHD subtypes were determined by algorithm and included all DSM-IV criteria.

LCA is a statistical method for finding subgroups within a data set based on a set of categorical data (McCutcheon, 1987). Thus, LCA may be thought of as a parametric clustering method where the model’s parameters are the prevalence of each latent subgroup (i.e., the probability that a subject belongs to the j th latent class) and the probability of a specific answer to a symptom given the subject is in the j th class. Subjects are placed in the class with the highest posterior probability of membership given his/her symptom profile, a value that can be easily computed using the model’s derived parameter values (McCutcheon, 1987). We assigned subjects in the MOTWIN sample to latent classes using the set of latent class parameters derived from a LCA of a large population-based sample of Australian male and female twins (Rasmussen et al., 2002) combined with a set of Missouri adolescent female twin pairs (MOAFTS; Heath et al., 1999; Todd et al., 2001). The structure of the derived latent classes of these two samples was shown to be comparable (Rasmussen et al., 2002). Furthermore, the estimates for the latent class parameters for each sample were within a 95% confidence interval of the combined sample solution. We used the software program LCAP-CA (available at <http://hardy.wustl.edu>) and these previously computed parameters to compute the posterior probabilities of class assignments for the MOTWIN sample.

Using the known results of the screening interviews and the diagnostic interviews, the positive and negative predictive values of the screening interview were calculated for each ADHD subtype. Population prevalences (Kp) could then be calculated for the total sample and male and female twins separately using the following standard equation:

$$Kp = \frac{\text{Pr(affected)} = \text{Pr(affected|screener positive)} \times \text{Pr(screener positive)} + \text{Pr(affected|screener negative)} \times \text{Pr(screener negative)}}{\text{Pr(screener positive)} + \text{Pr(screener negative)}}$$

This equation for Kp can be rewritten in terms of the positive and negative predictive values of the screener (PPV and NPV, respectively) and estimated using the proportion of positive and negative screeners as:

$$Kp = \text{PPV} \times (\text{Proportion of positive screeners}) + (1 - \text{NPV}) \times (\text{Proportion of negative screeners}).$$

The random control group was used to estimate negative predictive value. In addition, the sensitivity, specificity, and positive predictive value of the screener were estimated.

To correct for the lack of independence of the data (i.e., twin resemblance), 95% confidence intervals for

each Kp were estimated by bootstrapping (Efron & Tibishirani, 1993), using the family as the unit of resampling ($N = 2000$ bootstrapped samples).

Age of onset of DSM-IV and latent class subtypes was defined to be the age of first DSM-IV ADHD symptoms. If a parent could not recall the exact age of the first problems for the child, the child's age of onset was not used in the calculations to determine the mean age of onset of DSM-IV or latent class ADHD subtypes. The nonparametric Kruskal–Wallis test was used to test mean differences in quantitative variables between ADHD subgroups. Differences between two proportions were tested using standard methods (Fleiss, 1981).

Results

The diagnostic interview sample reported here consists of parental reports on 725 twin pairs of which 25.79% are monozygotic (MZ; 135 male, 52 female pairs), and 74.20% are dizygotic (DZ; 163 male, 61 female, 314 opposite-sex pairs). An additional 22 families had only one twin who participated: 6 MZ families (five male, one female) and 16 DZ families (four from male pairs, three from female pairs, nine from opposite-sex pairs). This represents participation of 58% of all potentially eligible males and 68% of all potentially eligible females, that is, families in which at least one twin passed the screener (74.6% participation of contacted families). The racial/ethnic composition of the sample was 13.6% self-identified African American for screening interviews and 15.5% self-identified African American for diagnostic interviews. Hispanic, American Indian, Asian American and other minorities comprised less than 2% of the sample with the remainder being composed people of self-identified European American decent.

When families who completed or refused the diagnostic phase of the study were compared, there were no significant differences in self-identified racial composition or zip code–based median income. Nor were there any significant differences between participants and nonparticipants with respect to age, zygosity or screening interview score. Families that refused to participate in the diagnostic interview section tended to have a slightly larger proportion of male twins than those who participated (68.4% vs. 62.6%, $p = .01$).

Age of Onset

A total of 213 twins qualified for a DSM-IV diagnosis of ADHD by the MAGIC-P interview; the parents of three children could not recall the exact age of first problem. The majority of cases were male (85.9%). Over half were primarily inattentive (51.1%), over one third (39.4%) were combined, and the remainder (9.4%) was primarily hyperactive/impulsive subtype. The average age of onset of DSM-IV ADHD problems among those with a positive diagnosis was approximately 3.5 years, irrespective of the subtype. The Kruskal–Wallis test was used to test for equality of the

average age of onset for males versus females stratified by DSM-IV subtype and for differences among the three DSM-IV ADHD subtypes. There were no significant age differences between the sexes for any subtype, nor were there any age differences jointly among the three DSM-IV ADHD subtypes.

For latent class assignments, the only class in which the age of onset for males and females differed was the mild–combined class (4.2 years vs. 4.6 years, respectively, $p = .01$). The same trend, the male age of onset being younger than the female age of onset, was seen in the severe combined class, although this difference was not statistically significant (3.8 years vs. 4.4 years, $p = .3$).

We compared age of onset between DSM-IV subtypes and the clinically important latent classes: the severe combined, inattentive and hyperactive classes. The age of onset for the DSM-IV primarily inattentive subtype (3.5 years) versus the severe inattentive latent class (5 years) were significantly different ($\chi^2_1 = 14.9$, $p = .0001$). This overall difference was reflected in the male inattentive subtypes (3.5 years vs. 5.1 years, $\chi^2_1 = 13.5$, $p = .0002$) but not the females (3.7 years vs. 4.6 years, $\chi^2_1 = 1.9$, $p = .17$). There was no statistically significant difference in age of onset between the DSM-IV combined and the comparable latent class combined subtype ($\chi^2_1 = 0.8$, $p = .4$). The DSM-IV hyperactive–impulsive and the comparable latent class subtype differed somewhat in their respective age of onset, 3.5 years versus 5.1 years, respectively ($\chi^2_1 = 3.8$, $p = .05$).

Screener Characteristics

Results of the MAGIC-P interview in the random controls were used as the 'gold standard' to determine the negative and positive predictive values (NPV and PPV, respectively) and the overall sensitivity and specificity of the screener. The NPV of the screener (i.e., the proportion of twins who did not have a DSM-IV ADHD diagnosis on the MAGIC-P given a screening interview score of less than 3) was over 96% for all DSM-IV types. The PPV for any DSM-IV ADHD was approximately 27% (32% for males and 11% for females). The PPV for the primarily inattentive, combined and hyperactive/impulsive subtypes in both nosologies were approximately 14%, 11% and 2.4%, respectively. Not unexpectedly, performance was poorer for the primarily hyperactive/impulsive subtype since the screener score was based only on inattentive symptom endorsements.

Sensitivity was approximately 70% for any DSM-IV ADHD and ADHD subtypes in both nosologies with the exception of the hyperactive/impulsive subtypes for which sensitivity was approximately 30%. This low sensitivity is not unexpected given that the screen was measuring inattentive symptoms. Specificity was high, over 85%, for any DSM-IV ADHD and all subtypes.

There were no significant differences in any of these screener characteristics between children (7 to 12 years of age) and adolescents (13 to 19 years of age: data not shown).

DSM-IV and Latent Class Subtype Prevalence Rates

Overall, the total population prevalence of any ADHD was 6.2% (95% CI 4.6–8.2). Prevalences of all DSM-IV ADHD subtypes are summarized by sex and twin pair type in Table 1. These *Kp* estimates for DSM-IV and latent class-defined ADHD subtypes were calculated using the above formula (see the Method section). For example, *Kp* for any DSM-IV ADHD was calculated as $(.273 \times .148) + [(1-.975) \times .852] = .0617$ where .148 and .852 were the proportion of subjects who screened positive and negative, respectively, and .273 and .975 were the PPV and NPV for the DSM-IV phenotype, respectively.

The most common subtypes were the primarily inattentive subtype (2.9%) followed by the combined subtype (2.4%) with only a small, statistically non-significant difference between them ($\chi^2_1 = 0.4, p = .5$). There was a significant difference in total ADHD prevalence between boys and girls (7.4% vs. 3.9%, respectively; $\chi^2_1 = 3.8, p = .05$). Among males, the DSM-IV inattentive subtype had the highest prevalence (4.5%), followed by the combined and hyperactive/impulsive subtypes (2.3% and 0.5%, respectively). In the data, males from opposite-sex pairs had the highest point prevalence for any DSM-IV ADHD diagnosis, 11.5% compared to males from MZ pairs (4.1%, $\chi^2_1 = 6.6, p = .01$) or DZ pairs (6.8%, $\chi^2_1 = 2.58, p = .1$). The most common DSM-IV subtype for the female twins was the combined subtype (2.1%); the lowest point prevalence for a subtype was the inattentive subtype (0.6%). This latter result was an artifact of our sample: no female from the control group who did not pass the screener was categorized as the inattentive subtype, that is, the NPV for this subtype in females was equal to 1.0. However, there were three female twins who did not pass the screener but were diagnosed as primarily combined subtype, and similarly, two females were diagnosed as hyperactive-impulsive. This anomaly, a NPV = 1 in the inattentive subtype and a somewhat lower NPV in the other two DSM-IV subtypes, decreased the overall point prevalence of the inattentive subtype and increased the prevalence of the combined and hyperactive-impulsive subtypes. However, the bootstrapped confidence interval for the hyperactive-impulsive subtype (0.0–3.0) indicates that the population prevalence of this subtype is not significantly different from 0, while the confidence interval for the inattentive subtype did not include 0 (0.2–1.0).

The prevalences of latent class-defined ADHD subtypes are shown in Table 2. Contrasted with the DSM-IV subtypes in which the inattentive subtype was most frequent (2.9%), in the latent class nosology, the severe combined class was more prevalent (3.3%) than the severe inattentive class (2.5%) but these prevalences were not statistically different ($\chi^2_1 = 1.1, p = .3$). Just as for DSM-IV subtypes, the severe inattentive and severe combined classes were more prevalent in males (3.7%, 3.5%, respectively) than

females (0.7%, 2.8%, respectively), while the few symptoms class was more prevalent among females (82.5% vs. 69.5% in males, $\chi^2_1 = 11.3, p = 8 \times 10^{-4}$). The low prevalence of the latent severe inattentive class among females, 0.7%, was the result of the same sampling irregularity as the DSM-IV inattentive subtype: a negative predictive value of 1.0. The severe hyperactive-impulsive class had a prevalence of 1.2% for females, but as with the DSM-IV subtype, the confidence interval contained 0 (0.0–3.1).

Discussion

The current study reports prevalences on DSM-IV and latent class ADHD subtypes in a population-based sample of twins ascertained from computerized birth records from the state of Missouri. To our knowledge no other study has reported birth record-based population prevalences or ages of onset for ADHD subtypes for boys and girls. Most previous studies of DSM-IV ADHD prevalences have been school or clinic-based leading to possible sampling biases in the prevalence estimates.

In contrast to the majority of past studies of either school, clinic-based studies (e.g., Lahey et al., 1994), or earlier conceptions of DSM ADHD, our study shows that the primarily inattentive subtype was the predominant subtype of ADHD with the combined subtype having a slightly lower point prevalence (2.4% vs. 2.9%, $\chi^2_1 = 0.4, p = .5$). Among males the prevalence of the DSM-IV inattentive and combined subtypes was 4.5% and 2.3%, respectively ($\chi^2_1 = 5.2, p = .02$), but there was no statistically significant difference between the inattentive and combined subtypes in females (0.6% vs. 2.1%, $\chi^2_1 = 1.3, p = .3$). Among the derived latent class subtypes of clinical significance, the severe combined type had a higher prevalence than the severe inattentive type (respectively, 3.3% and 2.5%, $\chi^2_1 = 1.1, p = .3$); prevalences of the males and females did not differ significantly between these two latent classes. The prevalences of the severe hyperactive-impulsive subtypes in either nosology were small, 0.9% in the DSM-IV subtype versus 1.1% in the hyperactive latent class subtype.

The results of this study confirmed that the DSM-IV inattentive and combined subtypes, and the latent class severe combined and inattentive subtypes are more prevalent in boys than girls. Furthermore, 75% of twins in our study have either no or very few ADHD symptoms (latent class 1), with the prevalence in girls significantly higher than boys for this class (82.5% vs. 69.5% respectively, $\chi^2_1 = 11.3, p = 8 \times 10^{-4}$). The finding of lower reported prevalences of any ADHD in male MZ twins (4.1%) versus all males (7.4%) is consistent with some reports that the mothers of MZ twins try to make the two twins appear more different and hence decrease the overall reporting of psychopathology (a so-called negative rater contrast; Eaves et al., 1997; Hudziak et al., 2000). The prevalence of MZ males assigned to the

Table 1

Population Prevalence (%) of DSM-IV ADHD Subtypes by Sex and Twin Type

	Total sample		Male			Female		
	N = 1472	Total N = 923	MZ N = 275	DZ same sex N = 330	DZ opposite sex N = 318	MZ N = 105	DZ same sex N = 125	DZ opposite sex N = 319
Any ADHD	6.2 (4.6–8.2)	7.4 (5.8–9.5) ^a	4.1 (2.8–5.5)	6.8 (5.4–8.4)	11.5 (6.8–17.6)	3.8 (0.0–10.8)	5.6 (1.1–11.3)	2.5 (0.5–6.2)
Inattentive	2.9 (2.0–4.0)	4.5 (3.0–6.6) ^b	2.3 (1.3–3.4)	3.5 (2.4–4.7)	8.0 (3.3–14.0)	0.3 (0.0–0.8)	1.6 (0.5–2.9)	0.3 (0.0–0.7)
Combined	2.4 (1.4–3.9)	2.3 (1.8–2.9)	1.2 (0.5–2.1)	3.1 (2.0–4.3)	2.7 (1.7–3.8)	3.6 (0.0–10.4)	2.0 (0.0–6.3)	0.5 (0.1–1.1)
Hyperactive	0.9 (0.3–1.8)	0.5 (0.3–0.8)	0.6 (0.1–1.2)	0.2 (0.0–0.6)	0.8 (0.3–1.4)	0.0 (0.0–0.0)	2.0 (0.0–6.1)	1.7 (0.0–5.2)

Note: Prevalence difference in males versus females: a = ($\chi^2 = 3.8, p = .05$), b = ($\chi^2 = 17.6, p = 3 \times 10^{-4}$)

Table 2

Population Prevalence (%) of Latent Class ADHD Subtypes by Sex and Twin Type

Latent class	Total sample		Male			Female		
	(N = 1472)	Total (N = 923)	MZ (N = 275)	DZ same sex pairs (N = 330)	DZ opposite sex pairs (N = 318)	MZ (N = 105)	DZ same sex pairs (N = 125)	DZ opposite sex pairs (N = 319)
75.0 (71.1–78.8)	69.5 (63.4–75.1)	69.5 (58.2–80.1)	65.7 (53.0–76.7)	73.0 (65.0–80.0)	82.5 ^a (77.6–87.1)	76.7 (67.6–85.1)	81.9 (73.3–89.4)	81.9 (73.3–89.4)
6.4 (4.6–8.4)	7.9 ^b (4.1–13.5)	8.4 (4.1–13.5)	9.2 (3.3–16.5)	6.5 (3.9–10.5)	4.2 ^b (1.9–6.8)	5.0 (0.6–10.8)	4.8 (1.2–9.6)	4.8 (1.2–9.6)
4.4 (2.6–6.4)	4.4 (2.7–13.2)	7.7 (2.7–13.2)	2.3 (0.0–7.1)	1.8 (0.0–5.4)	4.6 (2.0–7.8)	6.7 (1.2–13.5)	3.7 (0.3–8.7)	3.7 (0.3–8.7)
3.8 (2.6–5.3)	4.8 (2.0–8.9)	4.9 (2.0–8.9)	2.9 (1.9–4.1)	6.1 (2.5–11.0)	2.5 (1.2–4.4)	2.2 (0.9–3.6)	4.5 (1.0–9.5)	4.5 (1.0–9.5)
3.5 (1.9–5.3)	5.3 ^c (0.5–8.9)	4.2 (0.5–8.9)	10.5 (3.8–19.7)	2.5 (0.4–5.9)	1.5 ^c (0.2–3.3)	3.1 (0.3–7.5)	1.8 (0.0–5.3)	1.8 (0.0–5.3)
3.3 (2.1–4.9)	3.5 (0.8–2.6)	1.7 (0.8–2.6)	3.3 (2.3–4.5)	5.5 (3.1–9.4)	2.8 (0.8–5.7)	3.1 (0.3–7.6)	1.3 (0.7–2.1)	1.3 (0.7–2.1)
2.5 (1.8–3.4)	3.7 ^d (1.1–3.0)	2.1 (1.1–3.0)	5.6 (2.8–9.9)	4.1 (1.8–7.6)	0.7 ^d (0.3–1.1)	1.3 (0.3–2.6)	0.3 (0.0–0.7)	0.3 (0.0–0.7)
1.1 (0.3–2.2)	0.9 (0.2–2.1)	1.5 (0.0–4.2)	0.4 (0.0–0.8)	0.7 (0.2–1.2)	1.2 (0.0–3.1)	2.0 (0.0–6.1)	1.7 (0.0–5.2)	1.7 (0.0–5.2)

Note: Prevalence difference in males versus females: a = ($\chi^2 = 11.3, p = 8 \times 10^{-3}$), b = ($\chi^2 = 3.9, p = .05$), c = ($\chi^2 = 4.9, p = .03$), d = ($\chi^2 = 14.4, p = 1.5 \times 10^{-4}$)

severe inattentive and combined latent classes or diagnosed with DSM-IV inattentive or combined subtypes was lower than the overall male prevalence for these subtypes. However, the prevalence of these subtypes in female MZ twins was consistent with the overall population prevalence in females (3.8% and 3.9%, respectively). Interestingly, the prevalence of any DSM-IV ADHD for males from opposite-sex DZ twin pairs was 11.5%, higher than the prevalence among all males, while the prevalence for females from opposite-sex DZ pairs (2.5%) was somewhat lower than that for all females. This suggests a possible reporting bias by parents based on the sex of the co-twin.

Unlike earlier school-based studies of DSM-IV ADHD subtype prevalence, we employed birth records and parent report based diagnoses. In spite of these design differences, several patterns observed in previous school-based studies were confirmed (Table 3). First, the prevalence of all ADHD subtypes was higher in males than in females. This has been true for both teacher questionnaire reports about children aged 5 to 12 years (Baumgaertel et al., 1995; Gaub & Carlson, 1997; Wolraich et al., 1996) as well as self-report for 12- to 15-year-olds (Rohde et al., 1999). Second, in three of the four previous studies the most prevalent ADHD subtype was primarily inattentive (Baumgaertel et al., 1995; Gaub & Carlson, 1997; Wolraich et al., 1996). In the adolescent self-report study (Rohde et al., 1999), inattentive and combined subtypes were equally common. Finally, though the primarily hyperactive-impulsive ADHD subtype was the least prevalent in all studies, there was a significant prevalence of this subtype among adolescents for both sexes in three of the studies (Baumgaertel et al., 1995; Gaub & Carlson, 1997; Wolraich et al., 1996).

However, our prevalence and the prevalence found in Rohde et al. (1999) were less than 1%.

The reported ages of onset for the three DSM-IV subtypes did not differ overall or by sex. This is in contrast with previous theoretical discussions that viewed hyperactive-impulsive subtype as a developmental precursor to combined subtype (e.g., Barkley, 1997). From a family point of view, it seems more likely that DSM-IV primarily inattentive and combined subtypes are related since there is an increased frequency of these ADHD subtypes among relatives of probands with either subtype (Faraone, Biederman, & Friedman, 2000; Faraone, Biederman, Mick, et al., 2000; Smalley et al., 2000; Todd et al., 2001), while there is no increase in the prevalence of the inattentive or combined subtype among relatives of hyperactive-impulsive probands (Faraone, Biederman, & Friedman, 2000; Faraone, Biederman, Mick, et al., 2000; Todd et al., 2001). Hence, our age of onset results are most compatible with the DSM-IV defined hyperactive-impulsive subtype being a distinct entity.

The latent class severe inattentive prevalence for males and females was somewhat lower than those reported in the Australian twins, 8.3% and 2.2% respectively (Rasmussen et al., 2002) and for the females in the MOAFTS study, 3.6% (Todd et al., 2001). Part of this is likely to be an artifact of sampling of females in the current study, as discussed above. The severe combined and severe hyperactive-impulsive latent class prevalences for females and males respectively were similar to the two reports cited above. It should be noted, however, that compared to the few ADHD symptoms latent class, all the latent class ADHD subtypes are associated with academic problems (Todd et al., 2002).

Table 3

Comparison of Community Sample Prevalences of DSM-IV

Study	Sampling frame	Age range (years)	Information type	Any ADHD	Inattentive	Combined	Hyperactive/impulsive
				Prevalence (%) (M/F ratio)			
Baumgaertel et al. 1995	School	5–12	Teacher questionnaire	17.8 (nr)	9.0 (2.0)	4.8 (nr)	3.9 (5.0)
Wolraich et al., 1996	School	5–12	Teacher questionnaire	11.4 (2.9)	5.4 (2.2)	3.6 (3.5)	2.4 (4.3)
Gaub and Carlson, 1997	School	5–12	Teacher questionnaire	8.0 (2.7)	4.5 (2.3)	1.0 (2.8)	1.7 (4.1)
Rohde et al., 1999	School	12–14	Adolescent interview	5.8 (0.9)	2.9 (nr)	3.0 (nr)	0.8 (nr)
Graetz et al. 2001	Australian population	6–17	Parent interview	7.5 (2.4)	3.7 (2.2)	1.9 (1.7)	1.9 (4.6)
This study	Birth records	7–19	Parent interview	6.2 (1.9)	2.0 (7.5)	2.4 (1.1)	0.9 (0.4)

Note: nr = not reported

Compared to DSM-IV ADHD subtypes, the overall age of onset among the three severe population-based latent classes (severe combined, inattentive and hyperactive-impulsive) was older and differed significantly among themselves ($\chi^2_2 = 11.0, p = .004$). This significant age difference was restricted to males ($\chi^2_2 = 12.2, p = .002$), not the females ($\chi^2_2 = 0.35, p = .8$). Whether this older (but still preschool) age of onset reflects milder ADHD problems which only come to attention later, or whether this reflects true differences in developmental trajectories, is unknown. It should be noted that these severe population study-defined ADHD subtypes are family specific (Rasmussen et al., 2004; Todd et al., 2001).

Limitations

There are a variety of potential limitations to the current study. First, this is a twin-based sample. Hence, the question of whether the prevalences of ADHD DSM-IV subtypes and those of our population-based latent class subtypes derived from twins can be assumed to hold true in the general population remains an open question as, to our knowledge, there have been no population-based comparable studies of ADHD in a nontwin sample. We do note that prevalences of latent class-defined ADHD subtypes in nontwin siblings of twins were similar in the Australian twin study, which is a volunteer-based twin sample from the general population (Rasmussen et al., 2002, 2004).

A related question is whether there are sampling biases associated with ascertainment through birth registries. Heath et al. (2002) investigated potential biases associated with birth record ascertainment and showed that overall, sampling biases were small. Small negative effects on the ability to recruit a family into a study were noted in the case of the birth of twins to a teenage mother, having a parent born out of the state, having an absentee biological father, birth to a mother living in a neighborhood with high rates of poverty, or being African American. However, these same obstacles would be present for recruiting nontwin families into an epidemiologically based study. Another potential limitation is the knowledge that birth complications are more common to twin births and may contribute to the prevalence of ADHD. However, this seems unlikely since the prevalence of DSM-IV ADHD is lower in MZ than DZ twins for both males and females (Table 1). Similarly, prevalences of the severe latent classes are lowest in MZ pairs compared to DZ pairs with the exception of the females in the severe combined class. As discussed above, this may be due to parent rating biases trying to make identical twins appear more different (or, in other instances, more identical), discussed in detail in Eaves et al. (1997) and Hudziak et al. (2000). However, Cronk et al. (2002) have shown that twin studies of emotional and behavioral symptoms based on mother reports for female twins, including ADHD, are unbiased with respect to zygosity. We also note that our estimates of

DSM-IV ADHD subtypes do not differ significantly from estimates seen from the four school-based samples listed in Table 3. The fact that our analyses were based on parent reports only may be considered a limiting factor. However, we chose to restrict our analyses to the parent report since this is the basis of most clinical diagnoses of ADHD. Teacher reports lack an historical view of their students' problems and may underreport on student's current states secondary to successful treatment. The combination of self, teacher and parent reports of ADHD will be assessed in ongoing follow-up studies of these families. Finally, bias in the reporting of ages of onset may arise due to the retrospective nature of the interview. A birth records-based prospective study of infants will be required to address this issue

Clinical Implications

The current report has three clinical implications. First, since the most common form of educationally significant ADHD is inattentive problems, while the most common forms of clinically treated ADHD are combined, an important segment of the population is not receiving treatment. Second, the sex ratio for best estimates of DSM-IV ADHD overall is slightly less than two (boys 7.4%, girls 3.9%), while the sex ratio of those seen in a clinical setting, including our own, is often more than four boys for every one girl, suggesting that school-aged girls are under treated. Finally, there are many children who do not meet DSM-IV ADHD criteria but are in latent classes characterized by significant attention problems and school failure. Hence, there is a subgroup of children who probably would benefit from treatment but who would not be identified using the DSM-IV nosology. This suggests that this alternative nosology may target children for treatment who are currently under served.

Acknowledgments

This work was supported by: NIH Grants MH52813 and AA12239.

References

- American Psychiatric Association (APA). (1980). *Diagnostic and statistical manual of mental disorders* (3rd ed.). Washington, DC: Author.
- American Psychiatric Association (APA). (1987). *Diagnostic and statistical manual of mental disorders* (3rd ed., rev.). Washington, DC: Author.
- American Psychiatric Association (APA). (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.
- Barkley, R. A. (1997). *ADHD and the nature of self control*. New York: The Guilford Press.
- Baumgaertel, A., Wolraich, M. L., & Dietrich, M. (1995). Comparison of diagnostic criteria for attention deficit disorders in a German elementary school sample.

- Journal of the American Academy of Child and Adolescent Psychiatry*, 34, 629–638.
- Burd, L., Klug, M. G., Coumbe, M. J., & Kerbeshian, J. (2003). Children and adolescents with attention deficit-hyperactivity disorder: 1. Prevalence and cost of care. *Journal of Child Neurology*, 18, 555–561.
- Carlson, C. L., & Mann, M. (2002). Sluggish cognitive tempo predicts a different pattern of impairment in the attention deficit hyperactivity disorder, predominantly inattentive type. *Journal of Clinical Child Psychology*, 31, 123–129.
- Cronk, N. J., Slutske, W. S., Madden, P. A. F., Bucholz, K. K., Reich, W., & Heath, A. C. (2002). Emotional and behavioral problems among female twins: An evaluation of the equal environments assumption. *Journal of the American Academy of Child and Adolescent Psychiatry*, 7, 829–837.
- Eaves, L. J., Silberg, J. L., Meyer, J. M., Maes, H. H., Simonoff, E., Pickles, A., Rutter, M., Neale, M. C., Reynolds, C. A., Erikson, M. T., Heath, A. C., Loeber, R., Truett, K. R., & Hewitt, J. K. (1997). Genetics and developmental psychopathology: 2. The main effects of genes and environment on behavioral problems in the Virginia Twin Study of Adolescent Behavioral Development. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 38, 965–980.
- Efron, B., & Tibshirani, R. J. (1993). *An introduction to the bootstrap*. Boston, MA: Chapman and Hall.
- Faraone, S. V., Biederman, J., & Friedman, D. (2000). Validity of DSM-IV subtypes of attention deficit/hyperactivity disorder: A family study perspective. *Journal of the American Academy of Child and Adolescent Psychiatry*, 39, 300–307.
- Faraone, S. V., Biederman, J., Mick, E., Williamson, S., Wilens, T., Spencer, T., Weber, W., Jetton, J., Kraus, I., Pert, J., & Zallen, B. (2000). Family study of girls with attention deficit hyperactivity disorder. *American Journal of Psychiatry*, 157, 1077–1083.
- Faraone, S. V., Perlis, R. H., Doyle, A. E., Smoller, J. W., Goralnick, J. J., Holmgren, M. A., & Sklar, P. (2005). Molecular genetics of attention-deficit/hyperactivity disorder. *Biological Psychiatry*, 57, 1313–1323.
- Fleiss, J. L. (1981). *Statistical methods for rates and proportions*. New York: John Wiley.
- Gaub, M., & Carlson, C. L. (1997). Behavioral characteristics of DSM-IV ADHD subtypes in a school-based population. *Journal of Abnormal Child Psychology*, 25, 103–111.
- Graetz, B. W., Sawyer, M. G., Hazell, P. L., Arney, F., & Baghurst, P. (2001). Validity of DSM-IVADHD subtypes in a nationally representative sample of Australian children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*, 40, 1410–1417.
- Heath, A. C., Howells, W., Bucholz, K. K., Glowinski, A. L., Nelson, E. C., & Madden, P. A. F. (2002). Ascertainment of a mid-western US female adolescent twin cohort for alcohol studies: Assessment of sample representativeness using birth record data. *Twin Research*, 5, 107–112.
- Heath, A. C., Madden, P. A., Grant, J. D., McLaughlin, T. L., Todorov, A. A., & Bucholz, K. K. (1999). Resiliency factors protecting against teenage alcohol use and smoking: Influences of religion, religious involvement and values, and ethnicity in the Missouri Adolescent Female Twin Study. *Twin Research*, 2, 145–155.
- Heath, A. C., Nyholt, D. R., Neuman, R. J., Madden, P. A. F., Bucholz, K. K., Todd, R. D., Nelson, E. C., Montgomery, G. W., & Martin, N. G. (2003). Zygosity diagnosis in the absence of genotypic data: an approach using latent class analysis. *Twin Research*, 6, 22–26.
- Hudziak, J. J., Heath, A. C., Madden, P. A. F., Reich, W., Bucholz, K. K., Slutske, W. S., Bierut, L. J., Neuman, R. J., & Todd, R. D. (1998). Latent class and factor analysis of DSM-IV ADHD: A twin study of female adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*, 37, 848–857.
- Hudziak, J. J., Rudiger, L. P., Neale, M. C., Heath, A. C., & Todd, R. D. (2000). A twin study of inattentive, aggressive, and anxious/depressed behaviors. *Journal of the American Academy of Child and Adolescent Psychiatry*, 39, 469–476.
- Lahey, B. B., Applegate, B., McBurnett, K., Biederman, J., Greenhill, L., Hynd, G. W., Barkley, R. A., Newcorn, J., Jensen, P., Richters, J., Finkel, B., Kerdy, K. L., Frick, P. J., Ollendick, T., Perez, D., Hart, E. L., Waldman, I., & Shaffer, D. (1994). DSM-IV field trials for attention deficit hyperactivity disorder in children and adolescents. *American Journal of Psychiatry*, 151, 1673–1685.
- McBurnett, K., Pfiffner, L. J., & Frick, P. J. (2001). Symptom properties as a function of ADHD type: An argument for continued study of sluggish cognitive tempo. *Journal of Abnormal Child Psychology*, 29, 207–213.
- McCutcheon, A. L. (1987). *Latent class analysis: Sage University paper series on quantitative applications in the social sciences*, series no. 07–064. Beverly Hills, CA: Sage.
- Milberger, S., Faraone, S. V., Biederman, J., Testa, M., & Tsuang, M. T. (1996). New phenotype definition of attention deficit hyperactivity disorder in relatives for genetic analyses. *American Journal of Medical Genetics*, 67, 369–377.
- Neuman, R. J., Heath, A. C., Reich, W., Bucholz, K. K., Madden, P. A. F., Sun, L., Todd, R. D., & Hudziak, J. J. (2001). Latent class analysis of ADHD and comorbid symptoms in a population sample of adolescent female twins. *Journal of the American Academy of Child and Adolescent Psychiatry*, 42, 933–942.
- Neuman, R. J., Todd, R. D., Heath, A. C., Reich, W., Hudziak, J. J., Bucholz, K. K., Madden, P. A., Begleiter, H., Porjesz, B., Kuperman, S., Hesselbrock,

- V., & Reich, T. (1999). Evaluation of ADHD typology in three contrasting samples: A latent class approach. *Journal of the American Academy of Child and Adolescent Psychiatry*, 38, 25–33.
- Rasmussen, E. R., Neuman, R. J., Heath, A. C., Levy, F., Hay, D. A., & Todd, R. D. (2002). Replication of the latent class structure of attention-deficit/hyperactivity disorder (ADHD) subtypes in a sample of Australian twins. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 43, 1018–1028.
- Rasmussen, E. R., Neuman, R. J., Heath, A. C., Levy, F., Hay, D. A., & Todd, R. D. (2004). Familial clustering of latent class and DSM-IV defined attention-deficit/hyperactivity disorder subtypes. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 45, 589–598.
- Reich, W. (2000). Diagnostic interview for children and adolescents (DICA). *Journal of the American Academy of Child and Adolescent Psychiatry*, 39, 59–66.
- Rohde, L. A., Biederman, J., Busnello, E. A., Zimmermann, H., Schmitz, M., Martins, S., & Tramontina, S. (1999). ADHD in a school sample of Brazilian adolescents: A study of prevalence, comorbid conditions, and impairments. *Journal of the American Academy of Child and Adolescent Psychiatry*, 38, 716–722.
- Smalley, S. L., McGough, J. J., Del'Homme, M., NewDelman, J., Gordon, E., Kim, T., Liu, A., & McCracken, J. T. (2000). Familial clustering of symptoms and disruptive behaviors in multiplex families with attention deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 39, 1135–1143.
- Szatmari, P. (1982). The epidemiology of attention-deficit hyperactivity disorders. In G. Weiss (Ed.), *Child and adolescent psychiatry clinics of North America* (vol. 1, pp. 361–372). Philadelphia, PA: Saunders.
- Todd, R. D. (2000a). Genetics of attention deficit/hyperactivity disorder: Are we ready for molecular genetic studies? *American Journal of Medical Genetics*, 96, 241–243.
- Todd, R. D. (2000b). Genetics of childhood disorders: XXI. ADHD, part 5: A behavioral genetic perspective. *Journal of the American Academy of Child and Adolescent Psychiatry*, 39, 1571–1573.
- Todd, R. D., Joyner, C. A., Heath, A. C., Neuman, R. J., & Reich, W. (2003). Reliability and stability of a semi-structured DSM-IV interview designed for family studies. *Journal of the American Academy of Child and Adolescent Psychiatry*, 42, 1460–1468.
- Todd, R. D., Rasmussen, E. R., Neuman, R. J., Reich, W., Hudziak, J. J., Bucholz, K. K., Madden, P. A. F., & Heath, A. C. (2001). Familiality and heritability of subtypes of attention deficit hyperactivity disorder in a population sample of adolescent female twins. *American Journal of Psychiatry*, 158, 1891–1898.
- Todd, R. D., Rasmussen, E. R., Wood, C., Levy, F., & Hay, D. (2004). Should sluggish cognitive tempo symptoms be included in the diagnosis of attention deficit hyperactivity disorder? *Journal of the American Academy of Child and Adolescent Psychiatry*, 43, 588–597.
- Todd, R. D., Sitdhiraksa, N., Reich, W., Ji, T. H., Joyner, C. A., Heath, A. C., & Neuman, R. J. (2002). Discrimination of DSM-IV and latent class attention-deficit/hyperactivity disorder subtypes by educational and cognitive performance in a population-based sample of child and adolescent twins. *Journal of the American Academy of Child and Adolescent Psychiatry*, 41, 820–828.
- Wolraich, M. L., Hannah, J. N., Pinnock, T. Y., Baumgaertel, A., & Brown, J. (1996). Comparison of diagnostic criteria for attention-deficit hyperactivity disorder in a county-wide sample. *Journal of the American Academy of Child and Adolescent Psychiatry*, 35, 319–324.