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The heritability of clinically diagnosed Attention-Deficit/ Hyperactivity Disorder across the life span

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Abstract

Background—No prior twin study has explored the heritability of clinically diagnosed ADHD. Such studies are needed to resolve conflicting results regarding the importance of genetic effects for ADHD in adults. We aimed to estimate the relative contribution of genetic and environmental influences for clinically diagnosed ADHD across the life span with a specific focus on ADHD in adults.

Method—Information about zygosity and sex was obtained from 59,514 twins born between 1959 and 2001 included in the nation-wide population-based Swedish Twin Register. Clinical data of ADHD diagnosis was obtained from the Prescribed Drug (i.e., stimulant or non-stimulant medication for ADHD) and National Patient Registers (i.e., ICD-10 diagnosis of ADHD). Twin methods were applied to clinical data of ADHD diagnosis using structural equation modeling with monozygotic and dizygotic twins.

Results—The best-fitting model revealed a high heritability of ADHD (0.88; 95% CI, 0.83–0.92) for the entire sample. Shared environmental effects, on the other hand, were non-significant and of minimal importance. The heritability of ADHD in adults was also substantial (0.72; 95% CI, 0.56–0.84).

Conclusion—This study showed that the heritability of clinically diagnosed ADHD is high across the life span. Our finding of high heritability for clinically diagnosed ADHD in adults indicate that the previous reports of low heritability is best explained by rater effects and that gene-identification studies of ADHD in adults needs to consider pervasiveness (e.g., multiple raters) and developmentally (e.g., childhood onset criteria) informative data.

Keywords

ADHD; Twin study; heritability; Adults

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INTRODUCTION

Many twin studies have explored the heritable nature of Attention-Deficit Hyperactivity Disorder (ADHD), but none of these have been based on clinically diagnosed cases. Such a study is needed to clarify how genetic factors influence ADHD across different levels of severity, (Larsson et al 2012) and to resolve inconsistent results regarding the heritability of ADHD in adults (Franke et al., 2012).

Twin studies using parent or teacher ratings indicate that continuous measure of ADHD is highly heritable (~60–90) (Burt, 2009, Nikolas and Burt, 2010, Faraone et al., 2005). The few available twin studies using categorical measures of ADHD (see Table 1) suggest equally high heritability estimates (Lichtenstein et al., 2010, Sherman et al., 1997, Thapar et al., 2000, Larsson et al., 2011), but these studies suffer from limitations. In particular, they applied broad categories that contain milder cases which would not meet syndromal criteria for ADHD, and all studies lacked information on the age of onset or impairment criteria used in the DSM and ICD diagnostic definition. Thus, more stringent diagnostic methods and narrow definitions may generate different heritability estimates.

Twin studies suggest substantially lower heritability estimates (~30–40%) for ADHD in adults (Boomsma et al., 2010, Larsson et al., 2013a, Reiersen et al., 2008, van den Berg et al., 2006), but it has been difficult to resolve if the drop in heritability reflect true developmental changes or relate to rater effects (Franke et al., 2012). This is because twin studies on ADHD in adults have used self-ratings, while studies on children have used other informants (i.e., parent and teacher ratings). The few studies on this topic suggest that the heritability of self-rated ADHD is low in both adults and adolescents (Kan et al., 2013, Merwood et al., 2013), and that the heritability of ADHD in adults is substantial when both self and parent ratings are combined into a composite index of ADHD (Chang et al., 2013). Together, these findings suggest that the low heritability for ADHD in adults may be best explained by rater effects. Nevertheless, more rigorously characterized twin samples are desired, including clinically stringent measures of ADHD, to more firmly establish the heritability of ADHD in adults.

In the present report we use data from 59,514 twins born between 1959 and 2001 included in the Swedish Twin Register (Lichtenstein et al., 2006). Clinical data on ADHD from Swedish national registers was obtained. We aimed to estimate the relative contribution of genetic, shared environmental and non-shared environmental influences for clinically diagnosed ADHD across the life-span with a specific focus on ADHD in adults. Based on previously observed similarities between continuous trait measures and broad categorical definitions, we predicted similar heritability estimates for clinically diagnosed ADHD. Based on the recent cross-informant twin studies (Chang et al., 2013), we predicted high heritability also for ADHD in adults. This is because both cross-informant measures and clinical diagnosis focus on pervasive symptoms.

METHODS

SWEDISH TWIN REGISTER

We obtained the data from the nationwide population-based Swedish Twin Register (Lichtenstein et al., 2006). The target population in this study were all twins born in Sweden between 1959 and 2001 (N=89,174). Excluded from the analyses were twin pairs with unknown zygosity (N=21,714), twin pairs in which one or both died (N=3,250) or emigrated (N=4,696) before the start of follow-up in 2001; thus, the final sample of 59,514 twins (29,177 male twins, 49%) represented 67% of the targeted population. Twin analyses on ADHD in adults was based on a sub-sample of 37,714 twins (18,092 male twins, 48%) born 1959–1991.

Zygosity was established using DNA testing or standard zygosity questionnaires concerning twin similarity and confusion (Lichtenstein et al., 2006). When zygosity was determined based on questionnaire data, only twins with more than 95% probability of being correctly classified were assigned a zygosity. In the twin analyses, 17,026 were monozygotic (MZ), 16,554 were dizygotic (DZ), and 25,934 were opposite sex DZ twins.

NATIONAL REGISTERS

Data from the Swedish Twin Register was linked to the population based Prescribed Drug and Patient Registers, using each individual's unique personal identification number.

The Swedish Prescribed Drug Register (PDR) is a national healthcare register (administered by the National Board of Health and Welfare) with data on dispensed pharmaceuticals. Information regarding drug identity according to the Anatomical Therapeutic Chemical classification system, quantity and dosage of the prescribed drug, and date of prescription has been registered since July 2005. The register covers the entire population of Sweden, and the identity of the patients is available for > 99.7% of the population (Wettermark et al., 2007).

The Patient Register (held by the National Board of Health and Welfare) has nationwide coverage for psychiatric outpatient care since 2001. Every record has a discharge date, a primary discharge diagnosis, and up to seven secondary diagnoses assigned by the treating medical doctor according to WHO's International Classification of Diseases (ICD-10) (WHO, 1992).

VARIABLES

Twins treated with stimulant or non-stimulant medication for ADHD (methylphenidate [N06BA04]; atomoxetin [N06BA09]; amphetamine [N06BA01]; dexamphetamine [N06BA02]) at any time between July 2005 and July 2010 were identified via PDR. National guidelines for medication of ADHD, issued by the National Board of Health and Welfare in 2002, stated that medication should be reserved for cases where other supportive interventions have failed, indicating that pharmacological ADHD treatment most likely represents an indicator of the more severe cases of ADHD. The authority to prescribe ADHD drugs in Sweden is restricted to specialist physicians familiar with the treatment of

this disorder. In the total sample of 59,514 twins, 730 (1.23%) were treated for ADHD/hyperkinetic disorder at any time between 2005 and 2010.

Twins obtaining a diagnosis of hyperkinetic disorder between 2001 and 2009 were identified via the Patient Register (ICD-10: F90). In the total sample of 59,514 twins, 525 (0.88%) had received a diagnosis of hyperkinetic disorder from outpatient care. A substantial number of these twins (n=392, 74.7%) were treated with stimulant or non-stimulant medication at any time between 2005 and 2010.

To maximize power in the twin model fitting analyses, the present study applied an "or" approach to define clinically diagnosed ADHD resulting in 863 twins (1.45%) who either meet criteria for hyperkinetic disorder at any time between 2001 and 2009 or received stimulant or non-stimulant treatment at any time between 2005 and 2010. We have recently reported high specificity for this register-based definition of ADHD (Larsson et al., 2013b).

Twin model fitting on ADHD in adults was based on the sub-sample of 37,714 twins born between 1959 and 1991 (i.e., 18 years old or older at the end of follow-up) resulting in 241 (0.64%) twins with a clinical diagnosis of ADHD in adults; our definition only considered twins diagnosed with ADHD at the age of 18 years or older.

The study was approved by the research ethics committee at Karolinska Institutet, Stockholm, Sweden.

STATISTICAL ANALYSES

The concordance rate (i.e., the risk of ADHD for the cotwin of a twin with ADHD) was calculated as the proportion of individuals belonging to concordantly affected twin pairs out of all twins with the disorder. Correlation of liability (tetrachoric within-twin pair correlation) was also estimated for each sex-zygosity group. Higher concordance rates and correlations of liability in MZ than in DZ twins indicate a genetic contribution to the manifestation of disease. Shared environmental influences were inferred if the DZ correlation was greater than half of the MZ correlation (the DZ correlation higher than expected from sharing 50% of their segregating genes).

Biometric twin analyses were conducted on raw ordinal data using the Mx program (Neale, 2003) to determine the relative contribution of additive genetic factors (A, Heritability) reflecting additive effects of different alleles, shared environmental factors (C) reflecting environmental influences that make twin siblings similar to each other and non-shared environmental factors (E) reflecting non-genetic influences that make twin pairs dissimilar (Rijsdijk and Sham, 2002). In twin models based on ordinal raw data, each individual is coded as having the disease or not, and the threshold (*z* score) corresponds to the rate of the disease.

The following combinations of variance components were considered in the twin models: ACE and AE. Three sex-limitation models were fitted to the data. The full sex-limitation model allows quantitative and qualitative differences in the parameter estimates between males and females. The common effects sex-limitation model allows quantitative sex

differences between males and females, but no qualitative differences. The null model equates all genetic and environmental parameter estimates for males and females, testing the hypothesis that there are no sex differences. Goodness of fit for the different twin models was assessed by Akaike's Information Criterion (AIC); a lower AIC value indicates better fit of the model to the observed data.

The quantitative genetic models were performed under the usual assumptions of the classical twin designs: random mating, no gene–environment interaction, and equal environments of MZ and DZ twin pairs (Rijsdijk and Sham, 2002).

RESULTS

Concordance rates and tetrachoric correlations for the full sample (59,514 twins born 1959–2001) are shown in Table 2. Tetrachoric DZ correlations were half of the MZ correlations, suggesting genetic, but not shared environmental influences on ADHD. MZ correlations were less than 1, suggesting non-shared environmental influences (including measurement error). Tetrachoric twin correlations were similar for males and females, which suggest no quantitative sex-differences in the genetic and environmental contribution. In addition, twin correlations were similar for same-sexed DZ and opposite-sex DZ twins (DZOS), which suggest no qualitative sex-differences (Table 2).

Table 3 displays the age-adjusted model fitting results of ACE and AE sex-limitation models compared to the saturated model using the full twin sample (59,514 twins born 1959–2001). In all these models, thresholds were equated across twin 1 and twin 2, for MZ and DZ twins, but not across males (*z* score, 1.46) and females (*z* score, 2.06). As can be seen, the AE null model had the lowest AIC value (Table 3). That is, a model that constrained the genetic and environmental parameter estimates to be equal across sex, and excluded variance in liability due to the shared environmental factor provided the most parsimonious fit of the data. This best-fitting model estimated the heritability and non-shared environment contribution as 0.88 (95% confidence interval [CI], 0.83–0.92) and 0.12 (95% CI, 0.08–0.17), respectively.

Similar results were obtained when refitting all twin models using an "AND" approach (i.e., clinically diagnosed ADHD defined as meeting criteria for hyperkinetic disorder and received stimulant/non-stimulant treatment). The best fitting model (AE null model) estimated the heritability and non-shared environment contribution as 0.89 (95% CI, 0.82–0.94) and 0.11 (95% CI, 0.06–0.18), respectively. Similar genetic and environmental parameter estimates were also obtained when the twin modeling were restricted to either ADHD cases identified through ICD diagnoses (A=0.89; 95% CI, 0.83–0.93; E=0.11; 95% CI, 0.07–0.17) or pharmacological ADHD treatments (A=0.88; 95% CI, 0.83–0.92; E=0.12; 95% CI, 0.08–0.17), providing converging evidence across different outcome definitions Table 3.

Heritability of ADHD in adults

Analyses were also conducted on twins born between 1959 and 1991 (N=37,714 twins) to estimate the heritability of ADHD in adults. These twins were on average 23.0 years old at the start of the register follow-up. Importantly, we only considered twins diagnosed with

ADHD at the age of 18 years or older. The best fitting model (AE null model) estimated the heritability and non-shared environment contribution as 0.72 (95% CI, 0.56–0.84) and 0.28 (95% CI, 0.16–0.44), respectively.

DISCUSSION

This study showed that the heritability of clinically diagnosed ADHD is high across the life span. The finding of high heritability for clinically diagnosed ADHD in adults indicate that the previous reports of low heritability is best explained by rater effects and that gene-identification studies of ADHD in adults should not rely on self-ratings only.

In this study, using data from representative national registers, we estimated the heritability of clinically diagnosed ADHD at 88%. Our result is in line with the large number of twin studies using continuous trait measures of ADHD based on parent or teacher ratings (Burt, 2009, Faraone et al., 2005), and the few studies that have explored the genetic impact on categorically defined ADHD (Lichtenstein et al., 2010, Sherman et al., 1997, Thapar et al., 2000, Larsson et al., 2011). There are noteworthy differences between the present study and these prior twin studies, in particular related to differing assessment methodologies. In the present study subjects were diagnosed with ICD-10. These diagnoses are performed by clinicians, and thus based on structured interviews covering age of onset of the impairing symptoms and presence of impairment in multiple settings, while prior twin studies were based on quantitative measures of ADHD symptoms without addressing the childhood criteria and not systematically assessing the impairment in multiple settings criteria. Yet, remarkably similar heritability estimates for ADHD were obtained across studies suggesting strong genetic effects in ADHD regardless of whether it is assessed using continuous trait measures, broad categorical definitions or narrow diagnostic definitions, which in turn provides further support for ADHD as a quantitative extreme of genetic and environmental factors operating dimensionally throughout the distribution of ADHD symptoms (Chen et al., 2008, Larsson et al., 2012, Levy et al., 1997).

One novel finding of this study was that clinically diagnosed ADHD in adults was highly heritable. The finding is in line with a recent cross-informant twin study reporting that the heritability of ADHD in 19–20 year olds was 78%, when both self and parent ratings were combined into a composite index of ADHD symptoms to adjust for rater bias (Chang et al., 2013) and also with prior family studies suggesting a high familial loading on ADHD in adults (Biederman et al., 1996, Biederman et al., 1995, Faraone et al., 2000, Faraone, 2004), but is inconsistent with what has been reported in twin studies of self-rated ADHD in adults (Reiersen et al., 2008, Boomsma et al., 2010, van den Berg et al., 2006, Larsson et al., 2013a). One increasingly recognized explanation to previous reports of low heritability for ADHD in adults is increased contribution of measurement error (reflecting accuracy of the measures) associated with the use of self-ratings (Kan et al., 2013, Franke et al., 2012, Merwood et al., 2013, Chang et al., 2013). Another explanation is that the clinical diagnosis of ADHD in adults reflects persistence of the childhood disorder (i.e., childhood onset), whereas cross-sectional self-ratings may also reflect adult-onset ADHD-like symptoms (i.e., phenocopies) involving different genetic and environmental processes. Taken together, this indicates that self-ratings may not be the best measure to use in gene-identification studies

of ADHD in adults and that other factors such as childhood onset, pervasiveness and impairment should be taken into account.

Limitations

This study had some limitations. First, it was not possible to classify ADHD cases according to the three DSM-IV ADHD subtypes (i.e., combined, primarily hyperactive-impulsive and primarily inattentive type), since these were not recorded across the registers. However, prior twin research suggests similar heritability estimates for the inattentive and hyperactive-impulsive component of ADHD (Nikolas and Burt, 2010, Larsson et al., 2006).

Second, the validity of the non-standardized register diagnoses has not been explored using comparisons with research diagnoses based on independent semi-structured interviews and/or medical records. Even though our own validity checks of ADHD support high specificity for the register-based diagnosis, we could not rule out false negatives (i.e., individuals with ADHD who had never been recorded in any registers). This is because the Patient Register provided coverage of outpatient care after 2001 and the Swedish Prescribed Drug Register provided data on twins treated with stimulant or non-stimulant medication after 2005. However, bias due to such outcome miss-classification most probably applies equally to MZ and DZ pairs and would therefore not introduce a significant upward bias of the heritability estimate.

Third, the ascertainment of ADHD cases was predominantly based on ICD-10 diagnosis of hyperkinetic disorder and prescribed medication unique for the treatment of ADHD. The ICD-10 definition of ADHD is stricter compared with that in DSM-IV, and the Swedish National guidelines for medication of ADHD stated that medication should be reserved for cases where other supportive interventions have failed, indicating that our measure most likely represent an indicator of the more severe cases of ADHD. Thus, generalizations should be made with caution.

Fourth, even with a nationwide twin cohort born 1959–2001 the absolute numbers of clinically diagnosed concordant or discordant twin pairs remained limited, resulting in wide confidence intervals and limited power to detect shared environmental influences. Point estimates, especially for ADHD in adults, should therefore be interpreted with caution.

Conclusions

We have demonstrated that heritability estimates for clinically diagnosed ADHD is high across the life span. This indicates that the previous reports of low heritability for ADHD symptoms in adults are best explained by rater effects giving rise to measurement error, rather than by distinct developmental changes in the importance of non-shared environmental factors.

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Table 1

Twin studies exploring the heritability using categorical measures of ADHD.

Authors	Twin sample	Measure	Informant	% meeting cut-off criteria for ADHD	Heritability
Larsson et al 2011	Population: children/adolescents; 1,450 twin pairs; aged 8–17 years; Swedish	Longitudinal DSM-IV ADHD symptoms	Parents	**i.** High trajectory of Hyperactivity **ii.** High trajectory of inattention	**i.** 80% **ii.** 72%
Lichtenstein et al 2010	Population: 10,895 twin pairs; aged 12 years; Swedish	DSM-IV ADHD symptoms	Parents	1.8%	79%
Sherman et al 1997	Population: 288 twin pairs; aged 11–12 years; USA	DSM-III-R ADHD symptoms	Teachers and parents, combined	18%	79%
Thapar et al 2000	Population: 2,082 twin pairs; aged 11–12 years; UK	DSM-IV ADHD symptoms	Teachers and parents, combined	-	80%

Table 2

Concordance rates and tetrachoric correlations with 95% confidence intervals (95% CI) for clinical diagnosis of ADHD in 59,514 Swedish twins, by Sex and Zygosity

					Opposite-sex twins	
	MZM	**DZM**	**MZF**	**DZF**	**Case=Male**	**Case=Female**
Clinical diagnosis of ADHD						
No. of concordant affected pairs	35	13	11	5	29	29
No. discordant pairs	55	139	38	68	277	100
Concordance rates (95% CI)	0.56 (0.45–0.66)	0.16 (0.09–0.25)	0.37 (0.21–0.54)	0.13 (0.04–0.26)	0.17 (0.12–0.24)	0.37 (0.27–0.47)
Tetrachoric correlations (95% CI)	0.90 (0.84–0.94)	0.48 (0.33–0.61)	0.81 (0.68–0.90)	0.50 (0.28–0.67)	0.49 (0.40–0.58)	

MZM, monozygotic male; MZF, monozygotic female; DZM, dizygotic male; DZF, dizygotic female.

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Table 3

Model fitting results of univariate analysis of ADHD.

	Fit of model compared to saturated model				
Model	**-2LL**	**df**	**χ^2**	**Δdf**	**AIC**
Saturated model	8092.5	59489	-	-	-
1. ACE Univariate					
Full sex-limitation model[a]	8112.0	59505	19.5	16	−12.5
Common effects sex-limitation model [b]	8112.0	59506	19.5	17	−14.5
Null model[c]	8113.5	59509	21.0	20	−19.0
2. AE Univariate					
Full sex-limitation model[a]	8112.5	59507	20.0	18	−16.0
Common effects sex-limitation model [b]	8112.5	59508	20.0	19	−18.0
Null model[c]	**8113.7**	**59510**	**21.3**	**21**	**−20.7**

Best-fitting model indicated in bold. -2LL, likelihood fit statistic; df, degrees of freedom; χ^2, the difference in -2LL between the saturated and restricted model; Δdf, difference in df between the saturated and restricted model; AIC, Akaike's Information Criterion;

[a]The full sex-limitation model allows quantitative and qualitative differences in the parameter estimates between males and females;

[b]The common effects sex-limitation model allows quantitative sex differences between males and females, but no qualitative differences;

[c]The null model equates all genetic and environmental parameter estimates for males and females, testing the hypothesis that there are no sex differences