THE JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY

ACAMH THE ASSOCIATION FOR CHILD AND ADOLESCENT MENTAL HEALTH

Journal of Child Psychology and Psychiatry **:* (2016), pp **–** doi:10.1111/jcpp.12616

Familial aggregation of attention-deficit/hyperactivity disorder

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Background: Attention-deficit/hyperactivity disorder (ADHD) aggregates in families. To date, the strength, pattern, and characteristics of the familial aggregation have not been thoroughly assessed in a population-based family sample. **Methods:** In this cohort study, we identified relative pairs of twins, full and half-siblings, and full and half cousins from 1,656,943 unique individuals born in Sweden between 1985 and 2006. The relatives of index persons were followed from their third birthday to 31 December 2009 for ADHD diagnosis. Birth year adjusted hazard ratio (HR), that is, the rate of ADHD in relatives of ADHD-affected index persons compared with the rate of ADHD in relatives of unaffected index persons, was estimated in the different types of relatives using Cox proportional hazards model. **Results:** During the follow-up, 31,865 individuals were diagnosed with ADHD (male to female ratio was 3.7). The birth year adjusted HRs were as follows: 70.45 for monozygotic twins; 8.44 for dizygotic twins; 8.27 for full siblings; 2.86 for maternal half-siblings; 2.31 for paternal half-siblings; 2.24 for full cousins; 1.47 for half cousins. Maternal half-siblings had significantly higher HR than in paternal half-siblings. The HR did not seem to be affected by index person's sex. Full siblings of index persons with ADHD diagnosis present at age 18 or older had a higher rate of ADHD (HR: 11.49) than full siblings of index persons with ADHD diagnosis only before age 18 (HR: 4.68). **Conclusions:** Familial aggregation of ADHD increases with increasing genetic relatedness. The familial aggregation is driven by not only genetic factors but also a small amount of shared environmental factors. Persistence of ADHD into adulthood indexes stronger familial aggregation of ADHD. **Keywords:** Attention-deficit/hyperactivity disorder; diagnosis; family factor; sex differences; adulthood.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a complex multifactorial neurodevelopmental disorder. Males are more likely to be diagnosed with ADHD than females (Willcutt, 2012). Once considered a childhood disorder, ADHD is increasingly being diagnosed in adults (Asherson, Buitelaar, Faraone, & Rohde, 2016). The pooled worldwide prevalence of ADHD has been estimated to be 5.3%–7.2% in children and adolescents (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007; Thomas, Sanders, Doust, Beller, & Glasziou, 2015), and 2.5%–3.4% in adults (Fayyad et al., 2007; Simon, Czobor, Balint, Meszaros, & Bitter, 2009).

Despite clear evidence for familial aggregation of ADHD, its strength, pattern, and characteristics have not been thoroughly assessed in a population-based family sample. Previous studies have found a five- to ninefold increased risk of ADHD in first-degree relatives of ADHD patients compared to the general population (Chen et al., 2008; Faraone, Biederman, & Monuteaux, 2000). The estimated relative risks were sensitive to both the selected sample and the population prevalence of ADHD. These studies, based on small samples with restricted follow-up, were not capable of exploring specific influences, such as sex and persistence of ADHD into adulthood, on the familial aggregation. To date, little is known about the familial aggregation in half-siblings and cousins. Precise estimation of the strength and pattern of the familial aggregation in relatives of varying degrees of relatedness and its characteristics may not only provide valuable insights into the etiological origin of ADHD but also aid in identifying high-risk groups for diagnostic screening and predicting clinical course of the disorder.

While twin studies have repeatedly reported high heritability estimate of 70%–80% for ADHD (Chang, Lichtenstein, Asherson, & Larsson, 2013; Faraone et al., 2005) and the significance of both additive genetic and nonshared environmental factors to the phenotypic variance in ADHD, the relative importance of shared environmental factors on the variance remains under debate (Burt, 2009; Wood, Buitelaar, Rijsdijk, Asherson, & Kuntsi, 2010).

Using a Swedish population-based family sample consisting of relative pairs of twins, siblings, and cousins, we aimed to estimate the strength and pattern of the familial aggregation of ADHD with greater precision than previously reported. We further tested whether the familial aggregation in full siblings was affected by sex and persistence of ADHD into adulthood. Finally, we performed quantitative genetic analyses in an extended sibling sample to address the relative importance of genetic and

Conflict of interest statement: No conflicts declared.

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environmental contributions to the variance in the liability to ADHD.

Methods

Ethical approval for the study was provided by the regional ethics review board in Stockholm, Sweden. Demographic and health data in registers were collected by the Swedish National Board of Health and Welfare, and anonymized and linked by an independent government agency, Statistics Sweden, to ensure no information can be traced back to individual participants.

Study population

The Medical Birth Register contains data on approximately 98% of all births in Sweden since 1973 (Cnattingius, Ericson, Gunnarskog, & Kallen, 1990). The Multi-Generation Register links individuals born in Sweden since 1932 and registered as living in Sweden since 1961 to their biological parents, which enables identification of relatives of varying degrees of genetic relatedness (Ekbom, 2011). The Swedish Twin Register provides information on twin zygosity, which was primarily determined by questions on intrapair physical similarity in childhood and has been validated by DNA testing during recent years (Magnusson et al., 2013). By linking these three registers, we identified 8,618 monozygotic twin pairs, 26,458 dizygotic twin pairs, 2,030,117 nontwin full-sibling pairs, 315,267 maternal half-sibling pairs, 312,593 paternal half-sibling pairs, 4,612,179 full cousin pairs, and 958,457 half cousin pairs from 1,656,943 unique individuals born alive in Sweden between 1 January 1985 and 31 December 2006. Full cousins are children of full siblings and half cousins are children of half-siblings. In the cousin sample, single child families were excluded to ensure that it was comparable to the sibling sample. In each pair of relatives, the one used for ascertaining the family relationship was defined as the index person. The relatives of the index persons were followed from their third birthday until first ADHD diagnosis, death, emigration, or 31 December 2009, whichever occurred first.

Attention-deficit/hyperactivity disorder

Attention-deficit/hyperactivity disorder diagnoses were identified from the Swedish National Patient Register (NPR), the Prescribed Drug Register (PDR), and the Clinical Database for Child and Adolescent Psychiatry in Stockholm (Pastill). The NPR contains one primary and up to eight secondary discharge diagnoses as well as admission and discharge dates for psychiatric inpatient care since 1973 and has complete national coverage since 1987 (Ludvigsson et al., 2011). Outpatient visits have been included since 2001. Diagnoses are coded according to *International Classification of Diseases, 9th revision* (ICD-9) during 1987–1996 and ICD-10 from 1997 onwards. The PDR provides data on all drugs dispensed to the entire population in Sweden since July 1, 2005, including prescribing dates and active ingredients coded based on the anatomical therapeutic chemical classification system (Wettermark et al., 2007). Pastill contains information on diagnoses based on ICD-10 or *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) from Child and Adolescent Mental Health Services in Stockholm County since 2001 (Lindevall, 2009). During the follow-up, individuals who received diagnosis of hyperkinetic disorder (ICD-9: 314; ICD-10: F90) according to the NPR or Pastill, or drug prescription of methylphenidate (N06BA04), amphetamine (N06BA01), dexamphetamine (N06BA02), or atomoxetine (N06BA09) according to the PDR, or diagnosis of ADHD (DSM-IV: 314) according to Pastill, were defined as ADHD cases. Date of first ADHD diagnosis was defined as the date of the first registered diagnosis or drug prescription, whichever occurred first.

Covariates

The analyses took into account several covariates that might potentially explain the familial aggregation of ADHD, including birth year (1985–1991, 1992–1996, 1997–2001, 2002–2006), sex (male/female), maternal age at childbirth (<35 and ≥35 years), paternal age at childbirth (<45 and ≥45 years), and maternal and paternal psychiatric history (yes/no). Psychiatric history was defined as the presence of any psychiatric diagnosis (ICD 8: 290–315; ICD 9: 290–319; ICD 10: F00–F99) before the birth of the first-born child in a nuclear family during the study period.

Statistical analysis

We estimated the cumulative incidence of ADHD up to 20 years of age in all siblings and all cousins using Kaplan–Meier method. The strength of the familial aggregation of ADHD was measured by hazard ratios (HRs), that is, the rate of ADHD in relatives of ADHD-affected index persons compared with the rate of ADHD in relatives of unaffected index persons. Cox proportional hazards models were used to estimate both crude and birth year-adjusted HRs, together with 95% confidence intervals (CIs), in the different types of relatives. ADHD diagnosis in the index person was used as a time-varying exposure and attained age of the relative was used as the underlying time scale. Robust standard errors were calculated to account for the nonindependence of the family clustered data. Detailed description of the methodology can be found elsewhere (Sandin et al., 2014).

To assess the potential importance of shared environmental influence on the familial aggregation, we tested whether HRs in maternal half-siblings and paternal half-siblings significantly differ. A higher HR in maternal half-siblings than in paternal half-siblings would be expected if shared environmental factors are influential since both types of half-siblings share on average 25% of their segregating genes, but in the current study, maternal half-siblings are assumed to share more environmental factors than paternal half-siblings due to the fact that children in Sweden continued to live predominantly with their mothers following parental separation during the study period (Statistics Sweden, 1994).

Furthermore, we conducted subgroup analyses in full siblings. To examine the influence of index person's sex, we performed analyses stratified on sex combination of index persons and their siblings. When assessing the impact of persistence of ADHD into adulthood, we restricted analyses to sibling pairs born during 1985–1991, and further categorized ADHD-affected index persons by their age at last diagnosis (<18/≥18 years). To test the presence of time trends, we estimated HRs stratified on birth years (1985–1991, 1992–1996, 1997–2001, and 2002–2006). To explore if the familial aggregation can be attributed to other covariates, we estimated HRs adjusted for sibling's birth year and one of the following covariates at a time: sibling's sex, index person's sex, maternal age at childbirth, paternal age at childbirth, maternal psychiatric history, and paternal psychiatric history.

Two sets of sensitivity analyses were performed to assess the robustness of the results. First, we evaluated if the HR estimates were sensitive to the data source for ascertainment of ADHD by comparing birth year-adjusted HRs for ADHD diagnosis ascertained only by the NPR, only by the outpatient register in the NPR, only by the PDR, and by pooling data from the NPR and Pastill, respectively. Second, we repeated the main analyses in a younger cohort born during 1992–2000, to assess the potential influences of (a) the suboptimal coverage of the NPR for outpatient visits before year 2001, (b) the

improved public awareness of ADHD during the study period, and (c) the relatively short follow-up for later-born individuals.

Finally, we carried out variance decomposition analysis to examine the relative importance of genetic and environmental contributions to the liability of ADHD. We randomly selected one pair of siblings from each nuclear family to obtain an extended sibling sample (n = 1,029,423 pairs), comprising monozygotic twins, dizygotic twins, full siblings, and maternal and paternal half-siblings. For each type of sibling pairs, we calculated probandwise concordance rates defined as the proportion of ADHD-affected individuals whose siblings were also affected, with robust standard errors accounting for dependencies within pairs of siblings. Sex- and birth year-adjusted tetrachoric correlations of ADHD were calculated by assuming a liability threshold model of ADHD, where a continuous underlying liability to ADHD is normally distributed in the population and individuals with a liability surpassing a certain threshold develop ADHD. Structural equation modeling was used to decompose the variance in the liability to ADHD into additive genetic (A), dominant genetic (D), shared environmental (C), and nonshared environmental (E) components. Using likelihood ratio tests, we compared the full model containing all four components (ADCE model) with three restricted models (ACE, ADE, and AE models) by dropping only D, only C, and both D and C parameters, respectively, to identify the best fitting model, that is, the model with fewer parameters if it does not result in a significant deterioration of fit. All models were adjusted for sex and birth year.

All statistical hypotheses were two-sided, with a significance level of 5%. SAS software version 9.4 (SAS Institute Inc., Cary, NC) was used for data management and construction of analytic datasets. Survival package and OpenMx package (Neale et al., 2016) in R software version 3.2 (R Development Core Team, 2012) were used for statistical analyses.

Results

During the follow-up, 31,865 individuals received ADHD diagnosis (male to female ratio was 3.7), generating a lifetime prevalence of 1.9%. Additional descriptive characteristics of the participants are summarized in Table 1.

Figure 1 illustrates the cumulative incidences of ADHD diagnosis up to 20 years of age for all siblings and all cousins. For both siblings and cousins of unaffected index persons, the cumulative incidences of ADHD diagnosis at age 20 were around 3.6% (Figure 1A,B). For siblings and cousins of ADHD-affected index persons, the cumulative incidences of ADHD diagnosis at age 20 were 25.3% (Figure 1A) and 10.0% (Figure 1B), respectively. The incidence rates per 100,000 person-years for ADHD diagnosis in different types of relatives are shown in Figure 2.

Familial aggregation of ADHD

The strength of the familial aggregation of ADHD was measured by crude and birth year-adjusted HRs for ADHD diagnosis (Figure 2). Compared with crude HRs, birth year-adjusted HRs were somewhat attenuated in magnitude, with the estimates being 70.45 (95% CI = 38.19–129.96) in monozygotic twins, 8.44 (95% CI = 5.87–12.14) in dizygotic twins, 8.27 (95% CI = 7.86–8.70) in full siblings, 2.86 (95% CI = 2.61–3.13) in maternal half-siblings, 2.31 (95% CI =

Table 1 Descriptive characteristics of the study population

Characteristic	Total	Monozygotic twins	Dizygotic twins	Full siblings	Maternal half-siblings	Paternal half-siblings	Full cousins	Half cousins
Unique participants, *n*	1,656,943	8,618	26,458	1,435,220	220,716	212,227	1,093,610	268,105
Relative pairs, *n*	8,263,689	8,618	26,458	2,030,117	315,267	312,593	4,612,179	958,457
Females, %	48.8	54.4	49.5	48.6	49.0	49.3	48.7	48.9
ADHD, *n* (%)	31,865 (1.9)	96 (1.1)	468 (1.8)	24,282 (1.7)	8,953 (4.1)	7,644 (3.6)	21,303 (2.0)	8,124 (3.0)
Maternal age ≥ 35 years at childbirth, *n* (%)	243,114 (14.7)	1,650 (19.2)	7,172 (27.1)	199,383 (13.9)	34,832 (15.8)	31,462 (14.8)	144,575 (13.2)	29,057 (10.8)
Paternal age ≥ 45 years at childbirth, *n* (%)	49,690 (3.0)	284 (3.3)	1,210 (4.6)	39,216 (2.7)	7,546 (3.4)	10,580 (5.0)	20,940 (1.9)	5,058 (1.9)
Maternal psychiatric history, *n* (%)	46,148 (2.8)	226 (2.6)	846 (3.2)	33,447 (2.3)	11,840 (5.4)	11,438 (5.4)	28,590 (2.6)	12,018 (4.5)
Paternal psychiatric history, *n* (%)	41,585 (2.5)	198 (2.3)	696 (2.6)	30,629 (2.1)	11,777 (5.3)	8,638 (4.1)	25,261 (2.3)	11,097 (4.1)

ADHD, attention-deficit/hyperactivity disorder.

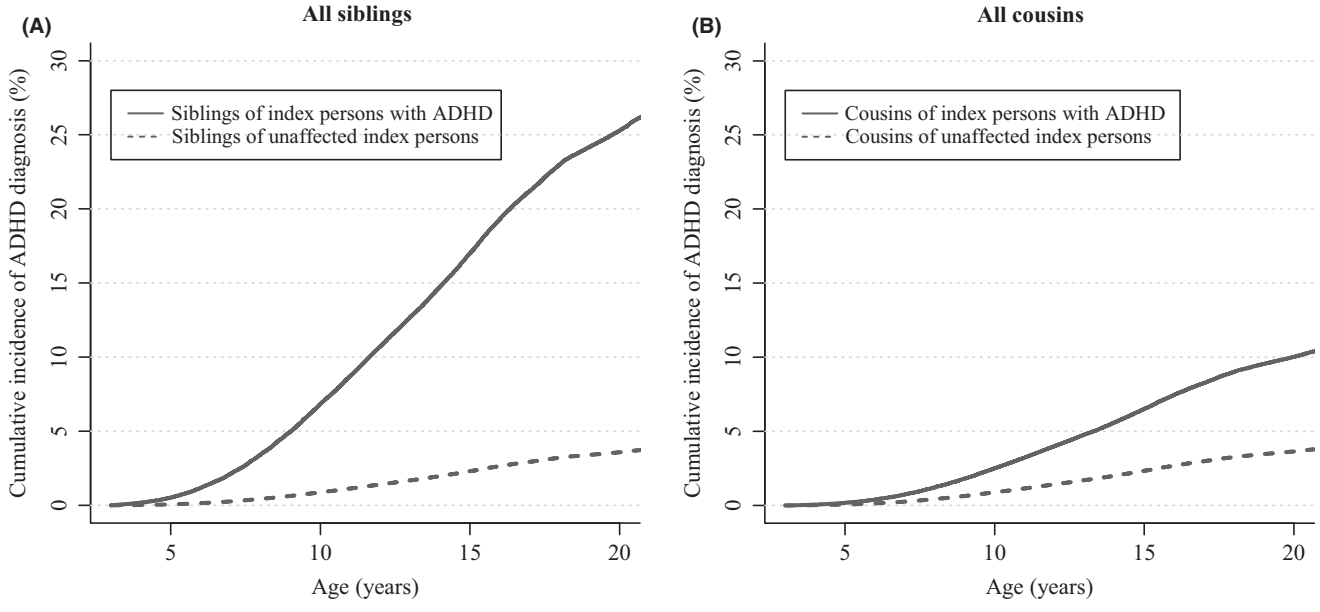
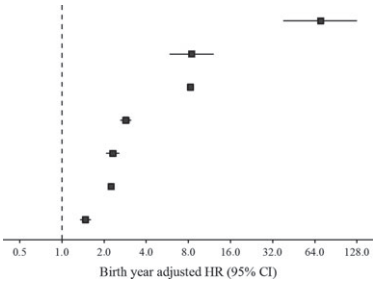


Figure 1 Cumulative incidence of attention-deficit/hyperactivity disorder (ADHD) diagnosis among all siblings and all cousins

Relation to index person	r_g[a]	Person-years of follow-up		Rates of ADHD per 100,000 person-years		HR (95% CI)	
		Exposed	Unexposed	Exposed	Unexposed	Model 1	Model 2[b]
Monozygotic twins	100%	121	93,482	13,223	86	127.15 (70.68–228.72)	70.45 (38.19–129.96)
Dizygotic twins	50%	1,317	255,105	2,582	170	11.42 (7.93–16.45)	8.44 (5.87–12.14)
Full siblings	50%	105,091	21,920,037	1,997	147	11.10 (10.55–11.69)	8.27 (7.86–8.70)
Maternal half siblings	25%	36,571	2,623,868	1,679	448	3.98 (3.64–4.35)	2.86 (2.61–3.13)
Paternal half siblings	25%	33,125	2,517,568	1,283	420	3.19 (2.86–3.56)	2.31 (2.07–2.58)
Full Cousins	12.5%	286,802	46,764,728	644	185	3.04 (2.86–3.23)	2.24 (2.11–2.38)
Half cousins[c]	6.25%	94,588	8,770,719	733	333	2.06 (1.89–2.26)	1.47 (1.35–1.61)



[a] r_g: genetic relatedness, i.e., the proportion of shared segregating genes between relative pairs

[b] The model was adjusted for birth year

[c] Half cousins were defined as children of half siblings

The upper limit of the 95% CI of the birth year adjusted HR for monozygotic twins was estimated to be 129.96.

Figure 2 Familial aggregation of attention-deficit/hyperactivity disorder (ADHD) among relatives of varying degrees of genetic relatedness

2.07–2.58) in paternal half-siblings, 2.24 (95% CI = 2.11–2.38) in full cousins, and 1.47 (95% CI = 1.35–1.61) in half cousins. The HR in maternal half-siblings was significantly higher than in paternal half-siblings (p = .004).

Among all full siblings, males had higher incidence rate of ADHD diagnosis than females (Table 2). Compared with siblings of unaffected index persons, male and female siblings of ADHD-affected index persons had around 8- and 10-fold increase in the rate of ADHD diagnosis, respectively (Table 2). The HRs did not significantly differ by index person's sex either in male siblings (p = .064) or in female siblings (p = .340). Among full siblings born during 1985–1991, siblings of index persons with ADHD diagnosis at age 18 or older had a higher rate of ADHD compared to siblings of index persons with ADHD diagnosis only before age 18 (Table 2). The HR was higher in the younger birth cohort (2002–2006) than in the older birth cohorts (1985–1991, 1992–1996, and 1997–2001; Table 2). Adjustment of parental age, and parental psychiatric history did not change the magnitude of the HRs (Table S1), but the HRs were slightly attenuated by adjustment of maternal (HR = 7.88, 95% CI = 7.48–8.30) and paternal psychiatric history (HR = 8.01, 95% CI = 7.61–8.44).

Ascertainment bias associated with different data sources only exerted negligible impact on the HRs (Table S2). The results based on the younger cohort (1992–2000) followed a similar pattern to that of the entire cohort (Table S3).

Table 2 Familial aggregation of ADHD among full siblings by sex, persistence of ADHD, and birth year

Full siblings		Person-years of follow-up		Rates of ADHD per 100,000 person-years		HR (95% CI)
		Exposed	Unexposed	Exposed	Unexposed	
Sex combination[a]						
Sibling	Index person					
Male	Male	40,725	5,761,421	2,468	207	7.61 (7.07–8.19)
Male	Female	10,726	5,480,820	2,974	219	8.57 (7.61–9.65)
Female	Male	42,169	5,470,212	1,373	75	10.05 (9.15–11.03)
Female	Female	11,471	5,207,585	1,709	81	10.85 (9.30–12.66)
Index person's age at last ADHD diagnosis[b]						
<18 years		14,980	7,447,765	668	87	4.68 (3.83–5.72)
≥18 years		13,572	7,447,765	1,724	87	11.49 (9.97–13.25)
Birth year						
1985–1991		46,257	11,153,142	1,293	97	8.18 (7.46–8.97)
1992–1996		34,908	6,726,329	2,552	199	7.98 (7.39–8.61)
1997–2001		18,131	3,103,900	2,807	222	8.92 (8.09–9.83)
2002–2006		5,795	936,666	1,743	118	12.28 (9.90–15.23)

ADHD, attention-deficit/hyperactivity disorder; HR, hazard ratio.
[a]The model was adjusted for birth year.
[b]Presence of diagnosis at age 18 or older was used as a proxy for the persistence of ADHD into adulthood; the analyses were performed in full siblings born during 1985–1991.

Table 3 Concordance rates and tetrachoric correlations

	Pairs, *n*	Concordant non-ADHD pairs, *n*	Discordant pairs, *n*	Concordant ADHD pairs, *n*	Concordance rate (95% CI)	Tetrachoric correlation (95% CI)[a]
Monozygotic twins	4,307	4,238	42	27	0.56 (0.46–0.66)	0.90 (0.83–0.95)
Dizygotic twins	13,187	12,757	393	37	0.16 (0.13–0.19)	0.51 (0.43–0.59)
Full siblings	909,582	883,493	24,455	1,634	0.12 (0.11–0.12)	0.44 (0.43–0.45)
Maternal half-siblings	54,006	50,070	3,755	181	0.09 (0.08–0.10)	0.24 (0.20–0.28)
Paternal half-siblings	48,341	45,247	2,997	97	0.06 (0.05–0.07)	0.18 (0.13–0.23)

ADHD, attention-deficit/hyperactivity disorder.
[a]Tetrachoric correlations were adjusted for sex and birth year.

Variance decomposition

The concordance rates and tetrachoric correlations in the different groups of siblings are shown in Table 3. The sex and birth year-adjusted tetrachoric correlation of ADHD was 0.90 (95% CI = 0.83–0.95) for MZ twins, 0.51 (95% CI = 0.43–0.59) for DZ twins, 0.44 (95% CI = 0.43–0.45) for full siblings, 0.24 (95% CI = 0.20–0.28) for maternal half-siblings, and 0.18 (95% CI = 0.13–0.23) for paternal half-siblings.

In the ADCE model, the variance of the liability of ADHD attributable to additive genetic effects was estimated to be 0.69 (95% CI = 0.50–0.88); dominant genetic effects, 0.14 (95% CI = 0.00–0.30); shared environment, 0.06 (95% CI = 0.00–0.13); nonshared environment, 0.10 (95% CI = 0.06–0.16). The likelihood ratio tests showed that the ACE model (dropping only D parameter) did not result in a significant loss in fit, whereas the ADE model (dropping only C parameter) did (Table 4). The AE model (dropping both D and C parameters) was selected as the best fitting model, where the heritability of ADHD was estimated to be 0.89 (95% CI = 0.87–0.91).

Discussion

With this population-based family sample comprising multiple types of relative pairs constructed from 1,656,943 unique individuals, this study represents the largest longitudinal study to date on familial aggregation of ADHD. Relatives of ADHD-affected index persons were at higher risk of ADHD compared with relatives of unaffected index persons. The familial aggregation increased along with increasing genetic relatedness. Among full siblings, the familial aggregation did not differ significantly by index person's sex. Persistence of ADHD into adulthood seemed to index stronger familial aggregation.

As expected from previous quantitative and molecular genetic studies (Lee et al., 2013; Wood & Neale, 2010), genetic influence played a more important role in explaining the pattern of the familial aggregation than shared environmental influence, given that the familial aggregation was remarkably higher in monozygotic twins than in dizygotic twins (who are different in genetic sharing but equivalent in environmental sharing) and similar between dizygotic twins and nontwin full siblings (who are equivalent in genetic sharing but different in environmental sharing). This

Table 4 Relative contributions of genetic and environmental influences on the variance in the liability to ADHD

	Model comparison				Estimated variance (95% CI)			
Model[a]	Parameters, *n*	−2LL	Diff−2LL	*p*-Value[b]	A	D	C	E
ADCE[c]	13	335375.2	NA	NA	0.69 (0.50–0.88)	0.14 (0.00–0.30)	0.06 (0.00–0.13)	0.10 (0.06–0.16)
ACE	12	335378.4	3.2	.075	0.84 (0.74–0.91)	NA	0.03 (0.00–0.08)	0.13 (0.09– 0.19)
ADE	12	335379.1	3.9	.049	0.87 (0.81–0.91)	0.03 (0.00–0.13)	NA	0.10 (0.05–0.13)
AE[d]	11	335379.5	4.3	.118	0.89 (0.87–0.91)	NA	NA	0.11 (0.09–0.13)

−2LL, −2*log-likelihood; Diff−2LL, 2*difference in log-likelihood between the model and the full model; NA, not applicable; A, additive genetic parameter; D, dominant genetic parameter; C, shared environmental parameter; E, nonshared environmental parameter; ADHD, attention-deficit/hyperactivity disorder.
[a]All models were adjusted for sex and birth year.
[b]*p* Value was calculated for testing the significant loss in fit when one or more parameters were dropped from the full model.
[c]The model including additive genetic, dominant genetic, shared, and nonshared environmental parameters (ADCE model) was chosen as the full model.
[d]The best fitting model was the model including only additive genetic and nonshared environmental parameters (AE model).

does not, however, automatically rule out shared environmental influence on the familial aggregation of ADHD. Indeed, our finding that the familial aggregation was significantly higher in maternal half-siblings than in paternal half-siblings suggests that part of the familial aggregation was due to shared environmental influence. This is because the two types of half-siblings are equivalent in their genetic sharing, but maternal half-siblings tend to share more environmental factors related to pregnancy, including intrauterine environment and perinatal conditions (Grønborg, Schendel, & Parner, 2013). Furthermore, children in Sweden were more likely to live with their mothers after parental separation during the study period (Statistics Sweden, 1994). The contribution of shared environmental influence relative to genetic and nonshared environmental influences on the variance in ADHD has been inconclusive (Burt, 2009; Wood et al., 2010), possibly owing to the lack of adequately powered sample (Wood et al., 2010) and the potential underestimation of shared environmental influence in classical twin studies, where dominant genetic and shared environmental components cannot be estimated in the same model (Wood et al., 2010). Our quantitative genetic analyses based on a sample of 1,029,423 sibling pairs enabled simultaneous estimation of dominant genetic and shared environmental influences on the variance in the liability to ADHD. While genetic factors (additive and dominant) accounted for over 80% of the variance, the ADCE model suggested that 6% of the variance was attributable to shared environmental factors. Dropping only the C parameter resulted in a significant loss in fit. Although the AE model was selected as the best fitting model among the four models, this does not mean that shared environmental factors exert no influence on the etiology of ADHD. Taken together, a very small yet potentially important shared environmental influence on ADHD can be expected.

Consistent with prior research (Faraone & Mick, 2010; Rucklidge, 2010), more males than females were diagnosed with ADHD during the follow-up, with the male to female ratio being 3.7:1. The sex difference in the prevalence of ADHD has been hypothesized to reflect a protective effect by the female sex. Under the hypothesis, stronger genetic load would be required for females to surpass the liability threshold for receiving an ADHD diagnosis (Hamshere et al., 2013). Consequently, more relatives of female patients would be diagnosed with ADHD than relatives of male patients. Our findings, however, provided little evidence for such female protective effect, given that the HRs did not differ significantly by index person's sex when the analyses were restricted to siblings of the same sex. One possible explanation for the lower prevalence of ADHD in females could be that due to higher rate of inattentiveness and lower rate of comorbid conduct disorder in females with ADHD, they attract less attention from caregivers and teachers, resulting in less frequent referral for treatment compared to males with ADHD (Biederman et al., 2002).

The relative risk for ADHD in full siblings of index persons with an ADHD diagnosis at age 18 or older (HR = 11.49) was more than double of that in full siblings of index persons with an ADHD diagnosis only before age 18 (HR = 4.68). In line with prior studies (Biederman et al., 1995; Faraone, 2004), the finding suggests that compared with remission of ADHD prior to adulthood, persistence of ADHD into adulthood indexes stronger familial aggregation, possibly due to a strong load of both genetic stability and innovation in adult ADHD (Chang et al., 2013; Pingault et al., 2015).

Analyses stratified on birth year showed a higher HR in younger cohort, indicating a secular trend associated with increased awareness of ADHD during recent years, especially among individuals who had family members with ADHD. Recent large-scale familial coaggregation studies have revealed substantive etiological overlaps between ADHD and other psychiatric comorbid conditions, including substance use disorder (Skoglund, Chen, Franck, Lichtenstein, & Larsson, 2015), suicidal behavior (Ljung, Chen, Lichtenstein, & Larsson, 2014), bipolar disorder, and schizophrenia (Larsson et al., 2013). In the present study, parental psychiatric history appeared to account for part of the

familial aggregation. These findings point to a common etiologic component shared by multiple psychiatric conditions (Pettersson, Anckarsater, Gillberg, & Lichtenstein, 2013).

This study has several strengths. By using a nation-wide representative family sample with prospective follow-up, the study may avoid many biases due to selection. The use of Swedish Multi-Generation Register enabled a comprehensive assessment of the strength and pattern of the familial aggregation in multiple types of relatives and quantitative genetic analysis in an extended sibling sample. This is an important strength, given that most of the previous genetic epidemiological studies of ADHD have been predominantly based on twins. Unlike ADHD traits assessed in cross-sectional surveys, where ADHD symptoms might derive from other physiological and psychiatric conditions, ADHD diagnoses assigned by trained clinicians and psychologists from a developmental perspective to a large extent minimized the risk of false positives.

Certain limitations could not be avoided in this study, as in many other register-based studies. First, the lifetime prevalence of ADHD in this study (1.9%) was lower than that reported in other countries. This was mainly due to incomplete follow-up for later-born individuals. Accordingly, we conducted time-to-event analyses to avoid bias arising from differences in follow-up time for different individuals. Second, since recent research has suggested the existence of adult ADHD even in the absence of childhood symptoms (Moffitt et al., 2015), it would be of considerable interest to examine whether the increased familial risk indexed by the presence of persistent ADHD was related to childhood or adulthood onset ADHD. Unfortunately, the data did not allow us to make a distinction between the two suggested types of the disorder; although it should be noted that childhood onset was a required criterion for clinical diagnosis of ADHD in adults (American Psychiatric Association, 2013, Verkuijl, Perkins, & Fazel, 2015). Third, paternity tests for excluding paternal discrepancy were not available in the current study. In the presence of paternal discrepancy (i.e., an individual's father is not the biological father), the assumed paternal half-siblings are genetically equivalent to unrelated individuals, which might in part account for the lower HR in paternal half-siblings than in maternal half-siblings.

Conclusions

The familial aggregation of ADHD increased with increasing genetic relatedness. While genetic liability serves as an explanation for the pattern of the familial aggregation, the results to some extent supports the role of shared environmental factors in the familial aggregation. Despite difference in the baseline rate of ADHD by sex, no reliable evidence supports differences in the etiology of ADHD between males and females. Close family members of individuals with persistent ADHD represent an important target group for diagnostic screening.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Familial aggregation of ADHD among full siblings after adjustment for birth year and other covariates.

Table S2. Familial aggregation of ADHD by data source from which ADHD status was ascertained.

Table S3. Familial aggregation of ADHD among relative pairs born 1992–2000.

Acknowledgements

The study was funded by the Swedish Research Council (2014-3831) and the Swedish Initiative for Research on Microdata in the Social and Medical Sciences (SIMSAM) framework (340-2013-5867). Dr. Larsson has served as a speaker for Eli-Lilly and has received a research grant from Shire; both outside the submitted work. The other authors declare that they have no competing or potential conflicts of interest.

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Key points

- Attention-deficit/hyperactivity disorder (ADHD) aggregates in families and the familial aggregation of ADHD increases with increasing genetic relatedness between family members.
- The familial aggregation of ADHD is significantly higher in maternal half-siblings than in paternal half-siblings, suggesting that part of the familial aggregation is due to shared environmental factors.
- Despite differences in the rate of ADHD diagnosis, the etiology of ADHD appears to be similar between males and females.
- Close family members of individuals with persistent ADHD represent an important target group for diagnostic screening.

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Accepted for publication: 24 June 2016