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Common etiological factors of attention deficit hyperactivity disorder and suicidal behavior: a population-based study in Sweden

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Therese Ljung contributed with conception and design, writing the manuscript draft, analyses and interpretation of the data, drafting the article and final approval of the version to be published. Qi Chen contributed with analyses and interpretation of the data, revising the article critically for important intellectual content and final approval of the version to be published. Paul Lichtenstein contributed with conception and design, acquisition and interpretation of the data, revising the manuscript critically for important intellectual content, and final approval of the version to be published. Henrik Larsson contributed with conception and design, interpretation of the data, revising the manuscript critically for important intellectual content, and final approval of the version to be published

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Abstract

Importance: The prevention of suicidal behavior is one of the most important tasks for mental health clinicians. Although a few studies have indicated an increased risk of suicidal behavior among individuals with attention deficit hyperactivity disorder, the development of more effective ways of identifying and modifying the risk is hampered by our limited understanding of the underlying mechanisms for this association.

Objective: To explore whether attention deficit hyperactivity disorder and suicidal behavior share genetic and environmental risk factors.

Design: Matched cohort design across different levels of family relatedness recorded from 1987 to 2009.

Setting and Participants: We identified 51 707 patients with attention deficit hyperactivity disorder (through the Patient and Prescribed Drug Registers) in Sweden and their relatives by linking longitudinal population-based registers. Controls were matched 1:5 on gender and birth-year.

Main outcome measure: Any record of suicide attempt or completed suicide defined by discharge diagnoses of the International Classification of Diseases.

Results: The risk of attempted (odds ratio=3.62), and completed suicide (odd ratio=5.91) was increased among individuals with attention deficit hyperactivity disorder (probands), even after adjusting for comorbid psychiatric disorders. The highest familial risk was observed among first-degree relatives, whereas the risk was considerably lower among more genetically distant relatives. These familial aggregation patterns remained similar across gender, after excluding relatives with attention deficit hyperactivity disorder and probands with suicidal behavior, and after excluding probands and relatives with severe comorbid disorders.

Conclusions and Relevance: Attention deficit hyperactivity disorder is associated with an increased risk of both attempted and completed suicide. The pattern of familial risks across different levels of relatedness suggests that shared genetic factors are important for this association. This is an important first step towards identifying the underlying mechanisms for the risk of suicidal behavior in attention deficit hyperactivity disorder patients and suggests that individuals with attention deficit hyperactivity disorder and their family members represent important targets for suicidal prevention and treatment.

Key words: ADHD, completed suicide, attempted suicide, family-based design, matched cohort

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent disorder that has been recognized as an important public health problem worldwide¹. In addition to having higher rates of psychiatric comorbidities [such as affective disorders^{2, 3}, schizophrenia^{4, 5}, disruptive behavior disorders^{6, 7}, and substance use disorders⁸], patients with ADHD have recently been shown to have an increased risk of suicidal behavior^{6, 9-12}. Therefore, developing more effective ways of identifying and modifying the risk of suicidal behavior is a clinical priority, but is hampered by our limited understanding of the causes of these behaviors in ADHD patients. Research has suggested that the overlap between ADHD and suicidal behavior may be attributable to ADHD drug treatment¹⁵ or co-occurring psychiatric disorders¹⁶; but no prior studies have explored the extent to which ADHD and suicidal behavior share genetic and environmental factors.

Genetic epidemiology studies (family, twin and genomic studies) suggest that susceptibility to ADHD is largely genetic in origin¹⁷. Similarly, the familial clustering of suicidal behavior is partly attributable to genetic factors¹⁸⁻²⁰. A genetic explanation would also be expected if, for example, impulsivity is a genetically influenced intermediate phenotype behind both ADHD and suicidal behavior^{13, 14}. On the other hand, the association between ADHD and suicidal behavior might also be influenced by environmental risk factors. For instance, previous reports have indicated that the negative parent-child relationship and childhood adversities (e.g., sexual and physical abuse) may represent important risk factors for offspring ADHD²¹ and suicidal behavior^{22, 23}.

Taken together, most previous research exploring the association between ADHD and suicidal behaviors has used small selected clinical samples and focused primarily on completed suicide¹², and no prior study has used genetically-informed data. Therefore, our objective was to explore the extent to which ADHD share genetic and environmental risk factors with suicidal behavior (both completed and attempted suicide) using a large population-based family sample. The use of family data from longitudinal registers allowed us to study not only the occurrence of suicide in individuals with ADHD, but also the familial risk across different levels of genetic relatedness. We conducted sensitivity analyses to rule out two plausible alternative explanations. First, we explored if the results were consistent even after excluding relatives with ADHD and probands with suicidal behavior. This analysis was one approach to deal with the possible adverse effect of ADHD medication (e.g. atomoxetine)¹⁵. Second, given that prior research has suggested that ADHD may increase the risk of completed suicide through comorbid conditions such as affective disorder, disruptive behavior disorders, schizophrenia and substance use disorders¹⁶, we explored the familial overlap between ADHD and suicidal behaviour after exclusion of probands, controls and relatives with such coexisting conditions.

Method

National registers

We linked several Swedish nationwide registers using the unique personal identification number. The National Patient Register (NPR) includes records of psychiatric inpatient care since 1973 with complete national coverage and psychiatric outpatient care since 2001. All discharge diagnoses, the main discharge diagnosis, and up to eight secondary diagnoses, are recorded

according to the International Classification of Diseases (ICD); 8th (1973-1986), 9th (1987-1996), and 10th (1997-2009) revision.

The Swedish Prescribed Drug Register was established in 2005 and provides complete national information on all dispensed prescribed pharmaceuticals. The register comprises drug classification according to the Anatomical Therapeutic Chemical (ATC), the date of prescription, quantity and dosage, and possible generic substitution. The register is almost complete with missing data on patient identification number for <0.3% of the population²⁴.

The Multi-Generation Register links everyone born since 1932 and living in Sweden at any time during 1961-2009 to their biological and adoptive parents. This information made it possible to identify parents, full-siblings, half-siblings and cousins to analyze potential familial aggregation at different levels of genetic relatedness. The Total Population Register provided information on sex, birth year, country of birth until 2009, and migration status during 1969-2009 for the entire population. From the Cause of Death Register, we obtained information on when individuals were alive and living in Sweden along with the underlying and multiple contributory causes of death. The register covers nearly all deceased persons registered in Sweden at the time of their death since 1952 and onward.

Measures

Patients with a discharge diagnosis of ADHD were identified from the national patient register (ICD9: 314; ICD10: F90) by having at least one record of inpatient or outpatient care between 1987 and 2009. We also identified individuals treated with medication for ADHD (methylphenidate [N06BA04]; atomoxetine [N06BA09]; amphetamine [N06BA01];

dexamphetamine [N06BA02]) from the Prescribed Drug Register between 2005 and 2009, and defined them as ADHD patients.

Probands were selected as ADHD patients between 3 and 40 years of age. A recent validity check indicated a high specificity for the register-based diagnoses of ADHD in the Swedish national registers. Importantly, similar results were obtained when these validity checks were restricted either to ADHD cases identified through ICD diagnoses (obtained from the Patient Register) or to ADHD medication (obtained from the Prescribed Drug Register). Previous research has shown that the comorbidity patterns of ADHD remains similar regardless of using a definition that requires one or at least two records of an ADHD diagnosis (Bahmanyar) and several of our own register-based studies of ADHD have shown that analyses restricted either to ADHD cases identified through ICD diagnoses (obtained from the Patient Register) or to ADHD medication (obtained from the Prescribed Drug Register) generates similar results (Larsson 2013 Sariaslan, Larsson2013 Chang). In addition, the fact that ADHD is the only licensed indication for methylphenidate and atomoxetine use in Sweden and that the authority to prescribe medication of ADHD in Sweden is restricted to physicians specialized on ADHD treatment indicate that a prescription of ADHD medication in the Swedish Prescribed Drug Register is a valid indicator of ADHD diagnosis (Lindblad 2010). Suicidal behavior was defined as any record of suicide attempt or completed suicide (including both definite and uncertain diagnoses). Specifically, we identified suicide attempts from the national patient register (ICD8-9: E950–E959, E980–E989; ICD10: X60–X84, Y10–Y34) and completed suicides from the cause of death register (ICD8-9: E950–E959, E980–E989; ICD10: X60–X84, Y10–Y34). To reduce possible misclassifications, suicidal behavior was only allowed in individuals aged 12 years or older²⁷.

In line with previous register-based research²⁸, we used an hierarchical approach with information from the NPR to define schizophrenia (ICD-8 and ICD-9: 295; ICD-10: F20), bipolar disorder (ICD8: 296.1, 296.3, 296.8; ICD9: 296A, 296C-E, 296W; ICD10: F30-F31), depression (ICD8: 296.2, 298.0, 300.4; ICD9: 296.2 296.3, 300.4; ICD10: F32-F34) and anxiety disorders (ICD8: 300 except 300.4; ICD9: 300 except 300E; ICD10: F40-F42, F44-F45, F48). The NPR also provided information on conduct disorder (ICD-9: 312; ICD-10: F91), antisocial personality disorder (ICD8-9: 301.7; ICD-10: F60.2), and substance use disorder (ICD8 codes: 303, 304; ICD9 codes: 303, 304, 305A, 305X and ICD10 codes: F10-F19)²⁹. Family educational level was assessed by highest attained education among the parents, categorized into three groups: elementary education (9 years or less), secondary education (10–12 years), and any higher education (13 years or more). *Statistical analyses*

We used a matched cohort design to estimate the risk of suicidal behavior within probands (individuals diagnosed with ADHD) and among relatives to patients with ADHD.

First, we evaluated the association between ADHD and suicidal behavior by comparing the risk of suicidal behavior among ADHD probands to five unaffected controls. Individuals were matched on gender and birth-year as an attempt to eliminate confounding, reduce misclassification of exposure and to ensure equal time at register follow-up.

Second, we used a family design where we estimated the risk of suicidal behavior among relatives of ADHD probands. For each type of relationship (parents, full-siblings, maternal- and paternal half-siblings, and cousins) we matched each case of ADHD proband and his or her exposed relative to five unaffected controls and their corresponding relatives. Several pairs could be descended from one proband (e.g if a proband has several siblings), and each individual in the population could appear in multiple relative groups (e.g. parent, siblings). Controls were chosen

among individuals who were alive, living in Sweden and not diagnosed with ADHD at the year of the proband's first ADHD diagnose. Similar to the within individual analyses, control-relative pairs were matched on gender and birth-year.

We compared the risk estimates separately for first-degree relatives (e.g. offspring and parents), second-degree relatives (e.g. half-siblings), and third degree relatives (e.g. cousins) to assess the genetic and environmental contribution to the overlap between ADHD and suicidal behaviors. An increased risk of suicidal behavior among first-degree, second-degree and third-degree relatives of ADHD probands would suggest familial effects for the overlap. Additionally, comparing the risk estimates among maternal half-siblings and paternal half-siblings provide information about the extent to which the observed familial association is primarily due to genetic or shared environmental factors. This is because maternal half-siblings are more similar with regard to shared environmental exposures than paternal half-siblings. Basically, if the observed familial association is primarily explained by shared environmental influences, we would expect higher risk estimates among maternal half-siblings than among paternal half-siblings, because offspring predominantly lives with their mothers when parents separate; that is, information from Statistics Sweden indicate that 91% of the mothers receive payment from the other parent in custody of the child following parental separation (Statistics Sweden, 1994), which strongly indicates that the majority of the offspring of divorced parents live with their mothers.

In an attempt to further elucidate the association between ADHD and suicidal behavior we conducted two sensitivity analyses.

First, we estimated the risk of suicidal behavior in relatives of ADHD probands after excluding relatives with ADHD and probands with suicidal behavior³⁰. These exclusions adjust

for the possibility that ADHD medication itself might increase or decrease the risk of suicidal behavior. Second, we estimated the risk of suicidal behavior in relatives of ADHD probands after excluding individuals with substance use disorder, depression, anxiety, conduct disorder, bipolar disorder, schizophrenia, and antisocial personality disorder in probands, controls and relatives. This was done to explore the extent to which an observed familial association between ADHD and suicidal behavior was explained by co-occurring psychiatric conditions.

We used conditional logistic regression to estimate odds ratios (ORs) of suicidal behavior with 95% confidence intervals. Analyses were performed in SAS version 9.3 along with a robust sandwich estimator to supply standard errors corrected for the dependence between repeated observations within families. We also fitted separate models for attempted and completed suicide for each gender. The study was approved by the Ethics Committee at Karolinska Institutet.

Results

Descriptive statistics

From the Swedish registers we identified 51 707 individuals (70% males) who met our criteria for ADHD. Among all probands, 17 349 (34%) had a comorbid disorder of substance use disorder, depression, anxiety, conduct disorder, bipolar disorder, schizophrenia, and antisocial personality disorder. The distribution of psychiatric disorders and socio-demographic variables for cases and controls are presented in Table 1. To understand the potential life circumstances of probands and controls we also identified different socio-demographic characteristics of both groups. In general, individuals with ADHD had lower socio-demographic characteristics compared to controls. With respect to the severity of the suicidal behavior, individuals with ADHD were more likely to use poisoning and hanging as a method of suicidal behavior

compared to controls, indicating a possible more impulsive behavior. However, controls were slightly younger than probands at time of suicide.

The overlap between ADHD and suicidal behavior

The percentage of ADHD probands with attempted suicide was 9.4% compared to 1.3% of the controls, while the percentage of ADHD probands who died by suicide was 0.2% compared to 0.02% of the controls. Individuals with ADHD had therefore an increased risk of both attempted and completed suicide compared to matched controls. The risk of attempted suicide was high with an odds ratio of 8.45 (95% CI=8.07-8.87). Similarly, we found an increased risk of completed suicide (OR=12.22, 95% CI=8.67-17.22). The result showed an increased risk of attempted suicide (OR=3.62, 95% CI=3.29-3.98) and completed suicide (OR=5.91, 95% CI=2.45-14.27) among ADHD probands, even after adjusting for substance use disorder, depression, anxiety, conduct disorder, bipolar disorder, schizophrenia antisocial personality disorder, and borderline personality disorder (Table 2).

The risk of attempted suicide among individuals with ADHD differed significantly by gender ($\chi^2=1271.0$, $P < .001$); the adjusted estimate was 2.93 (95% CI=2.60-3.29) for males and 5.41 (95% CI=4.60-6.36) for females (Table 2). In contrast, we could not observe a statistically significant gender difference for completed suicide ($\chi^2=2.56$, $P=0.110$).

Familial risk of suicidal behavior

Percentages of suicidal behavior for specific groups of individuals exposed and unexposed to a relative with ADHD are given in Table 3. There was strong evidence of familial influences for the overlap between ADHD and suicidal behavior.

The risk of attempted suicide was higher among first-degree relatives of ADHD probands compared to first-degree relatives of controls (Table 3). Specifically, the OR for attempted suicide was 2.42 (95% CI=2.36-2.49) among parents exposed to offspring ADHD and 2.28 (95% CI=2.17-2.40) among full-siblings of ADHD probands. Half-siblings and cousins of ADHD probands were also more likely to attempt suicide compared to relatives of controls; ORs from 1.57 to 1.59 among half-siblings and 1.39 among cousins. We found that the difference in the risk for first-degree (i.e., full-siblings) and second-degree (i.e., half-siblings) relatives were statistically significant ($\chi^2=99.54$, $P < .0001$), which suggest familial effects for the overlap between ADHD and attempted suicide. The difference in the risk of attempted suicide for maternal and paternal-half-siblings was on the other hand not statistically significant ($\chi^2=0.628$, $P 0.428$), which indicate that the familial effect most probably reflects genetic factors rather than shared environmental factors. Moreover, the estimates from separate analyses for males and females were similar in magnitude and showed the same pattern of familial risks, which suggests that shared genetic factors are important for these associations regardless of gender (data not shown).

Relatives of probands with ADHD had also a significantly increased risk of completed suicide. Again, the familial aggregation indicated genetic influences because first-degree relatives of individuals with ADHD were more likely to have completed suicide (ORs ranging between 2.23-2.24) than second-degree relatives (ORs between 1.51 and 2.02) and third-degree relatives (OR=1.51). The influence of shared environmental influences for the familial aggregation of ADHD and completed suicide were limited due to similar estimates among maternal and paternal half-siblings ($\chi^2=2.209$, $P 0.137$)

Sensitivity analyses

First, to further investigate the importance of shared etiological factors for this association we also investigated the risk of attempted and completed suicide among relatives after excluding relatives with ADHD and probands with suicidal behavior. The familial risks were slightly lower, but a similar pattern was observed across the different family relationships (see Table 3).

Second, we repeated the family analyses after excluding probands, controls and relatives with substance use disorder, depression, anxiety, conduct disorder, bipolar disorder, schizophrenia antisocial personality disorder, and borderline personality disorder. The pattern of familial risks of attempted suicide remained similar after these exclusions (see eTable 1). Unfortunately, the power to detect a genetic overlap behind ADHD and completed suicide was not sufficient.

Discussion

In this large longitudinal nationwide sample of Swedish families, we found that ADHD was strongly associated with attempted and completed suicide in males and females, even after adjusting for comorbid psychiatric disorders. The pattern of familial risks across different levels of genetic relatedness suggests that shared genetic factors contribute to the overlap between ADHD and suicidal behaviors. One potential explanation to these results are pleiotropic genetic effects³¹ for ADHD and suicidal behavior, possible reflecting genetic variants associated with impulsivity; a trait dimension that is highly heritable³², a core component of ADHD and strongly associated with suicidal behavior^{10, 14}. Our findings lend support to future studies investigating genetic and neurocognitive factors associated with suicidal behavior in ADHD, which are needed to identify novel biological markers for improved identification of individuals with ADHD at

high risk for suicidal behaviors. This is an important target given that ADHD shows considerable clinical heterogeneity in terms of both severity and developmental outcomes.

Although previous genetic epidemiology studies have emphasized the importance of genetic influences on ADHD, attempted suicide and completed suicide^{17,33,34} our study is the first to show that ADHD and suicidal behavior share genetic risk factors. The finding of genetic factors does not exclude the possibility of environmental influences on ADHD and suicidal behavior nor does it exclude outcome specific genetic and environmental factors and we cannot entirely rule out the influence of non-shared confounders and measurement errors. It is also important to note that this finding needs to be replicated in other settings using research methods (e.g., multivariate twin design and cross-disorder genome-wide association studies) with different strength and weaknesses in validity.

In addition to this main finding, our study contributes with a least three other important findings. .

First, we could show that the observed familial aggregation pattern remained when tested separately for attempted and completed suicide. This is important given that most studies have investigated the association between ADHD and completed suicide, while attempted suicide has been given little attention in previous research⁶. We found that the proportion of attempted suicide was 6.6% for parents and 3.4% for siblings of ADHD probands. This suggests that relatives of ADHD patients should be screened for suicidal behaviors given that untreated suicide attempts may lead to completed suicide and substantial adversity in the family environment³⁵.

Second, we could demonstrate that the familial risk of suicidal behavior remained similar even after excluding probands and controls with suicidal behavior as well as relatives with an

ADHD diagnosis (i.e. never been medicated for symptoms of ADHD), indicating that harmful effects of ADHD medication or imitation of suicide within families are unlikely explanations for the observed overlap between ADHD and suicidal behavior. This is particularly important given that previous research has suggested that stimulant or non-stimulant (atomoxetine) ADHD medication may increase the risk of suicidal behavior^{15, 36, 37}. Nevertheless, additional research is needed on the relationship between medication use and suicide risk in ADHD populations.

Third, we found that the risk of suicidal behavior in individuals with ADHD behavior attenuated, but remained substantial (ORs were 3.6 and 5.9 for attempted and completed suicide, respectively) even after adjusting for comorbid psychiatric conditions which indicates that the association between ADHD and suicidal behavior is only partly explained by coexisting diagnosis. A few studies have suggested that ADHD might only be a risk factor for suicidal behavior in combination with other psychiatric conditions⁶. For example, a recent study concluded that ADHD was only strongly associated with attempted suicide in the presence of anxiety disorders, bipolar disorders, conduct disorder, oppositional defiant disorder or substance use disorders¹⁶. The conflicting results may be explained by the fact that they used a small sample which reduced the possibility to detect a statistically significant independent association of ADHD. There are many examples of widespread pleiotropic effects of genetic risk variants across a broad range of diagnostic categories, including schizophrenia, bipolar disorder, autism, major depressive disorder and ADHD^{38, 39}. Our finding that the familial aggregation pattern remained similar even after adjusting for comorbid psychiatric disorders does not rule out such pleiotropic effects, but suggests that at least part of the genetic overlap is specific for ADHD and suicidal behavior.

The strengths of the present study include the use of nationwide longitudinal data, which made it possible to study the entire Swedish population until the end of 2009. Further, the family-based design allowed us to explore the genetic and environmental contribution to the overlap between ADHD and suicidal behavior. The use of register data also eliminates the risk of recall bias and reduces the risk of misclassification, although we could not avoid potential misclassification due to diverse diagnostic evaluations made by different clinicians. However, recent validation checks indicate low numbers of false-positive diagnoses of ADHD in Swedish registers^{25, 26}. 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) because these specific diagnoses were not recorded across the registers. Thus, future research needs to consider symptom data of ADHD to explore if the familial risk of suicide and attempted suicide is driven by the impulsive component of ADHD. The estimated risk of suicidal behavior among individuals with ADHD might be biased if ADHD medication by itself is associated with suicidal behavior. However, the robust association after excluding relatives with a diagnosis of ADHD in the familial risk analyses did not support strong bias of this type.

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 National guidelines for medication of ADHD, issued by the Swedish National Board of health and Welfare in 2002, state that medication should be reserved for cases where other supportive interventions have failed, indicating that our proxies for ADHD are most likely to underestimate the incidence of ADHD and identify severe cases of ADHD. Thus, generalizations to cases of less severe ADHD should be made with caution.

Moreover, although mortality statistics with regards to suicides has been validated with Swedish data⁴⁰, suicidal behavior might be underestimated due to misclassification in the registers. However, because suicide is such a rare outcome, possible misclassification would most likely not impact our estimates. Register data also have limitations in form of left truncation and right censoring which might lead to misclassification of outcome and exposure. For example, the outpatient register was not started until 2001 and have not yet complete nationwide coverage. Possible random misclassification would most likely only lead to underestimation of the familial risk. We handled these limitations by matching on birth year to ensure equal follow-up time. Some comparisons for completed suicide were based on small numbers resulting in large confidence intervals. However, separate analyses for attempted and completed suicide resulted in a similar pattern of familial risks.

Finally, family data make it possible to examine mechanisms for an association by combining different genetically informative designs. Here we compared the risk of suicidal behavior in maternal and paternal half-siblings to investigate the impact of shared environmental influences. This comparison was based on the assumption that maternal half-siblings are more similar with regard to shared environmental exposures than paternal half-siblings, supported by the fact that the majority (91%) of children among divorced parents in Sweden continue to live with their mothers (ref: Statistics Sweden). Nevertheless, if the difference in shared environment between maternal and paternal half-sibs is small, we will have limited power to identify shared environmental influences. However, the point estimates for maternal and paternal half-siblings were basically identical. Future research should use twin studies or other family-based designs in different settings and populations to more thoroughly examine the importance of shared environmental factors.

In summary, we have found an increased risk of both completed and attempted suicide among relatives of individuals with ADHD. The pattern of familial risks suggests that this association is partly due to shared genetic factors. This finding represents an important first step towards identifying the underlying mechanisms for the risk of suicidal behavior in ADHD patients and suggests that individuals with ADHD and their family members represent important targets for suicidal prevention and treatment.

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Author Contributions: T. Ljung had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

Study concept and design: Ljung, Lichtenstein, Larsson

Acquisition of data: Lichtenstein

Analysis and interpretation of data: All authors.

Drafting of the manuscript: Ljung

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Ljung

Obtained funding: Lichtenstein, Larsson

Study supervision: Larsson

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Relationship of neurocognitive deficits to diagnosis and symptoms across affective and non-affective psychoses

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Table 1. Distribution of study variables among ADHD probands and matched controls, and odds ratios for ADHD associated with each comorbid disorder

	No. (%)		Odds ratio (95% CI)
	Probands (n=51 707)	Controls (n=258 535)	
Comorbid disorders			
Substance use	7296 (14.1)	4230 (1.6)	11.07 (10.61, 11.55)
Depression	6615 (13.3)	3558 (1.4)	13.02 (12.42, 13.65)
Anxiety	4077 (9.5)	3033 (1.2)	10.53 (9.86, 11.14)
Conduct disorder	2421 (4.7)	383 (0.15)	34.41 (30.75, 38.50)
Bipolar disorder	1731 (3.4)	420 (0.2)	22.98 (20.51, 25.75)
Borderline personality disorder	1147 (2.2)	170 (0.07)	31.06 (26.23, 36.78)
Schizophrenia	384 (0.7)	220 (0.1)	9.79 (7.75, 10.89)
Antisocial personality disorder	348 (0.7)	42 (0.02)	42.97 (30.65, 58.56)
Suicidal behavior			
Attempted suicide	4875 (9.4)	3356 (1.3)	8.46 (8.07, 8.87)
Completed suicide	113 (0.22)	47 (0.02)	12.22 (8.67, 17.22)
Family educational level (% of column total)			
Elementary education	4899 (9.5)	18898 (7.3)	
Secondary education	28675 (55.4)	117826 (45.6)	
Higher education	17312 (33.5)	118917 (46.0)	
Missing data	821 (1.6)	2894 (1.1)	
Mean age at suicide			
Attempted suicide	21	20	
Completed suicide	26	24	
Suicide method			
Attempted			
Hanging or suffocation	93 (1.9)	40 (1.2)	
Poisoning	3374 (69.2)	1635 (48.7)	
Sharp object	434 (8.9)	211 (6.3)	
Other	974 (20.0)	1470 (43.8)	
Completed			
Hanging or strangulation	40 (35.4)	18 (38.3)	
Poisoning	46 (40.7)	13 (27.7)	
Firearms	-	3 (6.3)	
Other	27 (23.9)	13 (27.7)	

Table 2. Odds ratios of attempted and completed suicide among ADHD probands compared to matched controls

Variable	N		Odds ratio (95% CI)		
	Probands	Controls	Crude	Adjusted ^a	Adjusted ^b
Attempted suicide					
All	51 707	258 535	8.46 (8.07, 8.87)	8.26 (7.87, 8.66)	3.62 (3.29, 3.98)
Male	36 102	180 510	7.12 (6.68, 7.59)	6.88 (6.45, 7.34)	2.93 (2.60, 3.29)
Female	15 605	78 025	10.39 (9.67, 11.15)	10.22(9.51, 10.98)	5.41 (4.60, 6.36)
Completed suicide					
All	51 707	258 535	12.22 (8.67, 17.22)	12.33 (8.73, 17.42)	5.91 (2.45, 14.27)
Male	36 102	180 510	10.32 (7.04, 15.12)	10.37 (7.05, 15.25)	3.70 (1.38, 9.95)
Female	15 605	78 025	22.76 (10.06, 51.50)	23.23 (10.22 52.78)	-

^a Adjusted for SES^b Adjusted for psychiatric comorbidities in Table 1

Table 3. Odds ratios for attempted and completed suicide among relatives of ADHD probands compared to matched controls

	Relatives exposed to ADHD		Relatives not exposed to ADHD		Odds ratio (95% CI)	Odds ratio ^a (95% CI)
	No. of pairs	No. of suicides (%)	No. of pairs	No. of suicides (%)		
Attempted suicide						
First-degree relatives						
Parents	96 937	6429 (6.6)	467 048	13 209 (2.8)	2.42 (2.36-2.49)	2.27 (2.20-2.34)
Full-siblings	58 589	1977 (3.4)	276 741	4188 (1.5)	2.28 (2.17-2.40)	1.86 (1.75-1.98)
Second-degree relatives						
Maternal half-siblings	20 246	822 (4.1)	43 331	1093 (2.5)	1.59 (1.47-1.73)	1.50 (1.36-1.64)
Paternal half-siblings	21 631	808 (3.7)	45 647	1097 (2.4)	1.57 (1.45-1.70)	1.51 (1.37-1.66)
Third-degree relatives						
Cousins	265 120	6497 (2.5)	1 308 091	23 299 (1.8)	1.39 (1.35-1.43)	1.32 (1.28-1.37)
Completed suicide						
First-degree relatives						
Parents	96 937	664 (0.7)	467 048	1412 (0.3)	2.24 (2.06-2.43)	2.15 (1.98-2.34)
Full-siblings	58 589	112 (0.2)	276 741	224 (0.08)	2.23 (1.83-2.73)	2.19 (1.77-2.71)
Second-degree relatives						
Maternal half-siblings	20 246	43 (0.2)	43 331	54 (0.1)	1.51 (1.08-2.10)	1.47 (1.04-2.07)
Paternal half-siblings	21 631	53 (0.3)	45 647	55 (0.1)	2.02 (1.47-2.79)	1.99 (1.43-2.76)
Third-degree relatives						
Cousins	265 120	422 (0.2)	1 308 091	1353 (0.1)	1.51 (1.36-1.67)	1.43 (1.29-1.59)

^a Odds ratios after excluding relatives with ADHD and probands with suicidal behavior