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Genetic and Environmental Contributions to the Association Between Attention Deficit Hyperactivity Disorder and Alcohol Dependence in Adulthood: A Large Population-Based Twin Study

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Previous research indicates that attention deficit hyperactivity disorder (ADHD) frequently co-occurs with alcohol dependence; however, the extent to which shared genetic risk factors underpin this association remains unclear. The aim of this study is to investigate the relative importance of genetic, shared, and nonshared environmental factors for the overlap between ADHD and alcohol dependence in adults. Almost 18,000 adult twins aged 20–45 years, from more than 12,000 twin pairs (5,420 complete pairs), from the population-representative Swedish Twin Registry, were included. Self-ratings were used to assess symptoms of ADHD and alcohol dependence. Twin analysis was used to determine the role of additive genetic (A), shared (C), and nonshared environmental (E) factors. As a result, we found a significant association between ADHD and alcohol dependence (odds ratio 3.58; 95% confidence interval, 2.85–4.49). Twin analysis suggested that shared genetic risk factors explained 64% of the overlap between ADHD and alcohol dependence. Nonshared environmental factors accounted for the remaining 36%, whereas the contribution of shared environmental factors was minimal. We found no support for statistically significant sex differences in the overlap between ADHD and alcohol dependence. In conclusion the overlap between ADHD and alcohol dependence in adulthood was largely explained by shared genetic risk factors. This is an important step toward understanding the underlying nature of the risk of alcohol dependence in patients with ADHD and suggests that individuals with ADHD and their family members are important targets for alcohol prevention and treatment.

Key words: attention deficit hyperactivity disorder; ADHD; alcohol dependence; twin study; genetics; environment

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD), characterized by persistent and impairing symptoms of inattention, hyperactivity, and impulsivity, is highly comorbid with other psychiatric disorders, such as depression, anxiety, and substance-related disorder [Kessler et al., 2006].

Several studies have demonstrated an increased risk for alcohol use disorder in both teenagers [Molina et al., 2007] and adults with ADHD [Schubiner et al., 2000; Faraone et al., 2007; van Emmerik-van Oortmerssen et al., 2012]. Individuals with both ADHD and alcohol use disorder are at risk for other psychiatric comorbidities, such as mood and anxiety disorders, conduct disorder, antisocial personality disorder [Wilens et al., 2005], as well as poor outcome and poor quality of life. Alcohol dependence, the most serious form

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of alcohol use disorder according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) (American Psychiatric Association, 2000), which leads to substantial impairment, low quality of life, and shorter life expectancy, is increased in individuals with ADHD [Friedrichs et al., 2012; Ameringer and Leventhal, 2013]. Conversely, in a study on 152 patients with alcohol dependence, 23% showed evidence of ADHD [Ohlmeier et al., 2008]. Although there is ample evidence for a genetic contribution (i.e., heritability) to both ADHD [Faraone et al., 2005; Larsson et al., 2013b] and alcohol dependence [Hopfer et al., 2003; Agrawal and Lynskey, 2008], less is known about the genetic and environmental contribution to the overlap between the two phenotypes.

Previous family and twin studies have generated conflicting results regarding the etiologic overlap between ADHD and alcohol dependence. A family study on young adolescents with ADHD and their first-degree relatives [Biederman et al., 2008] suggested independent familial transmission of ADHD and alcohol dependence. In contrast, a recent longitudinal twin study found that the association between hyperactive/impulsive symptoms in childhood ADHD and substance use in adolescence was largely due to shared genetic risk factors [Chang et al., 2011]. Similarly, a study on 1,775 male twins reported shared genetic risk factors for hyperactivity (not inattention) in adolescence, assessed with retrospective self-report and alcohol dependence in adulthood [Edwards and Kendler, 2012].

Most of the previous family and twins studies have focused on the overlap between ADHD and alcohol use problems in adolescence. The only previous twin study on adults reported a statistically significant genetic overlap between ADHD and problem drinking [Derks et al., 2014], which suggests that shared genetic risk factors are also important in adulthood. This study found no evidence for sex differences in the genetic and environmental contribution to the overlap between ADHD and alcohol-related problems. The results of this previous study need to be replicated and further studies are necessary to explore whether a similar pattern of results emerges for more serious aspects of problem drinking, such as alcohol dependence.

The aim of this study is to investigate the relative importance of genetic, shared environmental, and nonshared environmental factors in the overlap between adult ADHD and alcohol dependence using twin analysis and to elucidate possible sex differences in the role of these factors.

MATERIALS AND METHODS

Sample

This study is based on data collected in the STAGE (Study of Twin Adults: Genes and Environment) [Lichtenstein et al., 2006] from the population-representative Swedish Twin Registry. The project has been reviewed and approved by the regional ethics committee of the Karolinska Institutet. A target population of 42,582 twins born in Sweden between 1959 and 1985 was invited to participate in the STAGE data collection conducted in 2005. Participants were given a personal login to the study's Website, containing a questionnaire with 1,300 questions [Furberg et al., 2008]. Nonresponders were approached with up to three reminders and offered the choice of a telephone interview with a trained interviewer using a computer-based data collection method supplemented with a self-administered paper questionnaire, instead of the Web questionnaire. A total of 25,321 (59.5%) twins participated, of whom 18,167 (72%) provided information about ADHD symptoms; 7,281 (40.1%) were male, mean age was 34.0 years (standard deviation [SD], 7.6 years; range, 19–47 years), and 10,886 (59.9%) were female, mean age was 33.6 years (SD, 7.6 years; range, 19–47 years). All participants provided informed consent.

Zygosity was established using standard physical similarity questions that had previously been validated through genotyping. A subsample of 200 twin pairs also provided DNA to determine zygosity [Lichtenstein et al., 2006]. It was not possible to assign zygosity with certainty to 456 individuals, resulting in a sample of 17,711 twins with known zygosity; 2,667 were monozygotic male (MZ), 2,209 were dizygotic (DZ) male, 4,223 were MZ female, 3,153 were DZ female, and 5,459 were DZ opposite-sex twins. All 17,711 individuals, 12,291 twin pairs, of which 5,420 were complete pairs, were included in the analyses.

ADHD Symptoms

ADHD symptoms were assessed using the 18 symptom criteria (nine inattentive and nine hyperactive-impulsive items) in DSM-IV (American Psychiatric Association, 2000), with a 3-point answer format (0 = no; 1 = yes, to some extent; and 2 = yes). In the twin analysis, symptoms were summed up to create a total score for ADHD symptoms [Larsson et al., 2013a].

For descriptive purposes, DSM-IV ADHD subtypes were defined using a cut-off at 2.0SD above the mean (i.e., above the 98th percentile) on the symptom count scales of inattention and hyperactivity-impulsivity, according to a method suggested by Barkley and coworkers [Barkley et al., 2002; Friedrichs et al., 2012]. Specifically, the norm-based primarily inattentive subtype (IN) was set at 2SD above the mean on the inattention scale, but below 2SD above the mean on the hyperactive-impulsive scale. The corresponding criterion for the primarily hyperactive-impulsive subtype (HI) was 2SD above the mean on the hyperactive-impulsive scale but not on the inattentive scale. The combined subtype (CO) was set if 2SD above the mean was reached for both scales. ADHD any was defined if any of the above (IN, HI, or CO) was positive.

Alcohol Dependence

Questions regarding alcohol use disorder were based on SCID I (Structured Clinical Interview for DSM-IV) (First et al., 1996) with response alternatives: yes, no, don't know/don't wish to answer. Alcohol dependence was set when at least three of seven criteria from DSM-IV (American Psychiatric Association, 2000) were positive: (i) development of tolerance, such as an increased amount of the substance necessary for the same effect; (ii) symptoms of withdrawal or avoidance of withdrawal symptoms by means of continued substance use; (iii) substance consumption for a longer time or higher amounts than intended; (iv) persistent desire to control substance use; (v) great amount of time spent on obtaining

the desired substance; (vi) decrease in social activity due to the substance use; and (vii) continued use of the substance despite proven negative effects.

Each criterion was defined by several questions and was set as positive if the answer to at least one of the questions was yes. For example, the criterion tolerance (i) was approached by: "During this period, did you notice you needed to drink more to get the same effect?" and "Did you notice being less affected by the same amount of alcohol during this period?".

Statistical Analysis

Descriptive statistics were used to characterize the study population (Table I). Prevalence odds ratios (OR) and 95% confidence intervals (CI), as measures of phenotypic association between ADHD and alcohol dependence, were obtained from age-, sex-, and socioeconomic status-adjusted mixed effect logistic regression, accounting for the random effect of twins, using Stata 11.2 (StataCorp LP, College Station, TX). We used the "lincom" command in Stata to analyze difference between HI, IN, and CO subtypes and alcohol dependence.

The twin method was used to investigate the relative importance of genetic and environmental factors. The twin method relies on the different within-pair similarities between genetically identical MZ twin pairs who share 100% of their genes and DZ, i.e., fraternal, twin pairs, who share an average 50% of their segregating alleles. This information is used to decompose the variance of a phenotype, as well as the covariance between phenotypes, into additive genetic (A), shared environmental (C), and nonshared environmental (E) factors (ACE-model, Neale and Cardon, 1992).

Twin correlations assessing twin similarity for a trait allowed for an initial examination of the relative contributions of A, C, and E. In general, MZ correlations higher than DZ correlations indicate A. DZ correlations higher than half the MZ correlations suggest C. The extent to which MZ correlations are less than 1 suggests E. Cross-twin cross-trait correlations (CTCT), namely the correlation between twin 1's status on trait 1 and the co-twin's status on trait 2, were used for an initial examination of the relative contributions of A, C, and E to the overlap between ADHD and alcohol dependence.

To assess appropriateness of the data for ACE twin analyses, we performed a series of tests whereby we fitted a saturated model (means and covariance matrices were assumed to be different for MZ female, MZ male, DZ female, DZ male, DZ female-male, and DZ male-female pairs) and then constrained the mean, regression, and (co) variance parameters to be equal across groups to test the assumptions needed for the ACE twin analyses. This initial assessment of the data revealed that (i) adjustment for age could be done linearly (a quadratic effect was nonsignificant), but that regression coefficients differed between males and females and between same-sex and opposite-sex twin pairs; (ii) means and prevalence could be assumed to be the same within gender in same-sex pairs but different in opposite-sex pairs; (iii) covariances within individuals could be assumed to be the same for all zygosity types and genders; and (iv) covariances across twins in a pair could be assumed to be the same across gender, for same-sex MZ and DZ pairs, but opposite-sex DZ pairs were borderline significantly different compared with same-sex DZ pairs ($P = 0.049$). This assessment proved that the data were suitable for ACE twin modeling, and revealed that sex differences could potentially be present. In subsequent models, we allowed for these mean/prevalence differences.

We used structural equation modeling to perform maximum likelihood model-fitting analyses with raw data using OpenMx [Boker et al., 2011]. This method allows the inclusion of individuals in the analysis, where information from only one twin in a pair is available. A bivariate correlated factors model was used to estimate the additive genetic (r_A), shared (r_C), and nonshared (r_E) environmental correlations between ADHD and alcohol dependence. These statistics vary from -1.0 to $+1.0$ and indicate the extent to which genetic and environmental influences on one measure overlap with those on the other. We also calculated the proportion of the phenotypic overlap between ADHD and alcohol dependence explained by A, C, and E. The bivariate correlated factors model was fitted separately for males and females, as well as collapsed across sex according to the findings in the sex difference analyses.

TABLE I. Distribution of ADHD Symptoms, ADHD Subtypes (Norm-Based 2SD Method), and Alcohol Dependence in Population

	All, n (column % of total number)	Sex, n (column % of total number)		Age, n (column % of total number)		
		Male	Female	≤25 years	26–35 years	36–46 years
Total (n = 18,167)	18,167 (100.0)	7,281 (40.08)	10,886 (59.92)	3,478 (19.14)	6,566 (36.14)	8,123 (44.71)
ADHD (n = 18,167)						
ADHD any	1,598 (8.80)	637 (8.75)	961 (8.83)	376 (10.81)	608 (9.26)	614 (7.56)
Hyperactive-impulsive	578 (3.18)	229 (3.15)	349 (3.21)	125 (3.59)	211 (3.21)	242 (2.98)
Inattentive	753 (4.14)	298 (4.09)	455 (4.18)	194 (5.58)	286 (4.36)	273 (3.36)
Combined	267 (1.47)	110 (1.51)	157 (1.44)	57 (1.64)	111 (1.69)	99 (1.22)
Alcohol dependence (n = 17,734)	1,070 (6.03)	568 (8.01)	502 (4.72)	258 (7.64)	447 (6.97)	365 (4.60)

Two types of potential sex differences were considered in our analysis: (i) quantitative sex differences where the magnitude of the components of A, C, and E was assumed to be different for males and females and (ii) qualitative sex differences referring to opposite-sex twin pairs having lower correlation for the A parameters than same-sex twin pairs. Three parameters were used to model qualitative sex differences: two parameters allowing the overlap of the A parameter in opposite-sex twins to be lower than for same-sex twins for each of the traits separately, and one additional parameter allowing the overlap between traits to be lower between opposite-sex twins than same-sex twins independently of the other two parameters. These parameters were bounded between 0 and 1; a value of 1 indicates that opposite-sex twins share the A component to the same extent as same-sex twins, and a value of 0 indicates that opposite-sex twins share no A component (i.e., values significantly below 1 support qualitative sex differences).

The goodness of fit for the different twin models was assessed by a likelihood ratio χ^2 test, where submodels were compared with the full sex difference model, including both quantitative and qualitative sex differences (for a model including A, C, and E [ACE] and a model including only A and E [AE] separately). Akaikes Information Criterion (AIC) was computed ($-2 \times$ log likelihood $- 2 \times$ degrees of freedom) and used to assess the overall best-fitting model (in ACE and AE separately, as well as across all models). Lower AIC values indicate a better fit of the model to the observed data. To assess whether sex differences were present, we fitted models where the quantitative and qualitative sex differences in each trait were dropped individually and tested whether the model fitted the data worse. We further fitted models where the quantitative and qualitative sex differences in the covariation between the traits were dropped separately. In a final model (for ACE and AE separately), we chose to include the sex differences where a likelihood ratio test against the full sex differences model showed a significantly worse fit when excluded (in ACE and AE separately).

RESULTS

Descriptive statistics of the study population are shown in Table I. ADHD was observed in 1,598 participants (8.8%) and the distribution was similar in males and females ($P = 0.85$). ADHD was significantly more common in the younger age group (<25 years). Alcohol dependence was present in 1,070 participants (6.0%), with a significantly higher prevalence in men 8.01% (n = 568) compared with women 4.72% (n = 502) ($P < 0.001$).

We found a strong phenotypic association between ADHD and alcohol dependence. Individuals with ADHD had a 3.58-fold (95% CI, 2.85–4.49) increased risk for alcohol dependence ($P < 0.001$) compared with those without ADHD. The OR did not differ significantly for complete and incomplete twin pairs ($P = 0.12$). All ADHD subtypes were associated with an increased risk for alcohol dependence; for HI: OR, 2.52; 95%CI, 1.75–3.63; for IN: OR, 3.63; 95%CI, 2.69–4.91; and for CO: OR, 6.29; 95%CI, 4.01–9.87). The OR for HI and IN did not differ significantly ($P = 0.108$). However, the OR for IN and CO (P = 0.035), as well as for HI and CO, did ($P = 0.001$) differ significantly, with higher OR for the CO subtype.

All of the following analyses concern ADHD (any ADHD, not subtypes) and alcohol dependence. Twin correlations are presented in Table II. Higher MZ correlations compared with DZ correlations indicated that A was important for both ADHD and alcohol dependence. For both phenotypes, MZ correlations were lower than 1 suggesting E. Higher MZ CTCT compared with corresponding DZ correlations suggested A for the overlap between ADHD and alcohol dependence (Table II).

To further investigate the genetic and environmental influences, we first fit an ACE model including all sex differences (ACE in Table III), then models excluding the sex differences one by one (Table III). The only significantly worse-fitting model was when qualitative sex differences in ADHD were excluded (Table III; $\chi^2 = 4.48$, degrees of freedom [df] = 1, $P = 0.034$). We then fitted a model including only the qualitative sex difference in ADHD; the model did not fit the data worse than the full sex difference model (Table III; $\chi^2 = 5.67$, df = 10, $P = 0.842$). We then proceeded to fit a full sex difference AE model, which did not fit the data worse than the full sex difference ACE model (Table III; $\chi^2 = 0.82$, df = 6, $P = 0.992$), indicating that the C parameters were negligible. Sex differences were tested as for the ACE models; the only model fitting the data significantly worse than the full AE model was the one where the qualitative sex difference for ADHD was dropped (Table III; $\chi^2 = 8.58$, df = 1, $P = 0.003$). A final AE model, including only the qualitative sex difference in ADHD, did not fit the data worse than the full AE model (Table III; $\chi^2 = 4.85$, df = 7, $P = 0.678$). These results suggest that there were no sex differences present for the overlap between ADHD and alcohol dependence. The only sex difference present was a qualitative sex difference in ADHD. Furthermore, shared environmental effects were found to be negligible, and the best-fitting model according to the AIC was the AE model allowing only for qualitative sex differences in ADHD (Table III).

Estimates from the best-fitting model (Table IV) showed moderate heritability estimates for ADHD and for alcohol dependence; that is, A factors explained 41% (95%CI, 38–44) of the variation in ADHD and 57% (95%CI, 27–66%) of the variation in alcohol dependence. E factors explained the remaining 59% (95%CI, 56–62) of the variance for ADHD and 43% (95%CI 34–53) of the variance for alcohol dependence. Parameter estimates from the full ACE model and sex-stratified results are also shown for descriptive purposes.

The bivariate estimates for ADHD and alcohol dependence (e.g., r_A, r_C, and r_E) are also shown in Table IV. We observed a statistically significant genetic correlation between the two phenotypes ($r_A = 0.33$; 95%CI, 0.24–0,42) as well as a significant nonshared environmental correlation ($r_E = 0.18$; 95%CI, 0.10–0.26). A explained 64% (95%CI, 47–80) of the covariance between ADHD and alcohol dependence. E was also significant, whereas the role of C was small and not statistically significant. Parameter estimates from the ACE model for females, males, and collapsed generated a similar pattern of results.

DISCUSSION

This study explored the association between ADHD and alcohol dependence in a large population-based sample of Swedish adult

TABLE II. Phenotypic Correlations, Intraclass Correlations, and CTCT Correlations for ADHD and Alcohol Dependence in 17,711 Twins (5,420 Complete Twin Pairs).

Correlation		Adjusted estimate (CI)[a,b]
Phenotypic correlation	MZ female	0.25 (0.19, 0.30)
	MZ male	0.25 (0.19, 0.31)
	DZ female	0.26 (0.20, 0.32)
	DZ male	0.24 (0.18, 0.31)
	DZ opposite sex	0.23 (0.19, 0.28)
Intraclass correlation, ADHD	MZ female	0.43 (0.39, 0.47)
	MZ male	0.38 (0.32, 0.44)
	DZ female	0.24 (0.18, 0.29)
	DZ male	0.15 (0.06, 0.23)
	DZ opposite sex	0.12 (0.07, 0.17)
Intraclass correlation, alcohol dependence	MZ female	0.64 (0.51, 0.74)
	MZ male	0.48 (0.29, 0.64)
	DZ female	0.34 (0.08, 0.56)
	DZ male	0.25 (−0.03, 0.49)
	DZ opposite sex	0.23 (0.05, 0.41)
CTCT correlation	MZ female	0.17 (0.11, 0.24)
	MZ male	0.14 (0.05, 0.22)
	DZ female	0.12 (0.03, 0.21)
	DZ male	0.06 (−0.04, 0.17)
	DZ opposite sex	0.04 (−0.03, 0.11)

Phenotypic correlations between traits (ADHD, alcohol dependence) in the same individual; intraclass correlations within traits between twin pairs.
[a]Adjusted for age, linear, and quadratic, different for zygosity-gender groups, but symmetric between twin 1 and twin 2 in each group except for opposite-sex twins.
[b]Means and prevalence are assumed symmetric between twin 1 and twin 2 except for opposite-sex twins. Phenotypic correlation assumed the same in twin 1 and twin 2, CTCT assumed to be the same between twin 1 and twin 2 as between twin 2 and twin 1.

TABLE III. Model-Fitting Results and Modelled Sex Differences

	Fit of model compared to saturated model			
	Minus 2 × log likelihood	Degrees of freedom	AIC	*P*-value*
Saturated	56,816.27	34,926	−13,035.73	NA
ACE	56,898.11	35,011	−13,123.89	NA
ACE; no quantitative differences in ADHD	56,900.29	35,014	−13,127.71	0.535
ACE; no quantitative differences in alcohol dependence	56,900.42	35,013	−13,125.58	0.314
ACE; no quantitative differences in overlap of ADHD and alcohol dependence	56,899.66	35,014	−13,128.34	0.671
ACE; no qualitative differences in ADHD	56,902.58	35,012	−13,121.42	0.034
ACE; no qualitative differences in alcohol dependence	56,898.20	35,012	−13,125.80	0.764
ACE; no qualitative differences in overlap of ADHD and alcohol dependence	56,898.14	35,012	−13,125.86	0.867
ACE; qualitative differences for ADHD, otherwise no difference	**56,903.78**	**35,021**	**−13,138.22**	**0.842**
AE	56,898.93	35,017	−13,135.07	NA
AE; no quantitative differences in ADHD	56,900.51	35,019	−13,137.49	0.452
AE; no quantitative differences in alcohol dependence	56,901.18	35,018	−13,134.82	0.133
AE; no quantitative differences in overlap of ADHD and alcohol dependence	56,899.67	35,019	−13,138.33	0.691
AE; no qualitative differences in ADHD	56,907.51	35,018	−13,128.49	0.0031
AE; no qualitative differences in alcohol dependence	56,899.76	35,018	−13,136.24	0.361
AE; no qualitative differences in overlap of ADHD and alcohol dependence	56,899.09	35,018	−13,136.91	0.686
AE; qualitative differences for ADHD, otherwise no difference	***56,903.78***	***35,024***	***−13,144.22***	***0.678***

NA, not applicable.
Lower AIC indicates better fit.
Bold type indicates the best-fitting model within ACE or AE. Bold italic type indicates the best fit of all models (according to AIC).
*P-value of likelihood ratio test of model fit against fit of full ACE or AE model.

TABLE IV. Parameter Estimates (95% CI) for Best-Fitting ACE and AE Models for ADHD, Alcohol Dependence, and the Overlap Between ADHD and Alcohol Dependence

	Genetic/environmental contribution to variance			Genetic/environmental correlations for ADHD and alcohol dependence			Genetic/ environmental contribution ADHD and alcohol dependence		
	A	C	E	r_A	r_C	r_E	Bivariate A[a]	Bivariate C	Bivariate E
ADHD									
Female[b]	0.38 (0.24, 0.46)	0.04 (0.00, 0.16)	0.58 (0.55, 0.61)	–	–	–	–	–	–
Male[b]	0.38 (0.25, 0.44)	0.00 (0.00, 0.11)	0.62 (0.57, 0.67)	–	–	–	–	–	–
Collapsed[c]	0.41 (0.38, 0.44)	0.00 (0.00, 0.10)	0.59 (0.56, 0.62)	–	–	–	–	–	–
AE collapsed[d]	**0.41 (0.38, 0.44)**	**–**	**0.59 (0.56, 0.62)**						
Alcohol dependence									
Female	0.52 (0.06, 0.73)	0.11 (0.00, 0.52)	0.37 (0.27, 0.50)	–	–	–	–	–	–
Male	0.38 (0.00, 0.64)	0.09 (0.00, 0.49)	0.53 (0.36, 0.71)	–	–	–	–	–	–
Collapsed	0.57 (0.27, 0.66)	0.00 (0.00, 0.24)	0.43 (0.34, 0.53)	–	–	–	–	–	–
AE collapsed	**0.57 (0.47, 0.66)**	–	**0.43 (0.34, 0.53)**						
ADHD and alcohol dependence									
Female	–	–	–	0.24 (−0.14, 0.75)	1.00 (−1.00, 1.00)	0.17 (0.05, 0.28)	0.42 (−0.16, 1.19)	0.27 (−0.39, 0.77)	0.31 (0.10, 0.52)
Male	–	–	–	0.34 (−1.00, 1.00)	0.64 (−1.00, 1.00)	0.19 (0.06, 0.32)	0.53 (−0.20, 0.85)	0.01 (−0.42, 0.61)	0.46 (0.15, 0.77)
Collapsed	–	–	–	0.33 (0.15, 0.64)	1.00 (−1.00, 1.00)	0.18 (0.09, 0.26)	0.64 (0.24, 1.00)	0.00 (−0.28, 0.30)	0.36 (0.19, 0.53)
AE collapsed				**0.33 (0.24, 0.42)**	–	**0.18 (0.10, 0.26)**	**0.64 (0.47, 0.80)**	–	**0.36 (0.20–0.53)**

[a]Bivariate A (bivariate heritability) refers to the amount of covariance between the two phenotypes explained by A, similarly for C and E.
[b]Female and male estimates from the full sex-limitation model.
[c]Collapsed estimates from the ACE model, with qualitative gender differences in ADHD.
[d]Collapsed AE from the AE model, with qualitative sex differences in ADHD. Best-fitting model in bold type.

twins. We were able to establish a statistically significant genetic overlap between ADHD and alcohol dependence in adults. Future studies are needed to further characterize the nature of the shared genetic factors using both genome-wide association techniques and neurocognitive approaches. A better understanding of the pathophysiologic mechanisms underlying the development of alcohol dependence in ADHD may in turn translate into novel prevention and treatment targets. Clinically, the genetic overlap highlights the importance of using a family perspective that acknowledges that children of adults with alcohol dependence are at higher risk of ADHD and parents of children with ADHD may be at risk for developing alcohol dependence.

The main finding of our study is in line with two previous twin studies supporting a genetic overlap between ADHD and problem drinking in adults [Derks et al., 2014], as well as between ADHD in adolescence and alcohol dependence in adulthood [Edwards and Kendler, 2012]. The limited support for sex differences in the genetic and environmental overlap is also consistent across the studies. This indicates that the genetic overlap is robust across different developmental periods, similar in males and females, and present for the milder to the more severe alcohol use problems.

Several studies [Young et al., 2000; Kendler et al., 2003; Dick et al., 2005; Edwards and Kendler, 2012] have found support for shared genetic risk factors across a broad range of externalizing disorders, including alcohol dependence, antisocial personality disorder, and conduct disorder. We were unable to explore whether the genetic factors for ADHD and alcohol dependence were shared with other externalizing disorders. However, based on previous research, we argue that at least part of the genetic overlap is specific to ADHD and alcohol dependence. For instance, one previous twin study [Edwards and Kendler, 2012] found that the genetic overlap between hyperactivity and alcohol dependence remained statistically significant even after controlling for other externalizing behaviors, suggesting that impulsive behaviors that are less destructive/harmful than those manifested in conduct disorder can be indicative of a genetic risk for adult alcohol dependence.

Consistent with the previous twin study of ADHD and problem drinking [Derks et al., 2014], we found that nonshared environment factors explained the remaining part of the overlap between ADHD and alcohol dependence, whereas shared environmental factors were of minimal importance. Future studies exploring environmental exposures for ADHD and alcohol dependence may benefit by considering risk factors, such as peer relationships, low birth weight, and exposure to toxins [Banerjee et al., 2007]. However, the finding that the shared environmental factors were nonsignificant does not preclude significant shared environmental factors for alcohol dependence in youths [Knopik et al., 2009] or for the overlap between other externalizing disorders [Kendler et al., 2003; Knopik et al., 2009].

Phenotype Association Between ADHD and Subtypes and Alcohol Dependence

Previous studies have produced conflicting evidence about how the three DSM-IV subtypes of ADHD are associated with alcohol dependence. The results of our study suggest that all ADHD subtypes were associated with increased risk for alcohol dependence, with significantly higher OR for the CO subtype, which may suggest that the CO subtype represents a severe form of ADHD. Previous studies have found stronger phenotypic associations with the HI subtype of ADHD [Elkins et al., 2007; Chang et al., 2011; Lee et al., 2011; Edwards and Kendler 2012] and with HI symptoms [Elkins et al., 2007; Ameringer and Leventhal 2013], whereas other studies have reported a stronger association with the IN subtype of ADHD [Friedrichs et al., 2012]. More research is needed to elucidate whether DSM subtypes have any clinical relevance in predicting risks for alcohol dependence.

Limitations

These results should be considered in the context of several limitations. Dropout rates seemed to be due to a general unwillingness to respond to a lengthy survey [Larsson et al., 2013a]. However, nonresponders were significantly more often male, had at least one parent born outside Sweden, and had more often been diagnosed with a psychiatric disorder and convicted of any type of crime [Furberg et al., 2008; Friedrichs et al., 2012; Larsson et al., 2013a], which probably indicate that the most severe cases did not respond to the questionnaire. This limits generalizations to the more severe cases of the ADHD spectrum. We compared complete and incomplete twin pairs regarding ADHD and alcohol dependence status, as well as sex, age, and education level, to examine the extent to which missing values are non-random. No significant difference was observed regarding ADHD status ($P = 0.51$) and alcohol dependence ($P = 0.06$); however, individuals in complete pair were more often female ($P < 0.001$), were slightly younger (mean age: 33.44 compared to 34.26, $P < 0.001$), and had a higher education level ($P < 0.001$).

In a previous study, we have shown that our self-rating measure of ADHD symptoms shows acceptable reliability [Larsson et al., 2013a], but overlap with clinical diagnosis remains to be investigated. Moderate heritability estimates for ADHD 41% are in line with twin studies based on self-report epidemiological data, which do not include childhood onset and functional impairment [Boomsma et al., 2010], in contrast with clinically diagnosed ADHD in adults where heritability is higher, around 80% [Larsson et al., 2013b; Franke et al., 2012].

The prevalence of alcohol dependence in our data was somewhat lower compared with earlier international studies [Ameringer and Leventhal, 2013], although it is in line with previous Swedish data on alcohol use. For instance, in Sweden, serious problem drinking has been estimated to occur in around 10–15% of men and 3–5% of women (SOU, 2011:35).

The twin design assumes that the genetic and environmental factors influence ADHD and alcohol dependence independently of each other. There is some evidence that genetic and environmental factors not only exert their influence separately but may also interact, as for example in a study by [Kiive et al., 2010] who found that α-2A-adrenoceptor genotype variability and maltreatment in boys act together to increase the expression of hyperactive and inattentive symptoms in adolescents. How such possible interactions contribute to the overlap between symptoms of ADHD and alcohol dependence is unknown. Further studies are necessary to

elucidate the role of environmental factors and their possible interplay with genetic factors.

CONCLUSIONS

The overlap between ADHD and alcohol dependence in adulthood was largely explained by shared genetic risk factors; the nonshared environment also played a significant role in the overlap. This is an important step toward understanding the underlying nature of the risk of alcohol dependence in patients with ADHD and suggests that individuals with ADHD and their family members are important targets for alcohol prevention and treatment.

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