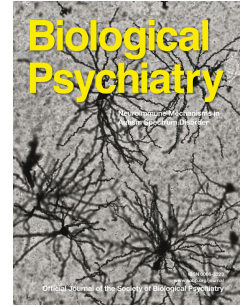


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Isabell Brikell, MSc, Laura Ghirardi, MSc, Brian M. D'Onofrio, PhD, David W. Dunn, MD, Catarina Almqvist, PhD, Søren Dalsgaard, PhD, Ralf Kuja-Halkola, PhD, Henrik Larsson, PhD

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Familial liability to Epilepsy and ADHD: A Nationwide Cohort Study

Short title: Familial liability to Epilepsy and ADHD

Isabell Brikell, MSc¹, Laura Ghirardi, MSc¹, Brian M. D'Onofrio, PhD^{1,2}, David W. Dunn, MD³, Catarina Almqvist, PhD^{1,4}, Søren Dalsgaard, PhD^{5,6}, Ralf Kuja-Halkola, PhD¹ & Henrik Larsson, PhD^{1,7}

¹ Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

² Department of Psychological and Brain Sciences, Indiana University, Bloomington, USA

³ Department of Psychiatry, Riley Child and Adolescent Psychiatry Clinic, Indiana University School of Medicine, Indiana University Health Physicians, Indianapolis, USA

⁴ Astrid Lindgren Children's Hospital, Karolinska University Hospital, Stockholm, Sweden

⁵ National Centre for Register-based Research, Department of Economics, Aarhus University, Aarhus, Denmark, The Lundbeck Foundation Initiative for Integrative Psychiatric Research- iPSYCH, Aarhus, Denmark

⁶ Department for Child and Adolescent Psychiatry, Hospital of Telemark, Kragerø, Norway

⁷ School of Medical Sciences, Örebro University, Örebro, Sweden

Corresponding Author: Isabell Brikell, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, 171 77, Stockholm, Sweden, Tel +0046 8524 822 31, Email Isabell.Brikell@ki.se

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Abstract

Background: Epilepsy and ADHD are strongly associated, however, the underlying factors contributing to their co-occurrence remain unclear. A shared genetic liability has been proposed as one possible mechanism. Our goal was therefore to investigate the familial co-aggregation of epilepsy and ADHD, and to estimate the contribution of genetic and environmental risk factors to their co-occurrence.

Methods: We identified 1 899 654 individuals born 1987-2006 via national Swedish registers and linked each individual to their biological relatives. We used logistic regression to estimate the association between epilepsy and ADHD, within-individual and across relatives. Quantitative genetic modelling was used to decompose the cross-disorder covariance into genetic and environmental factors.

Results: Individuals with epilepsy had a statistically significant increased risk of ADHD (OR=3.47, 95%CI=3.33-3.62). This risk increase extended to children whose mothers had epilepsy (OR=1.85, 95%CI=1.75-1.96), children whose fathers had epilepsy (OR=1.64, 95%CI=1.54-1.74), full-siblings (OR=1.56, 95%CI=1.46-1.67), maternal half-siblings (OR=1.28, 95%CI=1.14-1.43), paternal half-siblings (OR=1.10, 95%CI=0.96-1.25), and cousins (OR=1.15, 95%CI=1.10-1.20). The genetic correlation was 0.21 (95%CI=0.02-0.40) and explained 40% the phenotypic correlation between epilepsy and ADHD, with remaining variance largely explained by non-shared environmental factors (49%, r_E 0.36, 95%CI=0.23-0.49). The contribution of shared environmental factors to the cross-disorder overlap was not statically significant (11%, r_C 0.32, 95%CI=-0.16-0.79).

Conclusions: This study demonstrates a strong and etiologically complex association between epilepsy and ADHD, with shared familial factors and risk factors unique the individual

contributing to co-occurrence between the disorders. Our findings suggest that epilepsy may share less genetic risk with ADHD, as compared to other neurodevelopmental disorders.

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Introduction

Epilepsy and ADHD are among the most common conditions in pediatric neurology and psychiatry (1, 2). Children with epilepsy have a 3 to 5-fold increased risk of ADHD (3, 4), and 10-30% meet diagnostic criteria for the disorder (1, 3, 5). This makes ADHD one of the most commonly co-occurring neurodevelopmental conditions in epilepsy (3, 6). Conversely, individuals with ADHD have a reported 4-fold increased risk of epilepsy (7). Despite the strong association, the underlying factors contributing to their co-occurrence are not well understood.

Several mechanisms have been proposed, including adverse effects of antiepileptic drugs and chronic seizures, lowered seizure threshold related to ADHD medications, and an underlying brain dysfunction increasing the risk for both conditions (5, 6). Although some antiepileptic drugs can increase inattention and hyperactivity problems, two studies have shown that ADHD symptoms are often present prior to first epileptic seizure, and in drug naïve patients. This suggests that epilepsy and ADHD are associated independently of the effect of seizures and medications (8, 9). There is evidence for common neurophysiological markers across the disorder. Frontal lobe dysfunction and adrenergic system dysregulation have been implicated in both epilepsy and ADHD (5). Further, subclinical epileptiform discharges are considerably more common in children with ADHD, compared to the general population (5, 10).

In the last years, specific genetic factors have been implicated in a range of clinically distinct neurodevelopmental disorders, including epilepsy and ADHD (11). Such findings, together with evidence of phenotypic and neurophysiological overlap, have led to the hypothesis that both disorders lie on a continuum of neurodevelopmental liability, that is underpinned by common genetic risk factors (11). However, there are few genetically-informative studies addressing the

common etiology of epilepsy and ADHD. In a study of 308 epilepsy cases, considerable familial clustering was found for behavioural disorders, although the association with ADHD in first-degree relatives was not statistically significant (12). A pilot study examining the co-morbidity between ADHD and epilepsy found that the prevalence of ADHD in mothers of children with ADHD and epilepsy was elevated (13). Similarly, results from a population-based Norwegian study found that children of mothers with epilepsy had a nearly two-fold increased risk of ADHD as adults (14), suggesting that ADHD symptoms and epilepsy may cluster in families due to genetic or environmental causes passed from the mother to the child. However, familial transmission cannot be disentangled from pregnancy related risk factors using only mother-offspring pairs.

Further research is therefore needed to assess the contribution, and source, of familial liability to the co-occurrence of epilepsy and ADHD. To address this, we used nationwide Swedish data to assess the association between epilepsy and ADHD across multiple types of relatives, and quantitative genetic modelling to estimate the genetic and environmental contributions to their co-occurrence.

Methods and Materials

Study population

The study population was identified using data from nationwide Swedish registers linked via personal identification numbers (15). All individuals born in Sweden between 1987-2006 were identified via the Medical Birth Register (MBR) (16). We obtained demographic information from the Total Population Register (TPR), the Migration Register, the Cause of Death Register, and the Multi-Generation Register (MGR) (17). We excluded individuals with a recorded congenital malformation in the MBR based on the International Classification of Diseases, 9th (ICD-9, 1987-1996) and 10th revision (ICD-10, 1997 onwards) (ICD-9 740-759: ICD-10 Q00-Q99) (18). Individuals who died or migrated prior to age seven, were adopted, or whose biological parents were not identifiable were also excluded, resulting in a study population of 1 899 654 individuals. Each individual was then linked to their mother, father, full-siblings, maternal and paternal half-siblings, and cousins using the MGR, to create six relative sub-cohorts (Table 1) (17). All possible combinations of sibling and cousin pairs were identified, meaning each individual contributed at least once as exposing relative and once as outcome relative. The number of parent-offspring pairs corresponds to the number of individuals in the cohort as we only estimated the association between parental epilepsy and offspring ADHD, due to incomplete coverage for parental ADHD (Table 1) (19).

Epilepsy and ADHD cases

We identified ADHD cases from the Swedish National Patient Register (NPR) (19) and the Swedish Prescribed Drug Register (PDR) (20) until December 31, 2013. Diagnoses in the NPR are coded according to the ICD (18). The PDR includes all medication dispensations in Sweden

since mid-2005 (19, 20). ADHD cases were defined as ever having received a discharge diagnosis of hyperkinetic disorder (ICD-9 314, ICD-10 F90) in the NPR, and/or ever having received a prescription of ADHD medication after age three. Approved medications for the treatment of ADHD in Sweden during the study period were methylphenidate, amphetamine, dexamphetamine, lisdexamfetamine and atomoxetine. Epilepsy cases were identified via the NPR and defined as ever having received a discharge diagnosis for any epilepsy (ICD-9 345, ICD-10 G40, G41). Earlier ICD revisions were included to identify epilepsy cases in the parent generation (ICD-7 353, ICD-8 345).

The study was approved by the regional ethics review board in Stockholm, Sweden and all personal information from the registers was anonymized by Statistics Sweden. By Swedish law, there is no requirement for informed consent in register based research.

Statistical Analysis

Familial co-aggregation analyses

We used a cohort design to evaluate the association between epilepsy and ADHD, coded as lifetime diagnoses (0/1). Logistic regression was used to estimate the within-individual association, comparing the risk of ADHD in individuals with epilepsy to the risk in individuals without epilepsy. To estimate the familial co-aggregation, we fitted a logistic regression in each relative sub-cohort, comparing the risk of ADHD in individuals with a relative with epilepsy, to the risk in individuals without a relative with epilepsy. A summary of the unique information provided by each relative sub-cohort is provided in Table 1. Associations are presented as odds ratios (ORs) with 95% confidence intervals. Analyses were adjusted for birth-year and sex. A higher risk of ADHD in relatives of individuals with epilepsy indicates that etiological factors shared among relatives contribute to the co-occurrence of the disorders. Further, differences in the magnitude of the association across different types of relatives can point to the sources (i.e. genetic or environmental) of familial co-aggregation. Parents and their offspring share 50% of their segregating genes. Mothers also provide the in-utero environment, meaning a higher risk in mother-offspring may indicate the importance of pregnancy related factors. Full-siblings share on average 50% of their segregating genes, whereas half-siblings share 25%. In addition, full-siblings and maternal half-siblings tend to share environmental factors to a greater extent than paternal half-siblings, since children more often reside predominantly with mothers after parental separation (21). A higher risk in full-siblings, relative to maternal half-siblings, may therefore suggest that genetic factors are operative, whereas a higher risk in maternal versus paternal half-siblings suggest that shared environmental factors may be of importance.

Sensitivity analyses

Sensitivity analyses were only performed in the full cohort and in full-siblings to ensure sufficient power. First, we used a stricter definition of epilepsy and ADHD to explore whether case definition affected our estimates. We required \geq two discharge diagnoses for ADHD and epilepsy from the NPR and excluded individuals who only ever had a diagnosis of status epilepticus (ICD-9: 345Q; ICD-10: G41). To assess the validity of using prescription data to define ADHD we also excluded information on ADHD from the PDR. Second, we used a restricted cohort born 1994-1999, excluding individuals who migrated or died during follow-up. This was done to assess potential bias due to differential follow-up time and incomplete coverage in the NPR, which only includes outpatient care from 2001(19). Third, we examined the hypothesis that a familial association between ADHD and epilepsy is better explained by direct effects of one disorder on the other, within an individual. This was done in the full-sibling cohort, firstly by adjusting for epilepsy in the outcome relative, and secondly by adjusting for ADHD in the exposing relative. If the OR's remain statistically significant after adjustment, the contribution of common familial risk factors to epilepsy and ADHD is further supported. A detailed description of the rationale for these analyses (based on directed acyclic graphs, DAGs) has been provided elsewhere (22, 23). Finally, we stratified the analyses by sex.

Data management was done in SAS version 9.4 (SAS Institute, Inc) and analyses in Stata version 13.1 (StataCorp). A cluster robust sandwich estimator was used to remove distributional assumptions and correct confidence intervals for the non-independence of family data.

Quantitative Genetic Modelling

Quantitative genetic modelling was used to estimate the contribution of genetic and environmental factors to the association between epilepsy and ADHD. Quantitative genetic models capitalize on the different levels of genetic and environmental sharing between different types of relatives, in order to decompose variance and covariance into additive genetic (A), dominant genetic (D), shared environmental (C), and non-shared environmental factors (E). Bivariate models also provide an estimate of the genetic (r_G) and environmental correlations (r_C , r_E) across disorders, which indicates the degree to which etiological factors are shared between disorders (24). As epilepsy and ADHD were binary, we used a liability threshold framework where diagnoses were assumed to represent an underlying normal distribution of liability (24). We used all possible full-sibling, maternal half-sibling, and paternal half-sibling pairs in our cohort, resulting in a sample of 1,186,306 sibling pairs (Table 3). We calculated phenotypic (i.e. the correlation between epilepsy and ADHD within individual), intra-class (ICC's; the correlation between the same trait across siblings), and cross-sibling-cross-trait correlations (CSCT; the correlation between trait one in one sibling with trait two in the other sibling) to glean what type of model to fit (ADCE, ACE, or AE). We proceeded to fit a quantitative genetic sibling model based on the following assumptions (25, 26); Additive genetic factors correlate 0.5 for full-siblings and 0.25 for half-siblings. Dominant genetic factors correlate 0.25 for full-siblings and zero for half-siblings. Shared environmental factors correlate at 1 for full-siblings and maternal half-siblings and 0 for paternal half-siblings. Non-shared environmental factors do not correlate across siblings. The model was fitted using the Weighted Least Squares method implemented in OpenMx (27). To obtain valid standard errors when including multiple sibling pairs per family, we used non-parametric bootstrap sampling (28). A bootstrap sample was created by repeatedly drawing (with replacement) families, sampling as many families as in original dataset. For a

given bootstrap sample, the estimates from the quantitative genetic model were computed. After repeating this process across 1000 bootstrap samples, standard errors were obtained from the bootstrap estimates and 95% confidence intervals were computed.

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Results

Descriptive statistics

Descriptive statistics for the full cohort are presented in Table 2. The prevalence at the end of follow-up was 1.1% for epilepsy and 4.3% for ADHD (Table 2). In comparison, 13.5% of those with epilepsy also had a diagnosis of ADHD, and 3.4% of those with ADHD had a diagnosis of epilepsy.

Within-individual and familial co-aggregation analyses

Individuals with epilepsy had a statistically significant increased risk of ADHD (OR=3.47, 95%CI 3.33-3.62), compared to individuals without epilepsy (Figure 1). Further, individuals with a relative with epilepsy also had a statistically significant increased risk of ADHD (Figure 1). The risk of ADHD in children whose mothers had epilepsy was elevated (OR=1.85, 95%CI=1.75-1.96), compared to the risk of ADHD in children whose mothers did not have epilepsy. The risk was also statistically significantly higher ($p=0.004$) than the risk in children whose fathers had epilepsy (OR=1.64, 95%CI=1.54-1.74). Individuals with a full-sibling with epilepsy also had an increased risk of ADHD (OR=1.56, 95%CI=1.46-1.67), which was statistically significantly higher ($p=0.002$) than the risk in maternal half-siblings (OR=1.28, 95%CI=1.14-1.43). The risk was attenuated, but remained statistically significant in cousins (OR=1.15, 95%CI=1.10-1.20). We did not observe a statistically significant risk increase in paternal half-sibling (OR=1.10, 95%CI=0.96-1.25).

Sensitivity analyses

Results from the sensitivity analyses are presented in Supplementary Table S1. Estimates using a stricter definition of epilepsy and ADHD (Model 1; S_1) were similar to results from the main analyses, suggesting that our definition (>1 or >2 diagnoses) and the use of prescription data from

the PDR did not affect the results. Risk estimates obtained in the restricted cohort born 1994-1999, excluding all deaths and migrations, were somewhat attenuated for the within-individual association (OR=3.11 in restricted cohort vs OR=3.47 in full cohort), whereas CI's for the OR in full-siblings were almost completely overlapping with those from the main analyses (Model 2; S₁). This suggests that censoring and incomplete follow-up may have slightly biased the estimated within-individual association, but had limited impact on the estimated familial association. Adjusting for the exposing condition (epilepsy) in the outcome relative attenuated the OR in full-siblings, as did adjusting for the outcome condition (ADHD) in the exposing relative (Model 3&4; S₁). However, the estimates remained positive and statistically significant, providing further support for the presence of common familial risk factors for epilepsy and ADHD (22, 23, 29). Estimates stratified by sex were not statistically significantly different (Supplementary Table S2).

Quantitative Genetic Modelling

The phenotypic correlation between epilepsy and ADHD was 0.24 (95%CI=0.23-0.25). ICC's and CSCT's were higher in full-siblings than in maternal half-siblings, indicating the contribution of genetic factors to variance and covariance (Table 3). Further, all correlations were somewhat higher in maternal than paternal half-siblings, indicating a possible contribution of shared environmental factors. As there was no indication of dominance genetic effects, indexed by maternal half-sibling correlations being less than half of the full-sibling correlations, we fitted a bivariate ACE model (Figure 2). Genetic and shared environmental factors together explained 51% of the phenotypic correlation between epilepsy and ADHD (additive genetic contribution 40%, 95%CI=9-70%; shared environmental contribution 11%, 95%CI=-3-25%), with the remaining overlap (49%, 95%CI=32-67%) attributable to non-shared environmental factors.

Although the genetic correlation was statistically significant ($p = 0.03$), confidence intervals were wide ($r_G=0.21$, 95%CI=0.02-0.40). The shared environmental correlation was not statistically significant ($p=0.20$) as confidence intervals crossed zero ($r_C=0.32$, 95%CI=-0.16-0.79). The non-shared environmental correlation (r_E) was estimated to 0.36 (95%CI=0.23-0.49). Parameter estimates are presented in Figure 2, and full results from the ACE model are presented in Supplementary Table S3.

Discussion

In this nationwide family-study, individuals with epilepsy had a 3.5-fold increased risk of ADHD, compared to individuals without epilepsy, which is in line with previous studies (3, 4, 7). We also show that relatives of individuals with epilepsy have a statistically significant increased risk of ADHD, suggesting that a shared familial liability contributes to the co-occurrence between epilepsy and ADHD.

Based on the pattern of risk across relatives, we found support for both environmental and genetic factors contributing to a shared familial liability. Maternal half-siblings had a somewhat higher risk of ADHD than paternal half-siblings, indicating that shared environmental factors may be operative. This is because both types of half-siblings share 25% of additive genetic factors, but maternal half-siblings tend to share more environmental factors (21). We also found that the risk of ADHD was higher in full-siblings compared to maternal half-siblings, suggesting that at least part of the familial liability is genetic in origin.

When estimating the genetic overlap across epilepsy and ADHD using quantitative genetic modeling, our results revealed a modest genetic correlation between the disorders. Shared genetic factors explained about 40% of the phenotypic cross-disorder correlation. A similar effect remains to be identified in molecular genetic data. In the largest study to date, including 7,779 epilepsy and 12,645 ADHD cases, result showed no statistically significant genetic cross-disorder correlation based on common genetic variants (30). Nevertheless, rare variants, including de novo mutations which are not inherited, may play a role for the within-individual association between epilepsy and ADHD (11, 31). The genetic correlation across epilepsy and ADHD in the current study was also lower than correlations previously reported in twin studies of ADHD and other neurodevelopment conditions, including autism spectrum disorder (ASD) and developmental co-

ordination disorder, which range from 0.50-0.90 (32-34). Further, our results also differ from estimates in two studies investigating the familial aggregation between ASD, intellectual disabilities and ADHD using similar cohorts and analytic approaches as the current study (26, 35). Both studies showed strong evidence for a genetic contribution to the cross-disorder familial aggregation; quantitative genetic analysis of the overlap between ADHD and intellectual disabilities indicated that 91% of phenotypic cross-disorder correlation could be attributed to genetic factors (26). This suggests that the modest genetic correlation between epilepsy and ADHD observed in our study is not merely due to methodological differences across studies. Rather, our results suggest that epilepsy may have a weaker genetic sharing with ADHD and the broader neurodevelopmental continuum, as compared to traditional neurodevelopment disorder such as ASD and ID (11).

Half of the phenotypic association between epilepsy and ADHD was attributed to factors unique to the individual. Pregnancy-related complications and pre-term birth have been associated with both epilepsy and ADHD in a potentially causal way (14, 36, 37). In the extent that such pre- and perinatal risk factors are not due to maternal effects consistent across pregnancies, they could potentially contribute to the strong non-shared environmental correlation we observed between epilepsy and ADHD. Another possible explanation is that part of the within-individual association is driven by one disorder increasing the risk of the other disorder. Nearly 75% of comorbid cases in our cohort were diagnosed with epilepsy prior to ADHD. This could indicate that epilepsy related factors may exacerbate ADHD symptoms, increasing the risk of a subsequent ADHD diagnosis. Indeed, previous research suggests that adverse effects of antiepileptic drugs and chronic seizures can lead to attention and hyperactivity problems (6). However, based on register data alone we cannot determine to what extent receiving an epilepsy

diagnosis prior to an ADHD diagnosis reflects the actual temporal order of diagnoses and to what extent it reflects clinical practices in Sweden. Further, the mean age for first ADHD diagnosis (14 years) was relatively late in our cohort and is therefore unlikely to represent the onset of ADHD symptoms.

Finally, we found that children of mothers with epilepsy had a nearly two-fold risk increase of ADHD, compared to children of mothers who did not have epilepsy. This is consistent with previous research (14). Further, the risk of ADHD in children of mothers with epilepsy was somewhat higher than the risk in children of fathers with epilepsy. We also found a higher risk of ADHD in full-siblings and maternal half-siblings, relative to the risk in paternal half-siblings. These findings converge with evidence from familial aggregation studies of epilepsy, which have consistently reported a higher risk in children of mothers with epilepsy relative to children of fathers with epilepsy (38). Our results indicate that this maternal effect may not be specific to epilepsy, as re-running the analysis in the mother-child and father-child sub-cohorts, adjusting for epilepsy in the child, did not change the pattern of higher risk in mother-offspring pairs (OR=1.77, 95%CI=1.67-1.88) compared to father-offspring pairs (OR=1.60, 95%CI=1.50-1.70). Maternal specific transmission could have several, not mutually exclusive, interpretations. Exposure to epilepsy related factors during pregnancy may further increase the risk of ADHD, over and above familial transmission. Intrauterine exposure to certain antiepileptic drugs has been associated with an increased risk of adverse neurodevelopmental outcomes, whereas evidence for a similar risk linked to seizures during pregnancy is less clear (39). Results have also been interpreted as suggestive of maternal-specific genetic transmission, however there is currently only limited evidence for such a parent-of-origin effect (40).

Limitations

Our results must be interpreted in the context of the study limitations. We relied on register-based diagnoses of epilepsy and ADHD and did not have access to structured interviews to diagnose ADHD or neurological assessments to confirm epilepsy. Nonetheless, prior research supports the validity of register based epilepsy and ADHD diagnoses. Two previous studies have shown that majority of individuals with epilepsy in Sweden are included in the NPR (41, 42). Further, the validity of epilepsy diagnosis in the Swedish Inpatient Register (a large part of the NPR) is fairly high, with positive predictive validity estimated at 79% (42). ADHD diagnosis in the Swedish NPR have been validated against childhood psychiatric symptoms assessed in 19,150 twins, showing that 70% of children with a NPR ADHD diagnosis meet screening-cut off for ADHD based on parent ratings (43). Chart validation studies in the Danish Psychiatric Central Register, a country with similar national health-care registers to Sweden, have shown strong agreement between ADHD register diagnosis and medical chart records (44, 45). Further, research using information on ADHD from the Swedish NPR and PDR show similar heritability (46), psychiatry comorbidity (35, 43, 44, 46-52) and adverse functional outcomes (49) as research using structured interviews to diagnose ADHD (50). Together, this suggests that our definitions ADHD and epilepsy are reasonably accurate and valid. Nevertheless, the use of register-based diagnoses has limitations. Firstly, we were not able to study the association between different ADHD subtypes (inattentive, hyperactive/impulsive and combined) and different types of epilepsy; partly because the ICD definition of hyperkinetic disorder only recognizes ADHD combined subtype, and partly due to insufficient power and discriminative validity to study different types of epilepsy (53). We can therefore not rule out that the strength of association, and the underlying etiology, may differ across disorder subtypes. Second, we were not able to study the bi-

directional relationship between parental ADHD and offspring epilepsy due to poor coverage of ADHD diagnosis in the NPR prior to 2001, when the outpatient register where most ADHD cases are recorded was included (19). Third, we did not account for differential follow-up time, censoring due to death or migration after age seven, or possible misclassification due to incomplete cover of ADHD diagnoses in the NPR prior to 2001. Nonetheless, sensitivity analyses suggested that the risk estimates did not differ substantially in a restricted birth cohort with a minimum of 14 years of follow-up time and no censoring (S_1). Some ADHD cases may also have been misclassified when defining ADHD from prescription data as certain ADHD medications are also approved for the treatment of narcolepsy. Nonetheless, narcolepsy is a very rare disorder and results from sensitivity analyses excluding cases identified only in the PDR did not differ markedly from those including information from the PDR. Fourth, we cannot exclude that detection bias may have artificially inflated the risk estimates. Patients with epilepsy, and their family members, are more likely to be in contact with clinical services than the general public, thus increasing the opportunity to detect and get help for ADHD, if present. However, the increased risk among cousins, who do not share parents and rarely live together, suggests that the observed familial risk is unlikely to be entirely explained by detection bias. Finally, despite the large sample size and the indication of shared environmental effects based on the observed ICC's and CSCT's (see Table 3), the estimated shared environmental correlation was not statistically significant. Quantitative genetic models using binary variables require very large samples sizes, particularly when modelling disorders with low prevalence and associations of small effect (24). It is therefore possible that shared environmental risk factors do contribute to the familial aggregation of epilepsy and ADHD, however we did not have the power to detect such an effect.

Conclusions

We demonstrate a strong association between epilepsy and ADHD and extend previous research by showing that the association is partly explained by a shared familial liability. Our results indicate a complex relationship between epilepsy and ADHD, where both shared familial factors and risk factors unique to the individual contribute to the co-occurrence between the disorders. We found only a modest genetic correlation between the disorders, indicating that shared genetics is not the primary factor underpinning the co-occurrence of epilepsy and ADHD. Future research aimed at identifying genetic risk variants shared across epilepsy and ADHD will likely require very large sample sizes. Further, the strong contribution of unique environmental factors to the cross-disorder association suggest that research focused on environmental risk factors, including direct effects of one disorder on the other, may prove more effective. For clinicians, evidence of familial co-aggregation suggest that ADHD should not merely be regarded as an epiphenomenon of epilepsy and may aid early identification of children at risk of both disorders.

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Title Figure 1. Within-individual and family level co-aggregation of ADHD and epilepsy.

Legend Figure 1. Odds ratios (OR) represent the association between ADHD and epilepsy, within-individual, and across different types of relatives. ORs are adjusted for birth year and sex and presented together with 95% confidence intervals.

Title Figure 2. Path estimates for the bivariate ACE model presented for one sibling only

Legend Figure 2. Rectangles represent the liability for ADHD and epilepsy and are fixed at a variance of 1. Circles represent latent additive genetic (A), shared environmental (C) and non-shared environmental (E) factors. Each latent variable has a variance of 1. Values within the square root sign are the squared path estimates and represent the percentage of variance accounted for by the A, C and E parameter for each trait. Curved double-headed arrows refer to the correlations between A (r_G), C (r_C) and E (r_E) across ADHD and epilepsy. 95% confidence intervals are presented in parentheses.

Table 1. Number of relatives in each sub-cohort and a summary of the unique information provided by each relative sub-cohort to the familial aggregation analysis

Type	N Individuals	N unique pairs	N pairs in analyses	Degree of genetic and environmental sharing
Mother-offspring	1 899 654	1 899 654	1 899 654	<ul style="list-style-type: none"> ▪ Mothers share on average 50% of additive genetic factors with their offspring. ▪ Mothers provide the early rearing environment to their offspring. ▪ Mothers also provide the in-utero environment to their offspring. ▪ A higher risk in mother-offspring than father-offspring pairs suggest a maternal-specific effect, over and above shared familial factors.
Father-offspring	1 899 654	1 899 654	1 899 654	<ul style="list-style-type: none"> ▪ Fathers share on average 50% of additive genetic factors. ▪ Fathers provide the early rearing environment to their offspring.
Full-siblings	1 312 567	914 824	1 829 684	<ul style="list-style-type: none"> ▪ Full-siblings share on average 50% of additive genetic factors. ▪ Environmental sharing is assumed to be 100%. ▪ Share pregnancy related factors, constant in the mother across pregnancies. ▪ A higher risk in full-siblings pairs, compared to half-siblings, indicate the importance of genetic factors.
Maternal half-siblings	193 186	136 269	273 924	<ul style="list-style-type: none"> ▪ Maternal half-siblings share on average 25% of additive genetic factors. ▪ Environmental sharing is assumed to be 100%. ▪ Share pregnancy related factors, constant in the mother across pregnancies. ▪ A higher in risk maternal versus paternal half-siblings indicates the importance of shared environmental factors, as they share their environment to a greater extent.
Paternal half-sibling	183 938	134 502	269 004	<ul style="list-style-type: none"> ▪ Paternal half-siblings share on average 25% of additive genetic factors. ▪ Environmental sharing is <100%, and is assumed to be 0% in quantitative genetic analysis, as children tend to reside predominantly with mothers after parental separation.
Full cousins	1 413 024	2 790 270	5 580 540	<ul style="list-style-type: none"> ▪ Full cousins share on average 12.5% of additive genetic factors. ▪ Environmental sharing is assumed to be 0% as cousins rarely reside together in Sweden. ▪ An observed risk across cousins provides strong support for the importance of genetic factors, since environmental sharing tends to be minimal across cousins.

¹ N of unique pairs refers to the unique number of relative pairs in the cohort. ² N pairs in analyses refer to the number of possible pair combinations that contributed to the analyses.

Table 2. Prevalence of epilepsy and ADHD, age of first diagnosis and % female in full cohort (N= 1,899,654) born 1987-2006

	N Cases Min 1 Diagnosis	N Cases ≥ 2 Diagnoses	Mean age first diagnosis (SD)	% Female
Epilepsy	20 625 (1.09%)	15 634 (0.82%)	9.29 (6.23)	47.24%
ADHD	82 399 (4.34%)	51 239 (2.70%)	13.72 (4.85)	33.54%
Comorbid cases	2789 (0.15%)	1463 (0.08%)	8.88 (5.94)/ 12.10 (5.01)	35.14%

Abbreviation: SD, standard deviation.

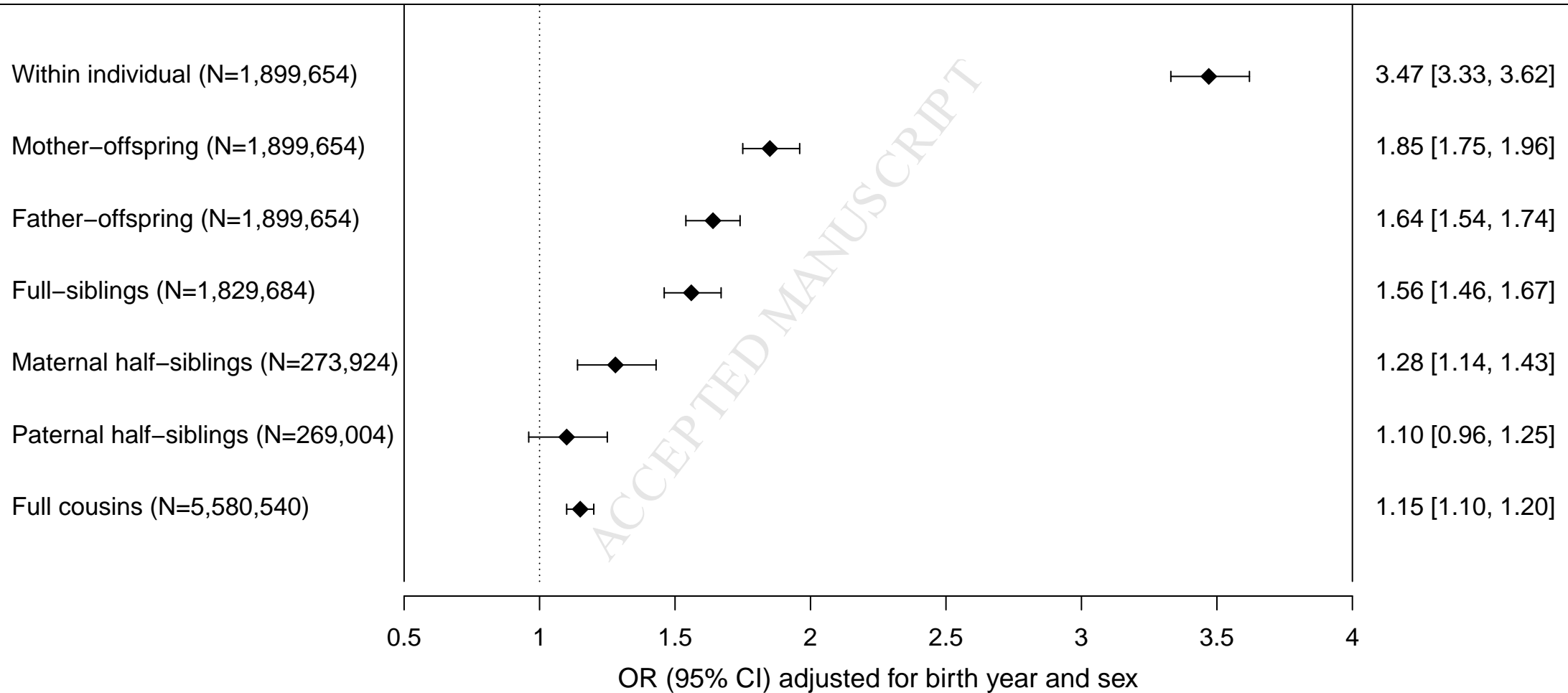
¹Prevalence refers to the number of diagnosed individuals in the cohort at the end of follow-up (December 31st, 2013). ²N Cases ≥ 2 only includes cases identified via the National Patients Register. In this definition of epilepsy, codes ICD-9, 345Q and ICD-10, G41 (Status Epilepticus) were excluded. ³In comorbid cases, age at first diagnosis is presented first for epilepsy and second for ADHD.

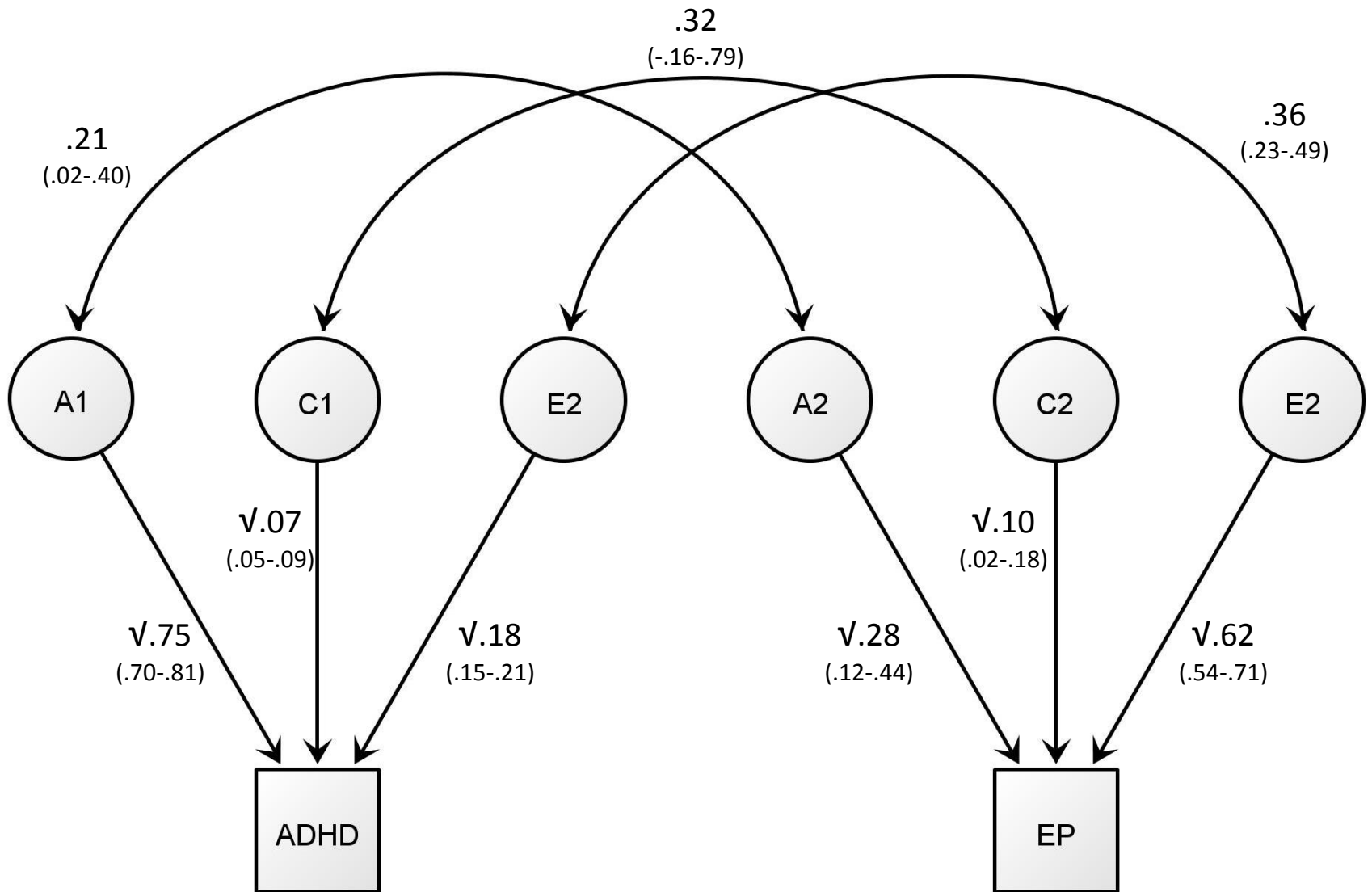
Table 3. Phenotypic, intra-class and cross-trait-cross-sibling correlations between ADHD and epilepsy, presented with 95% confidence intervals

	N pairs	N Concordant Pairs	Phenotypic r	ICC ADHD	ICC EP	CTCS
Full cohort	1 186 306	946	0.24 (0.23-0.25)	na	na	na
Full-siblings	914 842	598	0.25 (0.24-0.26)	0.45 (0.44-0.45)	0.24 (0.22-0.26)	0.08 (0.06-0.09)
Maternal half-siblings	136 962	198	0.22 (0.20-0.25)	0.26 (0.24-0.27)	0.17 (0.12-0.22)	0.04 (0.01-0.07)
Paternal half-siblings	134 502	150	0.22 (0.19-0.24)	0.19 (0.17-0.20)	0.07(0.02-0.13)	0.01(-0.02-0.05)

Abbreviation: ICC, intra-class correlation. CTCS, cross-trait-cross-sibling correlation. na, not applicable.

¹N concordant pairs refer to the number of sibling pairs where one sibling had a diagnosis of epilepsy and the other sibling a diagnosis of ADHD. 95% confidence intervals are presented in brackets.





**Familial Liability to Epilepsy and Attention-Deficit/Hyperactivity Disorder:
A Nationwide Cohort Study**

Supplementary Information

Supplementary Table S1. Sensitivity analyses of the within-individual and full-sibling association between epilepsy and ADHD

Supplementary Table S2. Odds ratios (ORs) and 95% confidence interval (CI) from sensitivity analyses stratified by sex

Supplementary Table S3. Genetic and environmental parameter estimates with Bootstrap standard errors and 95% confidence interval

Table S1. Sensitivity analyses of the within-individual and full-sibling association between epilepsy and ADHD

Model	N of individuals	Within-individual OR (95% CI)	N of pairs	Full siblings OR (95% CI)
Crude Estimates	1,899,654	3.53 (3.39-3.68)	1,829,684	1.56 (1.46-1.67)
Model 1	1,899,654	3.68 (3.45-3.89)	1,829,684	1.54 (1.40-1.69)
Model 2	514,345	3.11(2.90-3.34)	223,520	1.72 (1.49-1.99)
Model 3	na	na	1,829,684	1.46 (1.37-1.56)
Model 4	na	na	1,829,684	1.13 (1.06-1.21)

¹ Odd's ratios (OR) represent the risk of ADHD in individuals with a relative with epilepsy, compared to the risk in individuals without a relative with epilepsy. ² Excluding crude estimates, all estimates are adjusted for sex and birth-year of both outcome and exposure person.

Model 1. Stricter definition of exposure and outcome. 2 \geq ADHD and epilepsy diagnoses from the National Patient register. Information from the PDR were excluded, as were individuals with only a diagnosis of status epilepticus (ICD codes G41,345Q) and no other epilepsy diagnosis.

Model 2. Restricted birth-cohort born 1994-1999, excluding all individuals with a record of death or migration during follow-up.

Model 3. OR comparing the risk of ADHD in individuals with a relative with epilepsy, to the risk in individuals without a relative with epilepsy, adjusting for epilepsy in the outcome person.

Model 4. OR comparing the risk of ADHD in individuals with a relative with epilepsy, to the risk in individuals without a relative with epilepsy, adjusting for ADHD in the exposure person.

Table S2. Odds ratios (ORs) and 95% confidence interval (CI) from sensitivity analyses stratified by sex

Within Individual			
		OR (95% CI)	N
Male		3.41 (3.24-3.59)	972,428
Female		3.56 (3.32-3.81)	927,226
Full-siblings			
Exposure person	Outcome person	OR (95% CI)	N
Male	Male	1.66 (1.49-1.85)	483,218
Female	Female	1.52 (1.29-1.78)	432,264
Male	Female	1.64 (1.42-1.89)	457,101
Female	Male	1.43 (1.27-1.60)	457,101

¹Odds ratios (ORs) and 95% confidence interval (CI) expressing the association between epilepsy and ADHD, stratified by sex. OR are presented for the within-individual association in the full cohort and for the within-family association in full-siblings. ²N refers to number of individuals for the within individual analysis and number of pairs for the full sibling-analyses. ³All models were adjusted for birth-year of both exposure and outcome person.

Table S3. Genetic and environmental parameter estimates with Bootstrap standard errors and 95% confidence interval

Parameter	Estimate	SE	Lower bound 95% CI	Upper bound 95% CI	p-value
rG	.21	.10	.02	.40	.028
rC	.32	.24	-.16	.79	.191
rE	.36	.07	.23	.49	<.001
% PC due to A	40	16	9	70	.011
% PC due to C	11	7	-3	25	.135
% PC due to E	49	9	32	67	<.001
% ADHD due to A	75	3	70	81	<.001
% ADHD due to C	7	1	5	9	<.001
% ADHD due to E	18	2	15	21	<.001
% Epilepsy due to A	28	8	12	44	.001
% Epilepsy due to C	10	4	2	18	.013
% Epilepsy due to E	62	4	54	71	<.001

¹ Reported parameter estimates were derived based on data from available pairs of full-siblings (914,842), maternal half-siblings (136,962) and paternal half-siblings (134,502) in the full cohort. Reported standard errors (SE), 95% confidence intervals (CI) and p-values were derived using bootstrap resampling (see method section for details). rG, genetic correlation; rC, shared environmental correlation; rE, non-shared environmental correlation. PC, phenotypic correlation; A, additive genetic effects; C, shared environmental effects; E, non-shared environmental effects.