



Psychiatric comorbidities in epilepsy: population co-occurrence, genetic correlations and causal effects

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ABSTRACT

Background Psychiatric comorbidities are common in patients with epilepsy. Reasons for the co-occurrence of psychiatric conditions and epilepsy remain poorly understood.

Aim We aimed to triangulate the relationship between epilepsy and psychiatric conditions to determine the extent and possible origins of these conditions.

Methods Using nationwide Swedish health registries, we quantified the lifetime prevalence of psychiatric disorders in patients with epilepsy. We then used summary data from genome-wide association studies to investigate whether the identified observational associations could be attributed to a shared underlying genetic aetiology using cross-trait linkage disequilibrium score regression. Finally, we assessed the potential bidirectional relationships using two-sample Mendelian randomisation.

Results In a cohort of 7 628 495 individuals, we found that almost half of the 94 435 individuals diagnosed with epilepsy were also diagnosed with a psychiatric condition in their lifetime (adjusted lifetime prevalence, 44.09%; 95% confidence interval (CI) 43.78% to 44.39%). We found evidence for a genetic correlation between epilepsy and some neurodevelopmental and psychiatric conditions. For example, we observed a genetic correlation between epilepsy and attention-deficit/hyperactivity disorder ($r_g=0.18$, 95% CI 0.09 to 0.27, $p<0.001$)—a correlation that was more pronounced in focal epilepsy ($r_g=0.23$, 95% CI 0.09 to 0.36, $p<0.001$). Findings from Mendelian randomisation using common genetic variants did not support bidirectional effects between epilepsy and neurodevelopmental or psychiatric conditions.

Conclusions Psychiatric comorbidities are common in patients with epilepsy. Genetic correlations may partially explain some comorbidities; however, there is little evidence of a bidirectional relationship between the genetic liability of epilepsy and psychiatric conditions. These findings highlight the need to understand the role of environmental factors or rare genetic variations in the origins of psychiatric comorbidities in epilepsy.

INTRODUCTION

Epilepsy co-occurs with psychiatric conditions throughout life and contributes to the

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although psychiatric comorbidities are common in patients with epilepsy, the reasons for the co-occurrence of psychiatric conditions and epilepsy remain poorly understood.

WHAT THIS STUDY ADDS

- ⇒ Almost half of the 94 435 individuals diagnosed with epilepsy in Sweden were also diagnosed with psychiatric conditions during their lifetime.
- ⇒ Some psychiatric conditions share an underlying genetic architecture with epilepsy, which may be more pronounced in focal epilepsy.
- ⇒ Mendelian randomisation analyses did not support the hypothesis that epilepsy causally increases the risk of psychiatric conditions and vice versa.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ The lack of widespread genetic correlation and effects in either direction suggests that environmental factors may explain psychiatric comorbidities in epilepsy.

challenges faced by people with epilepsy. For example, Swedish register-based studies have suggested that the lifetime prevalence of a psychiatric diagnosis among people with epilepsy is as high as 40%, compared with ~10% of the general population.¹ Individuals with epilepsy are more likely to have neurodevelopmental disorders (eg, autism, attention-deficit/hyperactivity disorder, tic disorders and obsessive-compulsive disorders) as well as other psychiatric conditions (eg, anorexia nervosa, anxiety, bipolar disorder, depression and schizophrenia). However, the reasons for these co-occurrences remain largely unknown.^{2–4}

Few large-scale studies have examined the population-wide comorbidity of epilepsy and psychiatric disorders,^{5 6} possible genetic

correlations between comorbidities⁷⁻⁹ or the direction of the effects using Mendelian randomisation (MR).^{10,11} Psychiatric comorbidities in epilepsy may be a function of shared genetic aetiology, bidirectional relationships, shared environmental aetiology, chance and artefactual processes or a combination of these.² A better understanding of the mechanisms underlying psychiatric comorbidities in epilepsy may help identify targets for the prevention or treatment of these comorbidities.

It is often suggested that the psychiatric comorbidities in epilepsy are explained by bidirectional relationships,¹² where psychiatric conditions increase the risk of epilepsy, and vice versa, that epilepsy increases the risk of psychiatric conditions. This notion is supported by a series of neurobiological pathogenic mechanisms (eg, induced abnormalities in cortical and subcortical structures).¹³ Yet, observational studies contributing to this hypothesis¹² have typically been limited in sample size, liable to confounding factors and/or have been restricted to clinical cohorts with limited generalisability.

In this study, we used novel and standard methods to triangulate the relationship between epilepsy and psychiatric conditions (online supplemental figure 1). First, using Swedish health registers, we characterised the rate of comorbidity of different psychiatric conditions in the largest nationwide cohort of individuals with epilepsy. Second, we investigated whether any comorbidities could be attributed to a shared underlying genetic architecture by assessing genetic correlations using cross-trait linkage disequilibrium score regression.^{14,15} Finally, we examined the possibility of bidirectional effects by using MR, a design that leverages the random assortment of genotypes associated with epilepsy and psychiatric disorders, and allows for the exploration of the direction of effects.¹⁶

METHODS

All research was performed in accordance with the relevant guidelines and regulations.

Swedish population-based registries

To estimate the population-level co-occurrence of epilepsy and psychiatric conditions, we derived a nationwide cohort of 7 628 495 individuals born between 1954 and 2011 from the Swedish population registries (figure 1). Using the Total Population Registry and the National Patient Registry (initiation 1969, end of follow-up 2016), we collected information on vital statistics, immigration status (born in or outside Sweden), birth year and any inpatient diagnosis (and specialised outpatient after 1997) of the investigated psychiatric conditions and epilepsy (see online supplemental table 1 for International Classification of Diseases (ICD) 8/9/10 codes). We also identified disposable income quintiles for each year between 1968 and 2016 and retained the highest quintile obtained over a person's lifetime from the Income and Taxation Registry, which we conceptualised as both a socioeconomic proxy and a measure of resilience to morbidity manifestation. Individuals born after 1996 with missing disposable income values were designated as a distinct category, as they were probably too young to have accumulated disposable income.

The National Patient Registry records the date of diagnosis and not the date of onset. Therefore, we focused solely on estimating lifetime comorbidities of epilepsy and psychiatric disorders.

Statistical methods

Logistic regression was used to estimate the crude and conditional odds ratio (OR) and 95% confidence interval (CI) of a lifetime diagnosis of psychiatric conditions among individuals

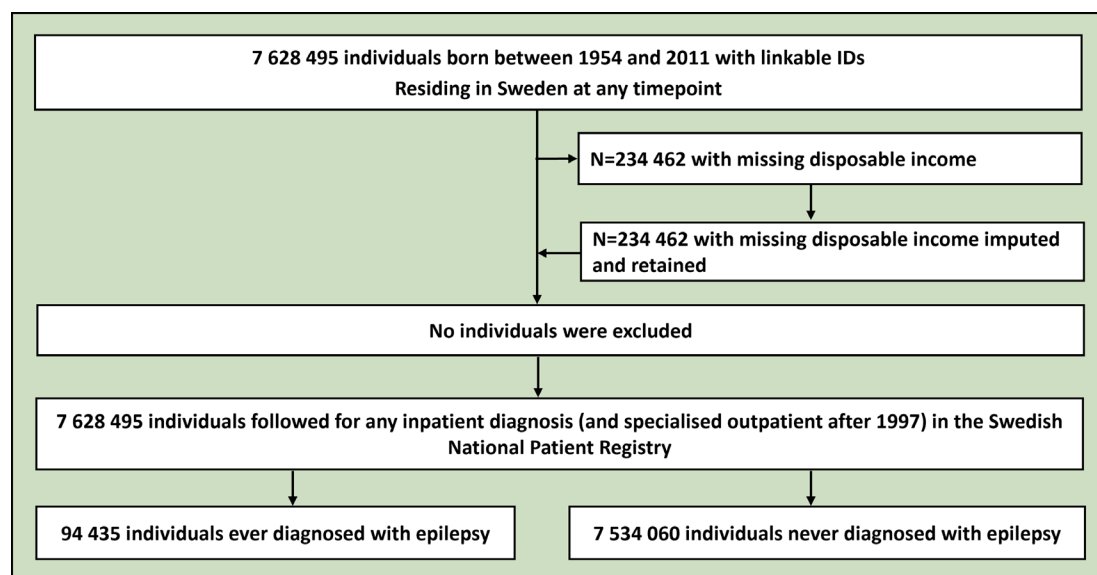


Figure 1 Flowchart depicting the derivation of the analytical sample from the Swedish registry data. No individuals were excluded from the analysis. Those missing disposable income were imputed, as they were either too young to have accumulated any disposable income, or this information was missing. Further details are available in the text.

ever diagnosed with epilepsy (n=94435) compared with those who were never diagnosed (n=7 534 060), controlling for birth year, sex, highest disposable income achieved and immigration status. We also estimated the crude and counterfactual probabilities of the outcomes (holding all covariates at their initial values). Hereafter, we refer to this quantity as the adjusted lifetime prevalence. This is because it captures the estimated prevalence among those with epilepsy if they had the same covariate distribution as those without epilepsy, and vice versa. In the primary analysis, we did not separate the types of epilepsy, as they are often not well characterised in the National Patient Registry and because many people with epilepsy often have multiple seizure types. However, in a complementary analysis, we classified individuals based on the most recent instance in which they received either a focal (n=24430, 25.9%) or generalised epilepsy diagnosis (n=19199, 20.3%), although some individuals remained uncharacterised (either unspecific (n=32468, 34.4%) or were never coded with sufficient detail (n=18079, 19.1%)). We chose not to classify 259 (0.3%) individuals who were discharged with both focal and generalised ICD codes on their most recent visit. In principle, there should be no missing data in the analysed variables (reporting mandated by Swedish law). However, there was some missing data in disposable income ($\approx 3\%$), and we treated these as a distinct income category.

Genome-wide association data sources and phenotypes

Summary statistics were retrieved from the largest European ancestry genome-wide association study (GWAS) of epilepsy performed by the International League Against

Epilepsy (ILAE) Consortium on Complex Epilepsies.⁷ In brief, all epilepsy cases were classified according to ILAE standard and all phenotypes were assessed by epilepsy specialists at individual sites. Controls (persons without epilepsy) were derived from the available population-based datasets within the Consortium on Complex Epilepsies and partially screened for the presence of neurological conditions. Extended phenotypic information is available in the original publication.⁷ To reduce bias from population stratification, we limited our investigation to a European ancestry sample, which was identified using principal component analysis in the original GWAS.⁷ Given the phenotypic and genetic heterogeneity of epilepsies, we retrieved summary statistics separately for epilepsy (all epilepsies) (n cases=27559), focal epilepsies (n cases=14939) and genetic generalised epilepsies (n cases=6952) (table 1) per the diagnoses of epilepsy specialists in the original GWAS.⁷

We then extracted summary statistics from the European ancestry GWAS of commonly studied psychiatric comorbidities of epilepsy (table 1). The recent ILAE GWAS⁷ performed linkage disequilibrium score regression (LDSC) on some psychiatric phenotypes. However, we extended this analysis by using larger GWAS datasets and investigating a broader spectrum of psychiatric conditions. These included GWAS on anorexia nervosa,¹⁷ anxiety,¹⁸ attention-deficit/hyperactivity disorder,¹⁹ autism,²⁰ bipolar disorder,²¹ depression,²² intelligence,²³ obsessive-compulsive disorder,²⁴ schizophrenia,²⁵ suicide attempts²⁶ and tic-disorders (Tourette syndrome).²⁷

Table 1 The investigated phenotypes, number of cases and controls contributing to the GWAS and the number of single-nucleotide polymorphisms qualifying as instruments for Mendelian randomisation

Phenotype	Study/Consortium	N cases	N controls	Number of instruments (mean F-statistic)
Epilepsy (broadly defined)*	ILAE ⁷	27 559	42 436	36–42 (25.38–25.54)
Generalised epilepsy	ILAE ⁷	6952	42 436	65–80 (27.63–27.93)
Focal epilepsy	ILAE ⁷	14 939	42 436	24–28 (23.06–23.15)
Anorexia nervosa	Watson <i>et al</i> ¹⁷	16 992	55 525	39 (24.33)
Anxiety disorder	Otowa <i>et al</i> ¹⁸	7016	14 745	3 (26.21)
Attention-deficit/hyperactivity disorder	Demontis <i>et al</i> ¹⁹	38 691	186 843	102 (27.19)
Autism	Grove <i>et al</i> ²⁰	18 381	27 969	21 (24.26)
Bipolar disorder	Mullins <i>et al</i> ²¹	41 917	371 549	187 (27.14)
Depression	Als <i>et al</i> ²²	176 143	528 770	174 (27.85)
Intelligence	Savage <i>et al</i> ²³	269 867	–	487 (30.96)
OCD	IOCDF-GC and OCGAS ²⁴	2688	7037	7 (22.04)
Schizophrenia	Trubetskoy <i>et al</i> ²⁵	67 390	94 015	489 (32.35)
Suicide attempts	Mullins <i>et al</i> ²⁶	26 590	492 022	29 (24.32)
Tic-disorders (Tourette syndrome)	Yu <i>et al</i> ²⁷	4819	9488	9 (23.81)

*For epilepsy, the number of instruments and mean F-statistic varied (past the decimal) due to individual harmonisation to outcome GWAS (a procedure employed to maximise power), reported values represent the minimum and maximum values. GWAS, genome-wide association studies; ILAE, International League Against Epilepsy; IOCDF-GC, International Obsessive Compulsive Disorder Foundation Genetics Collaborative; OCD, obsessive-compulsive disorder; OCGAS, OCD Collaborative Genetics Association Studies.

Detailed descriptions of the phenotypes and GWAS analyses can be found in the original publications.^{17–27}

Genetic correlations—cross-trait linkage disequilibrium score regression

To quantify the genetic correlation between epilepsy and psychiatric comorbidities, we employed cross-trait LDSC.^{14,15} LDSC leverages the pattern of linkage disequilibrium among common genetic variants to estimate the genetic correlation across phenotypes.¹⁵ We obtained precomputed linkage disequilibrium scores based on the 1000 Genomes Project European Reference Panel. We estimated the LDSC using an unconstrained intercept to allow for sample overlap and population stratification. Univariate LDSC criteria for consistent estimation appeared to be generally satisfied (heritability Z-score >1.5, mean χ^2 >1.02, single-nucleotide polymorphism (SNP) heritability intercept 0.9 to 1.1).²⁸ A Bonferroni correction of 11×3 test was applied for the genetic correlation analysis ($\alpha=0.001515$).

Mendelian randomisation

To assess the potential effect of epilepsy on psychiatric conditions and these conditions on epilepsy, we employed bidirectional two-sample MR. MR is based on the principles of instrumental variable analysis using common genetic variants that are robustly associated with a phenotype (exposure) of interest as instruments, yielding an estimate of the causal effect of genetic liability for a phenotype on the outcome of interest if the genetic variant is a valid instrument.¹⁶ A genetic variant is a valid instrument if (i) it is robustly associated with the exposure (relevance), (ii) it is not associated with any measured/unmeasured confounders of the exposure-outcome associations (independence) and (iii) it does not affect the outcome via pathways other than the potential effect on the exposure of interest (exclusion restriction).²⁹ Importantly, as genetic variants are fixed at conception and randomly assorted during meiosis, MR is considered robust against reverse causality and many forms of environmental confounding factors.

In two-sample MR, SNP-exposure and SNP-outcome estimates are extracted from two independent GWASs of the same underlying population.²⁹ In bidirectional MR, the procedure is repeated in both postulated directions in separate analyses.

To derive the instruments for our MR analyses, we pooled exposure and outcome GWAS data and excluded non-overlapping SNPs. To retain the highest number of SNPs, we repeated this procedure for each psychiatric GWAS separately. From these datasets, we then extracted all variants with a p value $<5 \times 10^{-6}$, a threshold employed to maximise power. This inclusive approach may, under some scenarios, lead to a conservative estimate in the two-sample MR because of weak instruments (so-called weak instrument bias), assuming the absence of sample overlap between GWASs. The same p value threshold has been previously employed in studies of psychiatric phenotypes.³⁰ The identified variants were clumped

using PLINK LD-clumping, with an $R^2 < 0.01$ and a 10000 kb window, based on the 1000 Genome European phase III reference panel. SNPs from the epilepsy GWAS were then extracted from the GWAS of each outcome and harmonised to ensure that the effect estimates were expressed on the same allele.³¹

For the primary analysis, we employed the inverse-variance-weighted (IVW) method, which estimates the causal effect under the assumption that all instruments are valid.²⁹ Specifically, the IVW method is the ratio of SNP-exposure and SNP-outcome associations weighted by their relative precision. Because the assumptions of IVW are strong³² (eg, no horizontal pleiotropy), we performed a series of standard sensitivity analyses to assess the robustness of the IVW causal effect estimates (see online supplemental material). A Bonferroni correction of 11×3×2 test was applied for the MR ($\alpha=0.00075758$).

RESULTS

Population-wide lifetime comorbidity

We observed substantial psychiatric morbidity among patients with epilepsy. Almost half of all individuals diagnosed with epilepsy were also diagnosed with a (neuro-) psychiatric disorder in their lifetime (adjusted lifetime prevalence (%) 44.09, 95% CI 43.78 to 44.39; OR 4.60, 95% CI 4.54 to 4.66, $p < 0.001$) (figure 2A), compared with 15.52% among those with no diagnosis of epilepsy (adjusted lifetime prevalence (%) 15.52, 95% CI 15.50 to 15.55) (for extended results, see online supplemental table 2). Each of the considered psychiatric disorders was more common among those diagnosed with epilepsy (figure 2B), than among those who were not, although the absolute lifetime prevalence of specific psychiatric disorders varied according to the underlying prevalence in the population. There was no apparent distinction between the co-occurrence of neurodevelopmental and psychiatric disorders; both forms of comorbidity were more common among those with epilepsy. The highest relative occurrence was observed for autism (OR 6.09, 95% CI 5.93 to 6.26) and intellectual disability. Intellectual disability was 27 times more common among those with epilepsy (adjusted lifetime prevalence (%) 11.12, 95% CI 10.94 to 11.30; OR 27.51, 95% CI 26.9 to 28.12), compared with those not diagnosed with epilepsy (adjusted lifetime prevalence (%) 0.51, 95% CI 0.51 to 0.52).

The estimated lifetime comorbidity did not materially differ before or after controlling for covariates, although all estimates were elevated in crude analysis (unadjusted lifetime prevalence of any psychiatric diagnosis (%) 48.61, 95% CI 48.29 to 48.93; OR 5.16, 95% CI 5.09 to 5.23, $p < 0.001$) (online supplemental figure 2 and online supplemental table 2). Lifetime comorbidity did not vary materially between men and women (online supplemental figure 3) or between focal and generalised epilepsy (online supplemental figure 4) and was not limited to recent birth cohorts (online supplemental figure 5).

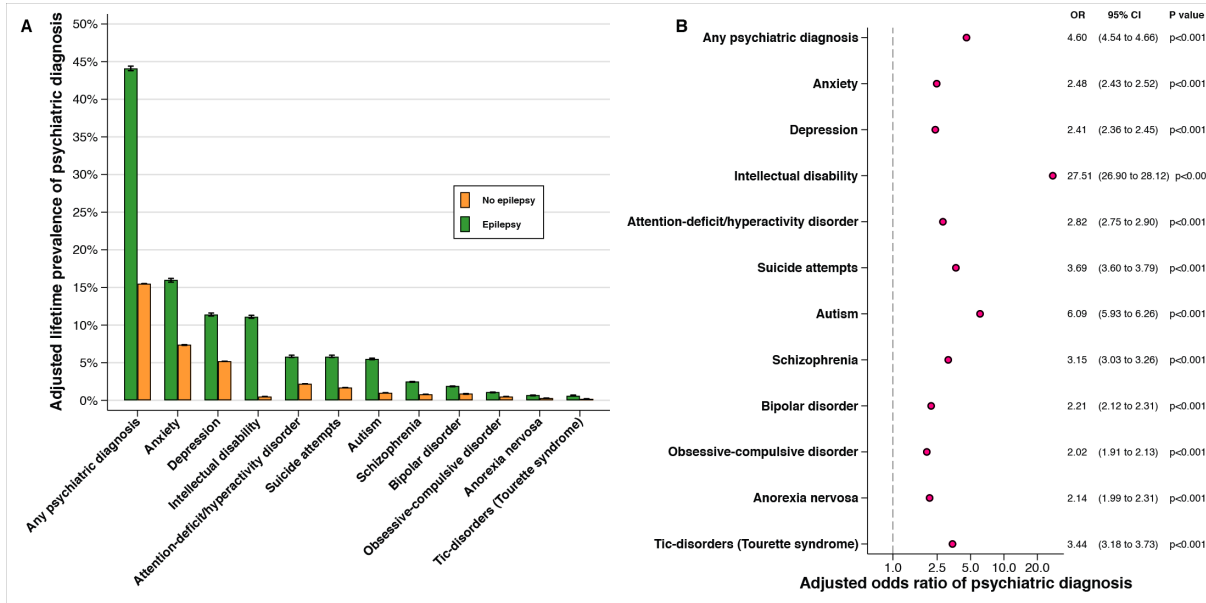


Figure 2 The population-wide co-occurrence of epilepsy and psychiatric morbidities. (A) The adjusted (marginal) lifetime prevalence of psychiatric diagnoses among those with (n=94 435) and without an epilepsy diagnosis (n=7 534 060). (B) The adjusted (conditional) OR of psychiatric diagnoses comparing those with and without an epilepsy diagnosis. All analyses are adjusted for birth year, sex, highest achieved disposable income and immigration status. Both panels are sorted according to the adjusted lifetime prevalence among those with an epilepsy diagnosis. Black lines indicate 95% CIs in both panels (CIs are plotted in (B) but they are smaller than the marker size, reflecting our large sample size). CI, confidence interval; OR, odds ratio.

Genetic correlation

We observed a positive genetic correlation between epilepsy and attention-deficit/hyperactivity disorder ($r_g=0.18$, 95% CI 0.09 to 0.27, $p<0.001$) (figure 3) (for extended results see online supplemental tables 3–5). The genetic correlation between epilepsy and

attention-deficit/hyperactivity disorder was more pronounced for focal epilepsy ($r_g=0.23$, 95% CI 0.09 to 0.36, $p<0.001$). Furthermore, we identified a negative genetic correlation between epilepsy and intelligence ($r_g=-0.20$, 95% CI -0.28 to -0.13 , $p<0.001$), which was also more pronounced for focal epilepsy ($r_g=-0.24$, 95%

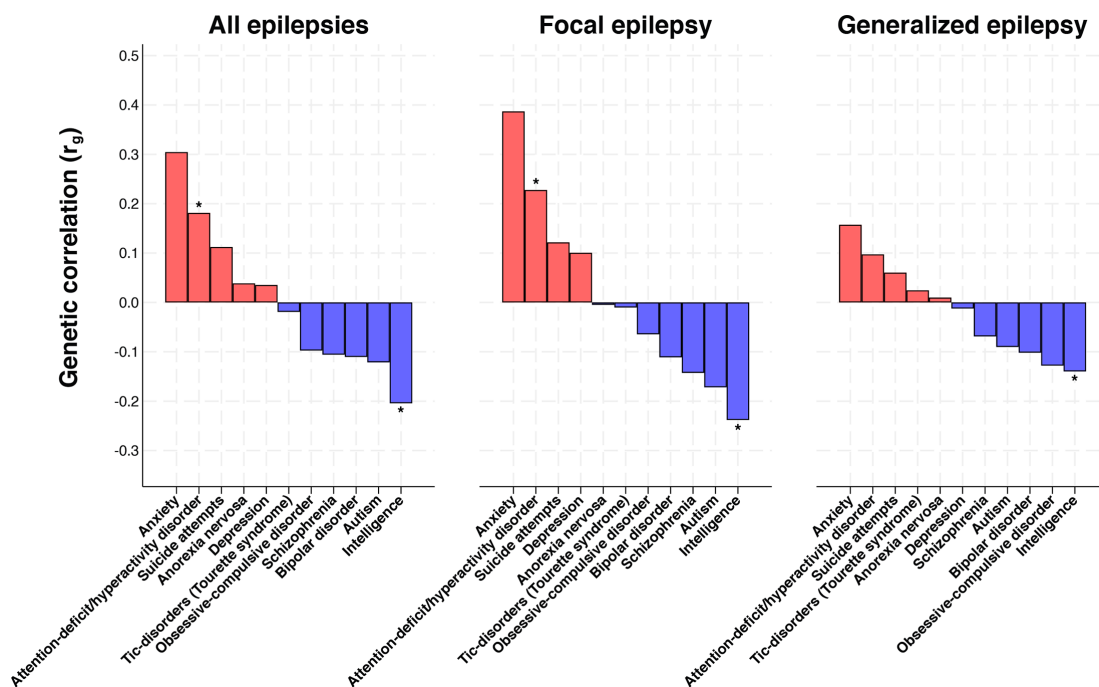


Figure 3 The genetic correlation between epilepsy (all epilepsies, generalised and focal) and common psychiatric comorbidities of epilepsy. Estimates represent the genetic correlation obtained from cross-trait linkage disequilibrium score regression. Asterisks reflect a p value lower than the Bonferroni-corrected threshold ($\alpha=0.001515$).

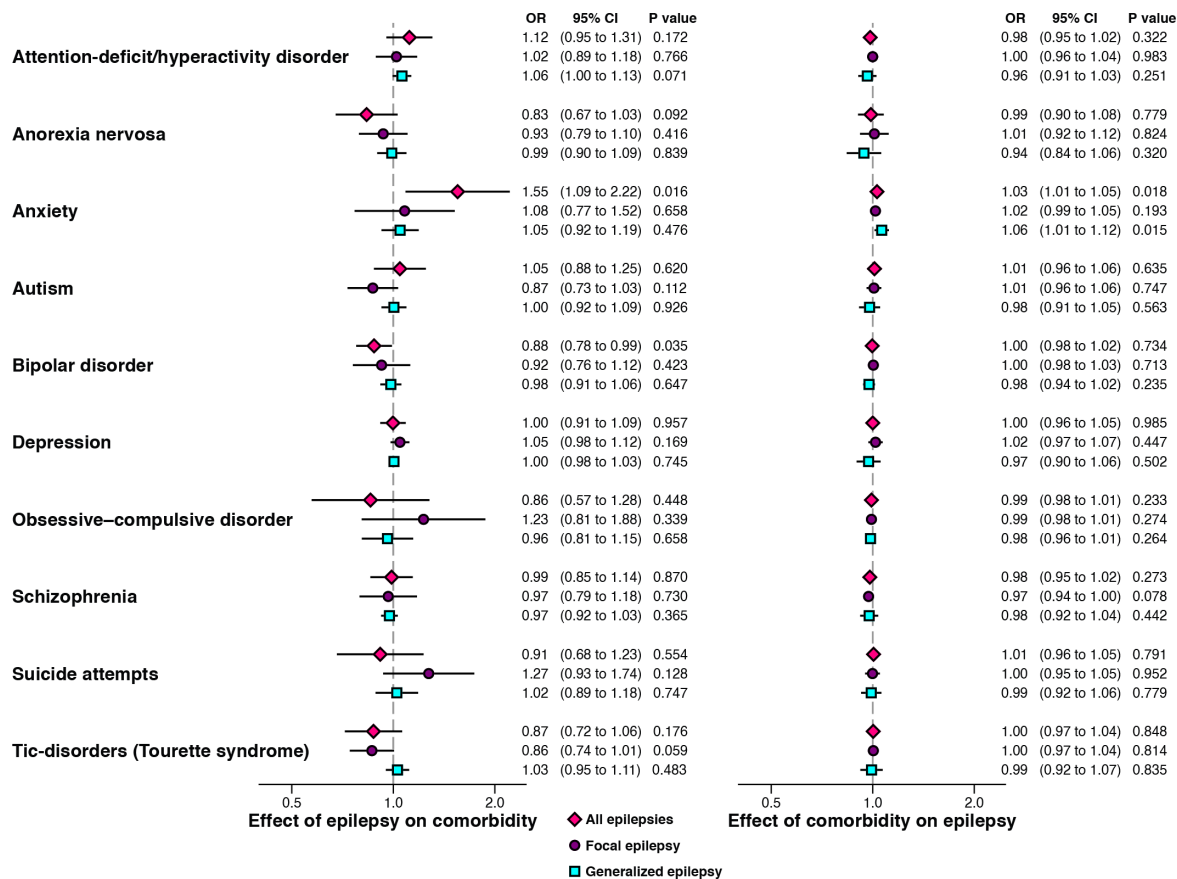


Figure 4 The bidirectional relationship between genetic liability to epilepsy (all epilepsies, generalised and focal) and genetic liability to common psychiatric comorbidities of epilepsy. The estimates are ORs obtained from an inverse-variance weighted regression, which assumes that all variants are valid instruments. Findings for intelligence are presented in-text, as intelligence is measured on a continuous scale and therefore not scale-comparable to the other traits. Both x-axes are plotted on the natural logarithmic scale. CI, confidence interval; OR, odds ratio.

CI -0.36 to -0.12, $p < 0.001$). The negative genetic correlation between epilepsy and intelligence may be consistent with the observational association between epilepsy and intellectual disability, as the intelligence scale is inversely related to intellectual disability. We observed modest-to-weak genetic correlations between the remaining psychiatric disorders and epilepsy, regardless of the type of epilepsy (figure 3).

Mendelian randomisation

In the MR analyses, limited evidence existed of an association between genetic liability to epilepsy and any of the considered psychiatric conditions after Bonferroni correction (figure 4) (for extended results, see online supplemental tables 3–5). The largest observed association was for genetic liability to epilepsy and anxiety disorder, which did not pass Bonferroni correction ($p > 0.000758$). Specifically, genetic liability to epilepsy was associated with an increased likelihood of anxiety disorder (OR 1.55, 95% CI 1.09 to 2.22, $p = 0.016$); a finding that was not replicated in sensitivity analysis (online supplemental methods and online supplemental table 7).

Limited evidence existed of an association between genetic liability to most psychiatric conditions and epilepsy (figure 4). One exception was intelligence.

Genetic predisposition to higher intelligence reduced the likelihood of epilepsy (OR 0.89, 95% CI 0.85 to 0.93, $p < 0.001$), and the focal (OR 0.88, 95% CI 0.84 to 0.92, $p < 0.001$) and generalised subtypes of epilepsy (OR 0.87, 95% CI 0.87 to 0.94, $p < 0.001$).

Although there were strong assumptions in our primary MR analysis (IVW), our findings were mostly consistent across sensitivity analyses (online supplemental table 7). Generally, our sensitivity analysis was inconsistent with widespread horizontal pleiotropy in our MR analysis (online supplemental figure 6 and online supplemental table 6). That is, the MR-Egger intercepts did not suggest that the selected genes were invalid instruments through an independent effect on the outcome (violation of the third MR assumption: exclusion restriction).

DISCUSSION

Main findings

Using data from nationwide health registries in Sweden, we found that individuals with epilepsy had a substantially higher prevalence of neurodevelopmental and psychiatric comorbidities. Using cross-trait linkage disequilibrium analysis, we found genetic correlations between epilepsy

and certain psychiatric conditions, which, in some cases, such as attention-deficit/hyperactivity disorder, were more pronounced in focal epilepsy. The majority of genetic correlations observed between epilepsy and psychiatric conditions were modest, supporting the partial role of a genetic basis for these comorbidities. Finally, by leveraging common genetic variations, we did not find strong evidence to suggest that these comorbidities are explained by the effects of epilepsy on psychiatric conditions or psychiatric conditions on epilepsy. Taken together, these findings suggest that there are important genetic correlations between epilepsy and some psychiatric conditions. However, these are unlikely to explain the full extent of psychiatric comorbidities in epilepsy.

Our finding that the genetic correlation between epilepsy and attention-deficit/hyperactivity disorder is more pronounced in focal epilepsy is novel, although the general correlation between epilepsy and attention-deficit/hyperactivity disorder is consistent with recent work.^{9 33} For example, a recent study on the co-aggregation of epilepsy and attention-deficit/hyperactivity disorder in Swedish families found a strikingly similar genetic correlation (0.21, 95% CI 0.02 to 0.40),³³ although they were unable to explore subtypes of epilepsy. Our findings suggest that focal epilepsy is the main cause of this association. This contrasts with the aim of a previous study that examined generalised epilepsy because of its higher heritability.⁹ However, using updated GWAS data, we also confirmed the identification of a shared genetic overlap between epilepsy and attention-deficit/hyperactivity disorder.⁹ Although focal epilepsy has a lower heritability than generalised epilepsy,⁷ our findings suggest that pleiotropic genes are distinctly associated with focal epilepsy and attention-deficit/hyperactivity disorder. However, we noted that there was no substantial difference in the population-wide prevalence of psychiatric comorbidities between focal and generalised epilepsy (online supplemental figure 4), although subtype characterisation of epilepsy in Swedish registries may not be accurately recorded, and many individuals may have multiple seizure types.

Consistent with the population rate of intellectual disability among those with epilepsy (OR 27.5, $p < 0.001$), we found that epilepsy and intelligence had a negative genetic correlation, and that genetic liability to higher intelligence was associated with a lower risk of epilepsy. Our findings are consistent with a shared genetic aetiology of intellectual disability and epilepsy. However, it is important to acknowledge that intelligence and intellectual disability are two distinct phenotypes. We were only able to perform MR and genetic correlation analyses of intelligence because of the absence of GWAS data for intellectual disabilities.

Intriguingly, using MR, we were unable to confirm the common assumption that epilepsy is a 'cause' of an increased risk of psychiatric disorders, or that these disorders are a 'cause' for an increased risk of epilepsy.¹² This finding should be interpreted in light of the MR

assumptions being met and the possibility of the role of rare genetic variations not captured within the GWAS data which comprise common variants.

However, this finding may also indicate the importance of environmental factors in the origin of psychiatric comorbidities in epilepsy. Future work could help identify the causal role of such factors (eg, prenatal or perinatal events unique to the individual, or discrimination, stigma and life events during the individual's lifetime, which are common risk factors for several neurological and psychiatric phenotypes^{2 33 34}), ideally using causal triangulation across study designs with orthogonal sources of bias.

Limitations

An important limitation to note is that existing epilepsy and psychiatric conditions GWAS are not sufficiently large, potentially leading to reduced power in identifying genetic correlations, and necessitating an inclusive threshold ($p < 5 \times 10^{-6}$) to identify instruments for MR analyses. Although this threshold has been widely employed in previous studies, the possibility of reduced specificity in instrument selection, leading to weak instrument bias, cannot be ruled out. Analyses like ours, repeated using a larger GWAS, when available, may provide stronger evidence. Furthermore, rare genetic variants are known to play an important role in the aetiology of epilepsy,⁷ and their contribution to psychiatric comorbidities in epilepsy cannot be excluded. Although rare genetic variants may not be sufficiently common in the population to explain the high rates of psychiatric conditions reported in observational studies including our nationwide study, they may still be common among individuals with epilepsy. Nonetheless, future studies will help clarify the role of rare genetic variants in the overlap between psychiatric conditions and epilepsy. We were also unable to perform any age-stratified or sex-stratified cross-trait genetic analysis; however, this could be a target for future analysis if sex-stratified GWAS data were available. Another limitation of the Swedish data analysis is that our study relied on the accuracy of the epilepsy and psychiatric diagnoses recorded in the registers. Validation studies of epilepsy³⁵ and a range of psychiatric and neurodevelopmental conditions suggest a high validity of these recorded diagnoses. However, the possibility of measurement bias in the data cannot be excluded. This limitation is common across large-scale epidemiological studies. Further large-scale efforts to estimate the burden of psychiatric conditions among people with epilepsy are warranted, with particular emphasis on including diverse and heterogeneous populations. Future work based on high-resolution phenotyping of smaller representative cohorts will shed further light on the complexities of the relationships studied.

Implications

Our study confirms the notable prevalence of psychiatric comorbidities among individuals with epilepsy and provides mechanistic insights into this co-occurrence. These findings underscore the importance of comprehensive patient care that acknowledges and addresses associated conditions during epilepsy diagnosis and treatment. This is particularly

important, as psychiatric comorbidities notably impact the prognosis of epilepsy, influencing mortality and life expectancy.^{36,37} While our study revealed some genetic correlations suggesting a potential genetic contribution to comorbidities, it did not strongly support bidirectional relationships. Consequently, our study emphasises the importance of exploring alternative factors, including environmental influences and rare genetic variations, to unravel the origins of psychiatric comorbidities in epilepsy. Understanding the underlying causes of comorbidities is crucial, as it can guide treatment decisions and offer more effective strategies for managing both epilepsy and associated psychiatric conditions. This may enhance the overall quality of care for individuals affected by epilepsy.

In conclusion, psychiatric comorbidities are common in patients with epilepsy. Genetic correlations may partly explain some comorbidities; however, little evidence exists of a bidirectional relationship between the genetic liability of epilepsy and psychiatric conditions. These findings highlight the need to understand the role of environmental factors or rare genetic variations in the origins of psychiatric comorbidities in epilepsy.

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Contributors VHA (CA) and DR conceptualised the study. VHA performed the formal analysis, drafted the original manuscript, had full access to all the data in the study, takes responsibility for the integrity of the data and the accuracy of the data analysis, and accepts full responsibility for the work as a guarantor. DR supervised the study. BKL, KL, CN, DR, NMD, CM and TT were involved in funding acquisition. ML performed data curation of Swedish registries. C Dardani, PMD, HF, JR, CZ, RMG, C Dalman, DB, and all other authors, critically revised the manuscript for important intellectual content and contributed to the development of the study methodology.

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Patient consent for publication Not applicable.

Ethics approval The Swedish Ethical Review Authority (DNR 2010/1185-31/5) gave ethical approval for the registry-based analysis and waived the need for informed consent. All genome-wide association studies-based analyses were performed using publicly available data and were covered by ethical approval in the original studies.

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Data availability statement No data are available. All genetic data produced in this study are publicly available in their original publication and upon reasonable request from the authors. Swedish privacy laws prohibit the authors from making registry data publicly available. The data supporting these findings were used under licence and ethical approval for this study. Readers interested in obtaining microdata or replicating this study may seek similar approval and enquiries from Statistics Sweden. For further advice, see <https://www.scb.se/en/services/guidance-for-researchers-and-universities/>, or contact Statistics Sweden at mikrodata@scb.se.

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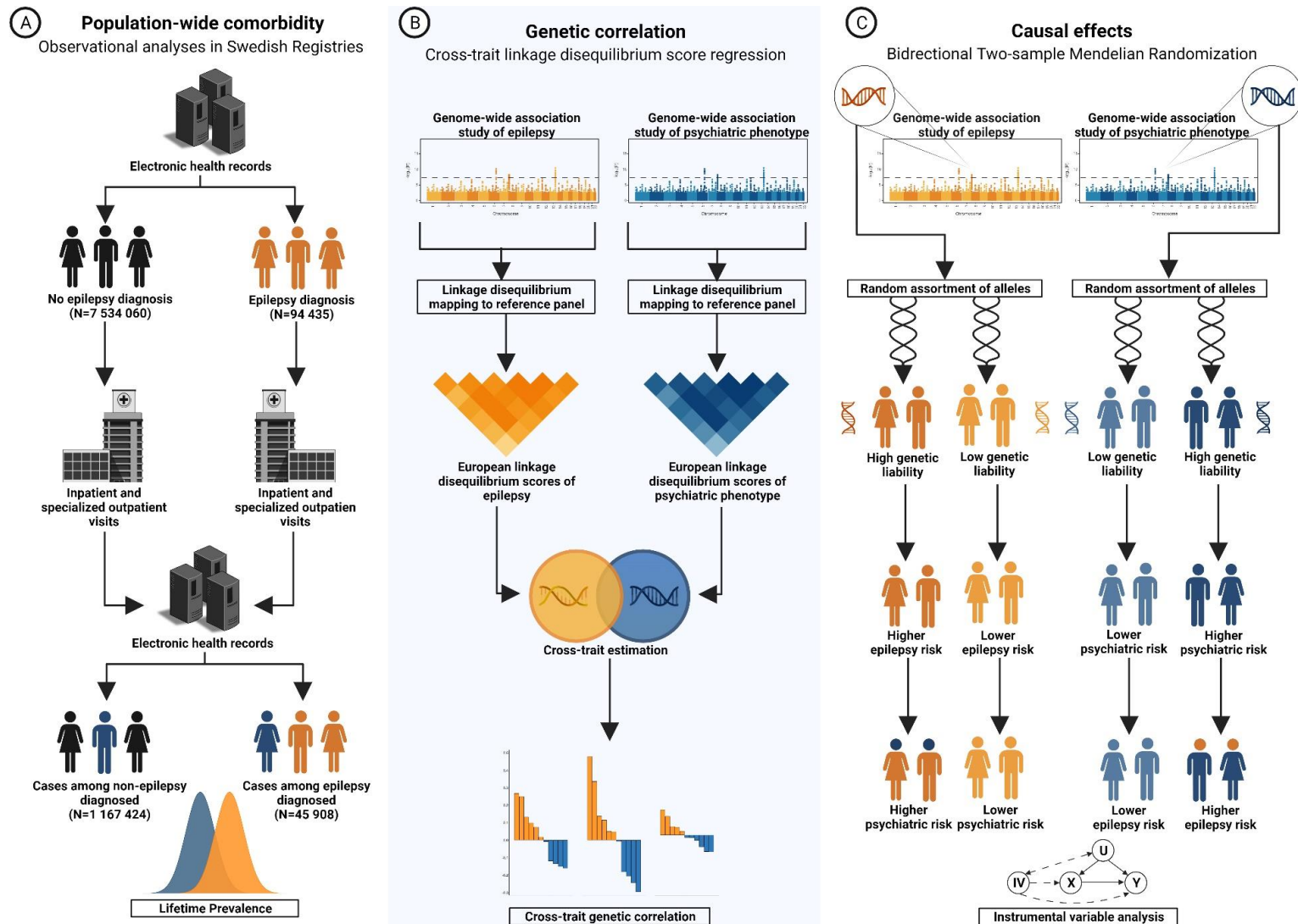
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Mr. Viktor H. Ahlqvist obtained his Master of Medical Sciences degree from the Karolinska Institutet in Stockholm, Sweden, in 2019. He enrolled as a doctoral student in 2019 in the Department of Global Public Health at the Karolinska Institutet. His research centres on epilepsy and its related comorbidities, with a specific focus on the factors associated with pregnancy and their influence on the health of both mothers and their offspring. His doctoral project investigates the benefits and potential risks associated with the use of antiseizure medications during pregnancy. In pursuit of these insights, Mr. Ahlqvist employs registry-based pharmacoepidemiological surveillance and causal modelling. One key aspect of his research involves exploring whether epilepsy is independently linked to the occurrence of various conditions observed in the offspring of mothers with epilepsy. Through his work, Mr. Ahlqvist aims to enhance our understanding of epilepsy and its implications, ultimately striving to improve the health outcomes of both mothers and their children.

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Supplemental Figure 1. Overview of the methodology employed to characterize the comorbidities of psychiatric conditions in individuals with epilepsy (A), outline the genetic correlation between epilepsy and psychiatric conditions (B) and examine the possibility of bidirectional relationship between epilepsy and psychiatric conditions (C). For a detailed description of the approaches and related assumptions see the Method section.

Supplemental Table 1. International Classification of Diseases codes used to identify conditions in the Swedish health registries.

Condition	ICD-10	ICD-9	ICD-8
Any psychiatric diagnosis	F00-F99	290-319	290-319
Attention-deficit/hyperactivity disorder	F90	314	308.3
Anorexia Nervosa	F50.0, F50.1	307.1	306.5
Anxiety Disorder	F40-F48	300.0, 300.2, 308, 309	300.0-300.2, 300.5-300.9
Autism	F84	299	299.99
Bipolar disorder	F30, F31, F34.0, F25.0	296.0, 296.2, 296.4, 296.8, 296.9	296.1, 296.3, 296.8
Depression	F32-F39	296.1, 298.0, 300.4, 311	298.0, 300.4
Epilepsy ^{1,2}	G40	345J-345P, 345W, 345X	345.0-345-3, 345.9
<i>Focal</i>	G40.0, G40.1, G40.2	345M, 345N	345.30, 345.31, 345.38, 345.39
<i>Generalized</i>	G40.3	345J, 345K	345.00, 345.09, 345.10, 345.11
<i>Other and unspecified</i>	G40.4, G40.5, G40.6, G40.7, G40.8, G40.9	345L, 345P, 345W, 345X	345.18, 345.19, 345.39, 345.32, 345.33, 345.9
Intellectual Disability	F70-F79	317-319	310-315
Obsessive-compulsive disorder	F42	300.3	300.3, 301.4
Schizophrenia	F20-F29	295.0, 295.4, 295.6, 295.8, 295.9	295.0, 295.4, 295.6, 295.8, 295.9
Suicide attempts	X60-X84	950-958	950-958
Tic-disorders (Tourette Syndrome)	F95	307.2	306.2

¹Individuals who only received a three-character ICD code were classified as a distinct category in subtype analysis (never characterized).

²We were unable to classify 259 individuals who were discharged with both focal and generalized ICD codes on their most recent visit, these were retained these individuals in the “never characterized” group.

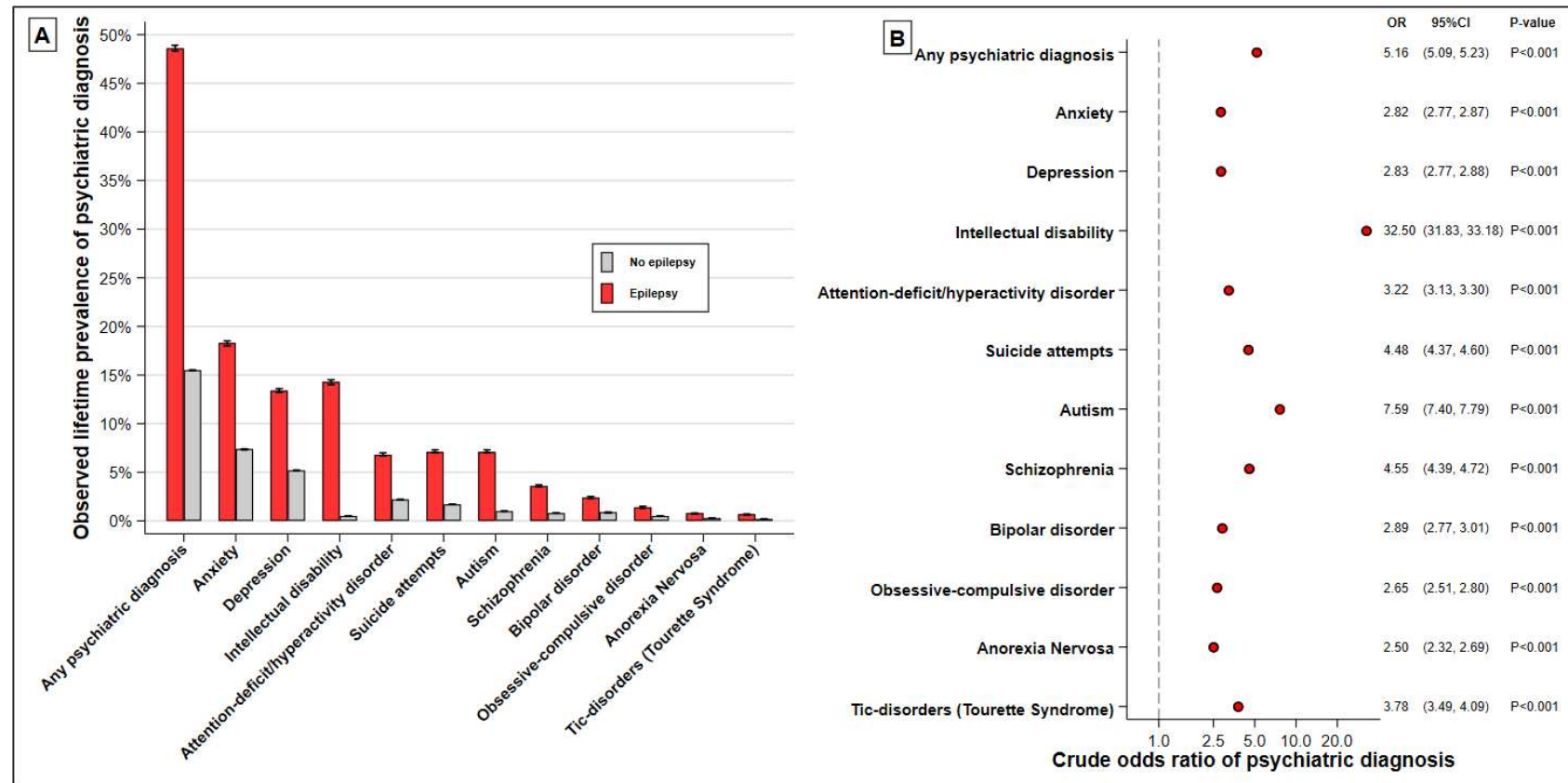
Extended observational results

Supplemental Table 2. Observational analysis¹ in Swedish health-care registries of epilepsy and psychiatric conditions.								
Phenotype	No Epilepsy (N=7 534 060)		Epilepsy (N=94 435)					
	N cases	Prevalence ² (%) (95% CI)	N cases	Crude prevalence (%) (95% CI)	Adjusted prevalence (%) (95% CI)	Crude Odds ratio (95% CI)	Adjusted Odds ratio (95% CI)	Percent attenuation ³ (95% CI)
Any psychiatric diagnosis	1 167 424	15.5 (15.5-15.5)	45 908	48.6 (48.3-48.9)	44.1 (43.8-44.4)	5.16 (5.09-5.23)	4.60 (4.54-4.66)	12.2 (11.8-12.5)
Anxiety	554 058	7.4 (7.4-7.4)	17 276	18.3 (18-18.5)	16 (15.7-16.2)	2.82 (2.77-2.87)	2.48 (2.43-2.52)	13.9 (13.5-14.4)
Depression	390 493	5.2 (5.2-5.2)	12 642	13.4 (13.2-13.6)	11.4 (11.2-11.6)	2.83 (2.77-2.88)	2.41 (2.36-2.45)	17.4 (17-17.9)
Intellectual disability	38 376	0.5 (0.5-0.5)	13 471	14.3 (14-14.5)	11.1 (10.9-11.3)	32.5 (31.83-33.18)	27.51 (26.9-28.12)	18.2 (17.1-19.2)
Attention-deficit/hyperactivity disorder	168 012	2.2 (2.2-2.2)	6 455	6.8 (6.7-7)	5.8 (5.7-6)	3.22 (3.13-3.3)	2.82 (2.75-2.90)	14.1 (13.3-14.9)
Suicide attempts	126 801	1.7 (1.7-1.7)	6 729	7.1 (7-7.3)	5.8 (5.7-6)	4.48 (4.37-4.6)	3.69 (3.70-3.79)	21.5 (20.9-22.1)
Autism	75 575	1.0 (1.0-1.0)	6 743	7.1 (7-7.3)	5.5 (5.4-5.6)	7.59 (7.4-7.79)	6.09 (5.93-6.26)	24.5 (23.5-25.5)
Schizophrenia	60 753	0.8 (0.8-0.8)	3 370	3.6 (3.5-3.7)	2.5 (2.4-2.5)	4.55 (4.39-4.72)	3.15 (3.03-3.26)	44.7 (43.5-46)
Bipolar disorder	64 165	0.9 (0.8-0.9)	2 287	2.4 (2.3-2.5)	1.9 (1.8-1.9)	2.89 (2.77-3.01)	2.21 (2.12-2.31)	30.7 (29.8-31.5)
Obsessive-compulsive disorder	40 491	0.5 (0.5-0.5)	1 335	1.4 (1.3-1.5)	1.1 (1-1.1)	2.65 (2.51-2.8)	2.02 (1.91-2.13)	31.4 (30.4-32.4)
Anorexia Nervosa	23 254	0.3 (0.3-0.3)	725	0.8 (0.7-0.8)	0.7 (0.6-0.7)	2.5 (2.32-2.69)	2.14 (1.99-2.31)	16.7 (15.5-18)
Tic-disorders (Tourette Syndrome)	13 874	0.2 (0.2-0.2)	654	0.7 (0.6-0.7)	0.6 (0.6-0.7)	3.78 (3.49-4.09)	3.44 (3.18-3.73)	9.8 (8.5-11.1)

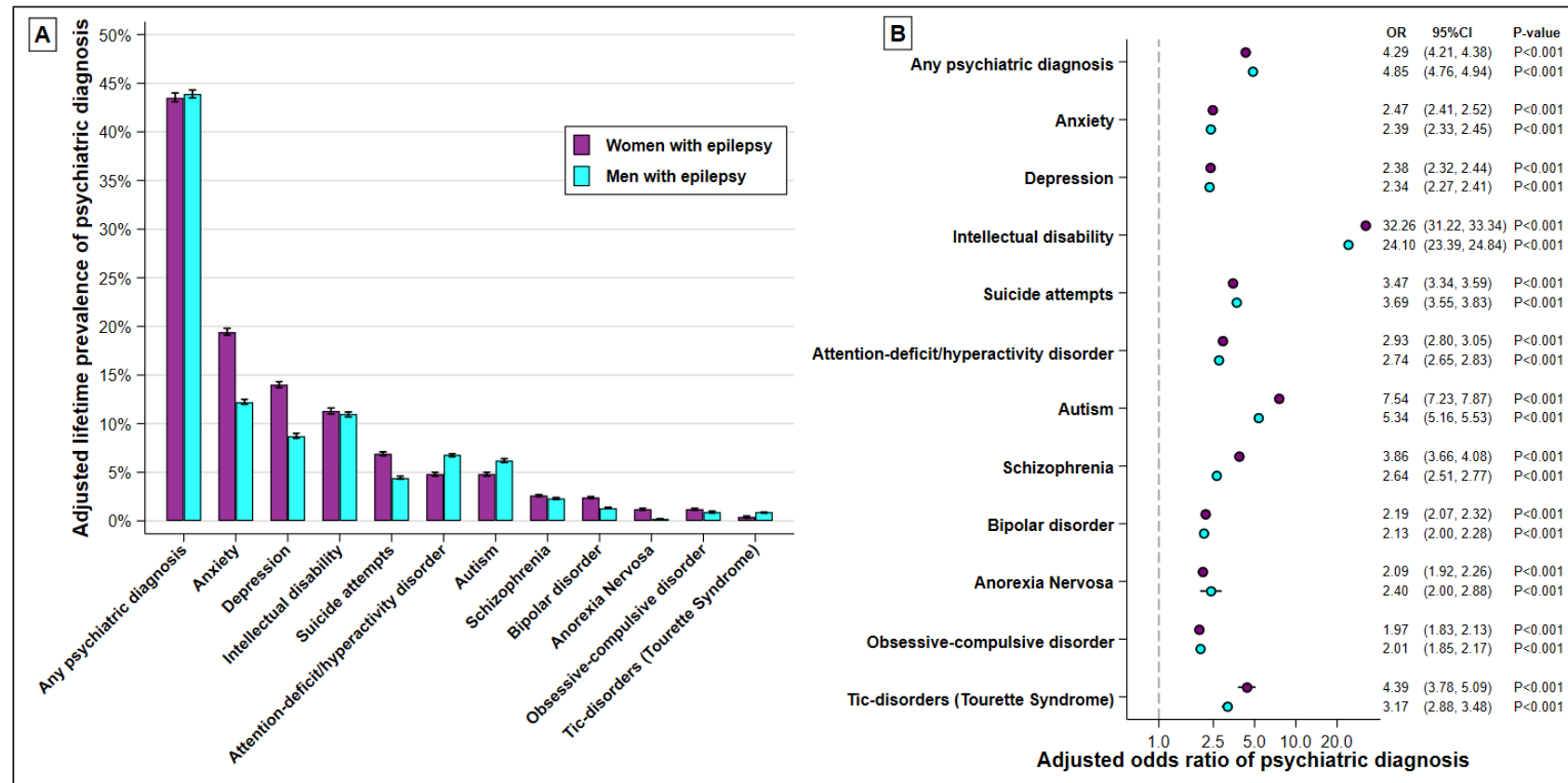
²Estimates are obtained from logistic regression(s). Where indicated, estimates are adjusted for birth year, sex, highest achieved disposable income, and immigration status.

²We omit the adjusted prevalence among those without epilepsy as it did not differ before the first decimal.

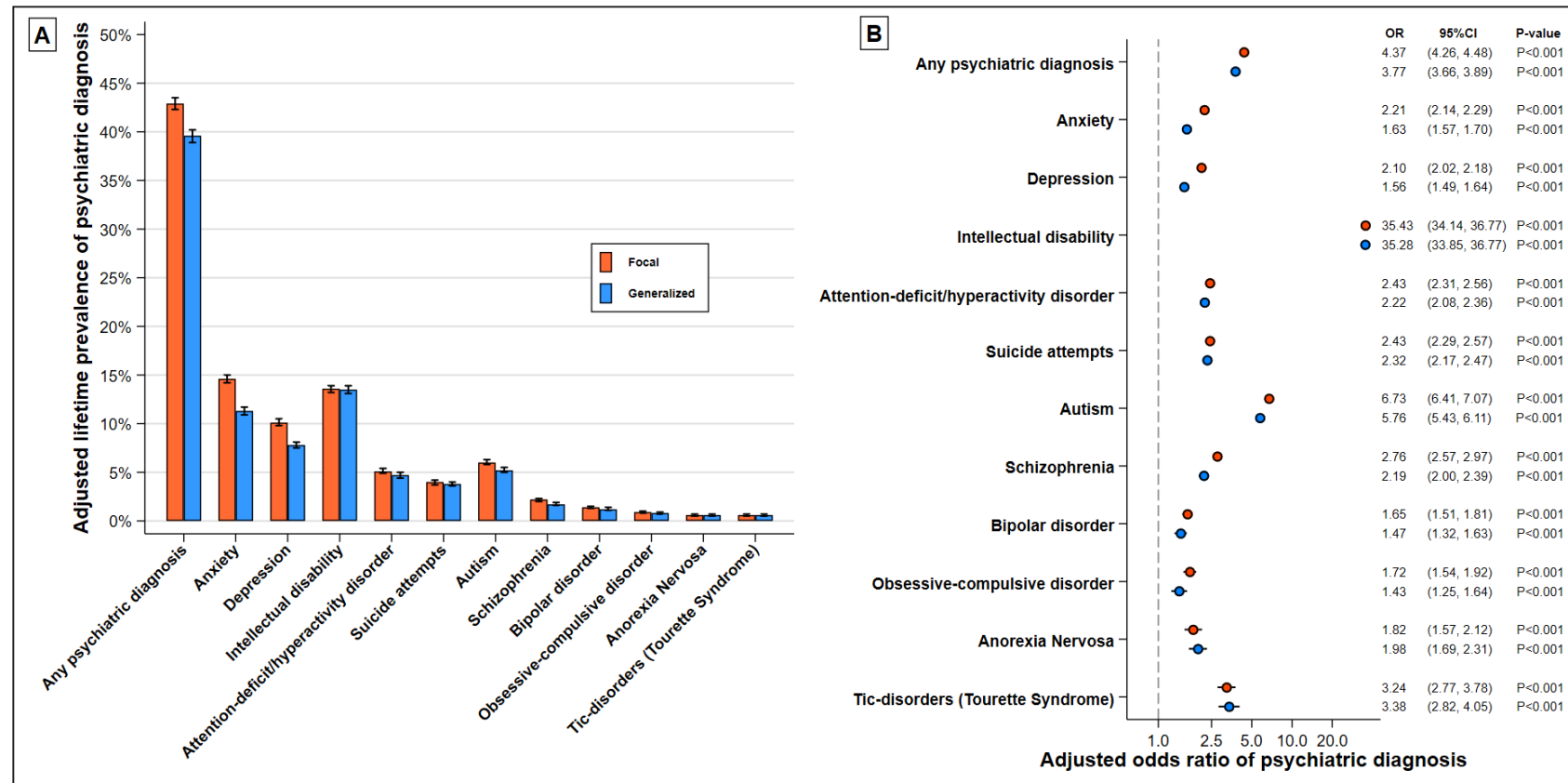
³The percent of attenuation comparing the crude odds ratio to the adjusted odds ratio.



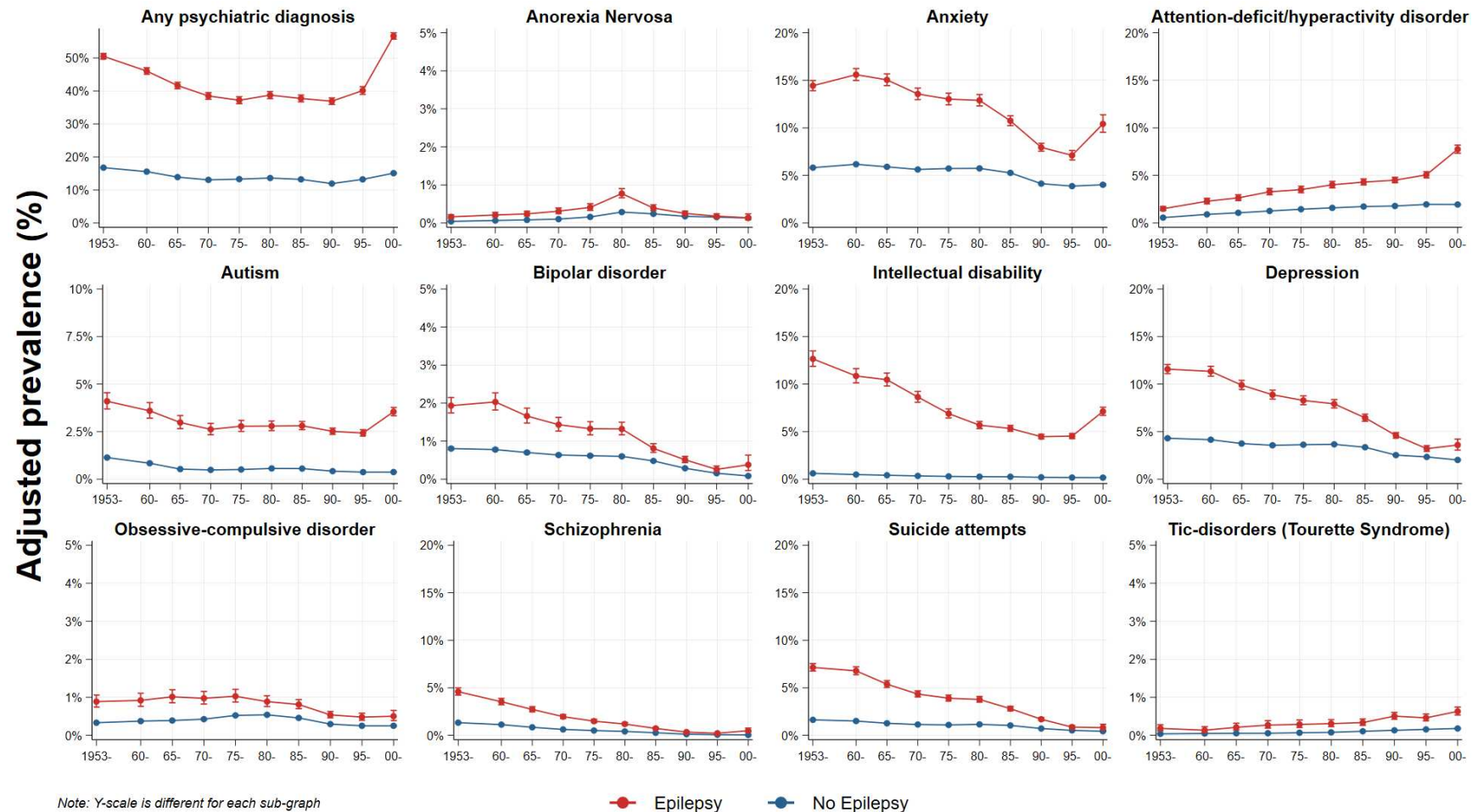
Supplemental Figure 2. The unadjusted population-wide co-occurrence of epilepsy and psychiatric morbidities. Panel A illustrates the observed lifetime prevalence of psychiatric diagnoses among those with (N=94 435) and without a diagnosis of epilepsy (N=7 534 060). Panel B illustrates the crude odds ratio of psychiatric diagnoses comparing those with and without a diagnosis of epilepsy. Black lines indicate 95% confidence intervals in both panels (confidence intervals are plotted in panel B but they are smaller than the marker size, reflecting our large sample size).



Supplemental Figure 3. The sex-stratified population-wide co-occurrence of epilepsy and psychiatric morbidities. Panel A illustrates the adjusted (marginal) lifetime probability of psychiatric diagnoses among those with a diagnosis of epilepsy (N=94 435), stratified by birth sex (purple indicating among women with epilepsy N=44 367, and cyan indicating among men with epilepsy N=50 068). Panel B illustrates the adjusted odds ratio of psychiatric diagnoses comparing those with and without a diagnosis of epilepsy, stratified by birth sex (purple indicating among women and cyan indicating among men). All analyses are adjusted for birth year, highest achieved disposable income, and immigration status. Black lines indicate 95% confidence intervals in both panels (width is sometimes smaller than marker size in panel B).



Supplemental Figure 4. The population-wide co-occurrence of epilepsy and psychiatric morbidities stratified by type of epilepsy. Panel A illustrates the adjusted (marginal) lifetime probability of psychiatric diagnoses among those with focal (N=24 430) or generalized epilepsy (N=19 199). Panel B illustrates the adjusted odds ratio of psychiatric diagnoses comparing those with focal and generalized epilepsy to those with no epilepsy diagnosis. All analyses are adjusted for birth year, highest achieved disposable income, sex, and immigration status. Black lines indicate 95% confidence intervals in both panels (width is sometimes smaller than marker size in panel B). For graphical purposes, we omit those who were never characterized (N=18 338) or other/unspecific forms of epilepsy (N=32 468) – these individuals did not differ materially in their rate of psychiatric diagnosis as compared to those with focal or generalized epilepsy.



Birth Cohorts (year)

Supplemental Figure 5. The population-wide co-occurrence of epilepsy and psychiatric morbidities stratified by birth cohorts. The vertical lines illustrate the adjusted (marginal) prevalence of psychiatric diagnoses among those with (N=94 435) and without a diagnosis of epilepsy (N=7 534 060). Horizontal lines indicate 95% confidence intervals.

Extended genomic results

Supplemental Table 3. Extended results from the LDSC and MR analyses of epilepsy (broadly classified) and selected psychiatric phenotypes.

Phenotype	Effect of epilepsy on comorbidity				Effect of Comorbidity on Epilepsy				Genetic correlation	
	N _{iv}	β	OR	P-value	N _{iv}	β	OR	P-value	rg	P-value
Focal epilepsy	N/A	-	-	-	N/A	-	-	-	0.86	<0.001*
Generalized epilepsy	N/A	-	-	-	N/A	-	-	-	0.92	<0.001*
Anorexia Nervosa	37	-0.18	0.83	0.092	39	-0.02	0.98	0.322	0.04	0.463
Anxiety (Case-control)	39	0.44	1.55	0.016	3	-0.01	0.99	0.779	0.30	0.016
Anxiety (Continuous) ¹	39	0.05	-	0.086	6	0.01	1.01	0.897	0.06	0.638
Attention-deficit/hyperactivity disorder	37	0.11	1.12	0.172	102	0.03	1.03	0.018	0.18	<0.001*
Autism	37	0.04	1.05	0.620	21	0.01	1.01	0.635	-0.12	0.059
Bipolar disorder	37	-0.13	0.88	0.035	187	0.00	1.00	0.734	-0.11	0.005
Intelligence	42	-0.03	0.97	0.384	487	-0.12	0.89	<0.001*	-0.20	<0.001*
Depression	36	0.00	-	0.957	174	0.00	1.00	0.985	0.04	0.412
Obsessive-compulsive disorder	37	-0.16	0.86	0.448	7	-0.02	0.98	0.273	-0.10	0.244
Schizophrenia	37	-0.14	0.87	0.176	489	-0.01	0.99	0.233	-0.11	0.004
Suicide attempts	36	-0.01	0.99	0.870	29	0.01	1.01	0.791	0.11	0.070
Tic-disorders (Tourette Syndrome)	37	-0.09	0.91	0.554	9	0.00	1.00	0.848	-0.02	0.799

¹In our primary analysis, we leverage the case-control anxiety definitions, to ensure that the findings reflect manifested anxiety. However, we chose to also analyse anxiety as a continuous score obtained from the original GWAS to enhance statistical efficiency.

*Statistically significant at Bonferroni correction ($\alpha=0.00075758$ for MR and $\alpha=0.001515$ for LDSC).

Supplemental Table 4. Extended results from the LDSC and MR analyses of focal epilepsy and selected psychiatric phenotypes.

Phenotype	Effect of epilepsy on comorbidity				Effect of Comorbidity on Epilepsy				Genetic correlation	
	N _{iv}	β	OR	P-value	N _{iv}	β	OR	P-value	rg	P-value
Epilepsy (broadly defined)	N/A	-	-	-	N/A	-	-	-	0.86	<0.001*
Generalized epilepsy	N/A	-	-	-	N/A	-	-	-	0.61	<0.001*
Anorexia Nervosa	25	-0.07	0.93	0.416	39	0.00	1.00	0.983	0.00	0.953
Anxiety (Case-control)	26	0.08	1.08	0.658	3	0.01	1.01	0.824	0.39	0.036
Anxiety (Continuous) ¹	26	0.00	1.00	0.990	6	-0.05	0.95	0.658	0.05	0.770
Attention-deficit/hyperactivity disorder	25	0.02	1.02	0.766	102	0.02	1.02	0.193	0.23	<0.001*
Autism	25	-0.14	0.87	0.112	21	0.01	1.01	0.747	-0.17	0.059
Bipolar disorder	25	-0.08	0.92	0.423	187	0.00	1.00	0.713	-0.11	0.058
Intelligence	28	-0.01	0.99	0.533	487	-0.13	0.88	<0.001*	-0.24	<0.001*
Depression	25	0.05	1.05	0.169	174	0.02	1.02	0.447	0.10	0.102
Obsessive-compulsive disorder	25	0.21	1.23	0.339	7	-0.03	0.97	0.078	-0.06	0.609
Schizophrenia	25	-0.15	0.86	0.059	489	-0.01	0.99	0.274	-0.14	0.005
Suicide attempts	24	-0.03	0.97	0.730	29	0.00	1.00	0.952	0.12	0.209
Tic-disorders (Tourette Syndrome)	25	0.24	1.27	0.128	9	0.00	1.00	0.814	-0.0103	0.925

¹In our primary analysis, we leverage the case-control anxiety definitions, to ensure that the findings reflect manifested anxiety. However, we chose to also analyse anxiety as a continuous score obtained from the original GWAS to enhance statistical efficiency.

*Statistically significant at Bonferroni correction ($\alpha=0.00075758$ for MR and $\alpha=0.001515$ for LDSC).

Supplemental Table 5. Extended results from the LDSC and MR analyses of generalized epilepsy and selected psychiatric phenotypes.

Phenotype	Effect of epilepsy on comorbidity				Effect of Comorbidity on Epilepsy				Genetic correlation	
	N _{iv}	β	OR	P-value	N _{iv}	β	OR	P-value	rg	P-value
Generalized epilepsy										
Epilepsy (broadly defined)	N/A	-	-	-	N/A	-	-	-	0.92	<0.001*
Focal epilepsy	N/A	-	-	-	N/A	-	-	-	0.61	<0.001*
Anorexia Nervosa	67	-0.01	0.99	0.839	39	-0.04	0.96	0.251	0.01	0.803
Anxiety (Case-control)	78	0.05	1.05	0.476	3	-0.06	0.94	0.320	0.16	0.137
Anxiety (Continuous) ¹	78	-0.02	0.98	0.151	6	0.02	1.02	0.916	0.05	0.692
Attention-deficit/hyperactivity disorder	67	0.06	1.06	0.071	102	0.06	1.06	0.015	0.10	0.009
Autism	67	0.00	1.00	0.926	21	-0.02	0.98	0.563	-0.09	0.088
Bipolar disorder	67	-0.02	0.98	0.647	187	-0.03	0.98	0.235	-0.10	0.003
Intelligence	80	0.00	1.00	0.906	487	-0.14	0.87	<0.001*	-0.14	<0.001*
Depression	66	0.00	1.00	0.745	174	-0.03	0.97	0.502	-0.01	0.728
Obsessive-compulsive disorder	67	-0.04	0.96	0.658	7	-0.02	0.98	0.442	-0.13	0.061
Schizophrenia	67	0.03	1.03	0.483	489	-0.02	0.98	0.264	-0.07	0.050
Suicide attempts	65	-0.03	0.97	0.365	29	-0.01	0.99	0.779	0.06	0.256
Tic-disorders (Tourette Syndrome)	67	0.02	1.02	0.747	9	-0.01	0.99	0.835	0.02	0.699

¹In our primary analysis, we leverage the case-control anxiety definitions, to ensure that the findings reflect manifested anxiety. However, we chose to also analyse anxiety as a continuous score obtained from the original GWAS to enhance statistical efficiency.

*Statistically significant at Bonferroni correction ($\alpha=0.00075758$ for MR and $\alpha=0.001515$ for LDSC).

eMethods - Mendelian sensitivity analysis

To allow for the potential of horizontal pleiotropy, whereby the instruments are related to the outcome through some pathway that is independent of the exposure, we employed MR-Egger regression.[1] In MR-Egger regression the intercept is unconstrained, in contrast to the IVW regression, and a non-zero intercept can be interpreted as the presence of horizontal pleiotropy and the slope the causal effect in presence of horizontal pleiotropy,[1] under the instrument independent of direct effects (InSIDE) assumption.

In addition to MR-Egger, we conducted a series of commonly employed MR analyses with relaxed instrumental variable assumptions. First, we conducted weighted median MR, which provides an unbiased estimate when at least 50% of the genetic variants are valid instruments. Second, we conducted a mode-based MR which assumes that more instruments estimate the true causal effect of the exposure than any other effect. The benefit of the median and mode-based regressions compared to MR Egger is that they are more efficient – at the cost of being less robust to horizontal pleiotropy.

Since we employed an inclusive approach to instrument selection (p -value $<5\times 10^{-06}$), and this may lead to bias towards the null under weak instrument bias and absence of sample overlap between GWAS studies, we repeated our primary analyses (IVW regression) using a more conservative p -value threshold (p -value $<5\times 10^{-08}$) for instrument selection.

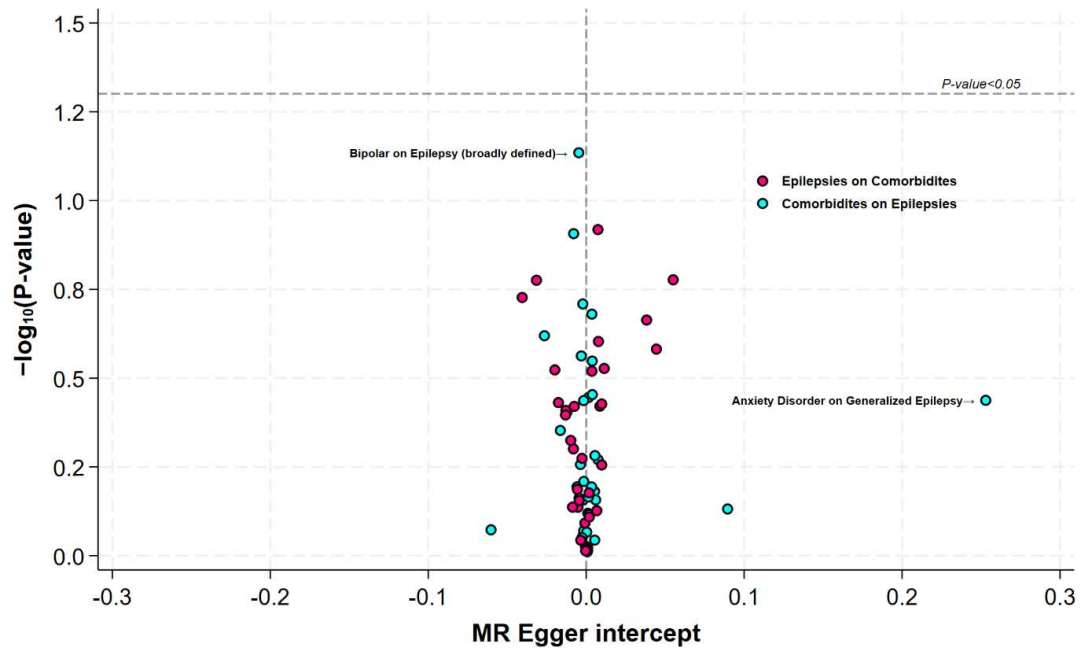
Findings of mendelian sensitivity analysis

There was no evidence of horizontal pleiotropy (Supplemental Figure 6 & Supplemental Table 6). The MR Egger intercept that had the lowest p -value was the association between genetic liability to bipolar disorder and epilepsy (Egger intercept -0.005 , $p=0.073$). The greatest egger intercept was identified for the association between anxiety disorder and generalized epilepsy (Egger intercept 0.089), although its standard error was large ($p=0.738$).

There was no consistent difference, at large, between our primary causal analyses and several sensitivity analyses (Supplement Supplemental Table 7). Specifically, using the weighted median, egger, simple mode, and weighted mode regression was consistent with the IVW regression (primary analyses). As in our primary analyses, there was a persistent negative effect of genetic liability to intelligence on epilepsy when employing median and mode-based analyses (Supplement Supplemental Table 7).

There was no difference between our primary analysis and when considering a more conservative p -value threshold (p -value $<5\times 10^{-08}$) for instrument selection, although the precision was reduced.

However, one deviation from our primary analysis is noteworthy. In our initial assessment, we identified a positive association between genetic predisposition to (broadly classified) epilepsy and anxiety. However, this association could not be reproduced when employing the continuous anxiety score or utilizing MR-Egger.



Supplemental Figure 6. Volcano plot of the MR-Egger intercept and corresponding intercept p-value for each Mendelian randomization analysis. Departure from zero of the egger-intercept is indicative of horizontal pleiotropy, which biases standard Mendelian randomization analysis. The grey dotted line horizontally marks the zero intercept and vertically marks the level above which a p-value is less than 0.05 on the standard scale. The mendelian analysis of genetic liability to bipolar on epilepsy is highlighted as the egger intercept with the lowest p-value (0.073269). The mendelian analysis of genetic liability to anxiety disorder on generalized epilepsy is highlighted as it was of the greatest magnitude (although its p-value is large).

Supplemental Table 6. Egger intercepts for all Mendelian analyses.

Epilepsy (broadly defined)	Epilepsy on Comorbidity		Comorbidity on epilepsy	
	Egger Intercept	P-value	Egger Intercept	P-value
Attention-deficit/hyperactivity disorder	0.011	0.297	0.004	0.283
Anorexia Nervosa	-0.005	0.729	-0.001	0.938
Anxiety (Case-control)	0.038	0.217	0.089	0.738
Anxiety (Continuous)	0.007	0.121	-0.002	0.875
Autism	-0.006	0.650	0.005	0.658
Bipolar disorder	-0.006	0.493	-0.005	0.073
Intelligence	-0.003	0.532	-0.002	0.195
Major depression	0.000	0.953	0.001	0.759
Obsessive-compulsive disorder	-0.041	0.187	-0.006	0.640
Schizophrenia	-0.012	0.394	0.001	0.358
Suicide attempts	-0.008	0.500	-0.002	0.696
Tic-disorders (Tourette Syndrome)	0.007	0.746	0.001	0.974
Focal epilepsy				
Attention-deficit/hyperactivity disorder	-0.013	0.390	0.004	0.351
Anorexia Nervosa	0.010	0.555	-0.002	0.850
Anxiety (Case-control)	0.044	0.262	-0.060	0.845
Anxiety (Continuous)	0.008	0.249	0.006	0.696
Autism	0.001	0.964	0.008	0.537
Bipolar disorder	-0.018	0.370	-0.003	0.274
Intelligence	-0.001	0.809	-0.002	0.365
Major depression	0.002	0.778	0.001	0.683
Obsessive-compulsive disorder	0.055	0.167	-0.005	0.687
Schizophrenia	-0.013	0.401	0.000	0.858
Suicide attempts	-0.009	0.729	-0.004	0.553
Tic-disorders (Tourette Syndrome)	-0.003	0.904	-0.003	0.889
Generalized epilepsy				
Attention-deficit/hyperactivity disorder	-0.008	0.380	0.003	0.640
Anorexia Nervosa	-0.010	0.473	0.001	0.949
Anxiety (Case-control)	0.024	0.218	0.253	0.365
Anxiety (Continuous)	0.004	0.302	-0.027	0.240
Autism	-0.004	0.698	0.001	0.970
Bipolar disorder	0.009	0.379	-0.008	0.124
Intelligence	0.002	0.665	-0.002	0.617
Major depression	0.000	0.960	0.002	0.765
Obsessive-compulsive disorder	-0.032	0.168	-0.016	0.444
Schizophrenia	0.010	0.374	0.004	0.209
Suicide attempts	0.000	0.968	0.005	0.522
Tic-disorders (Tourette Syndrome)	-0.020	0.300	0.005	0.903

Supplemental Table 7. Mendelian sensitivity analyses (see eMethods for description of each analysis).

	Epilepsy on Comorbidity				Comorbidity on Epilepsy			
	N _{IV}	β	OR	P-value	N _{IV}	β	OR	P-value
Epilepsy (broadly defined)								
<i>Anorexia Nervosa</i>								
MR Egger	37	-0.02	0.98	0.958	39	-0.01	0.99	0.919
Simple mode	37	-0.31	0.73	0.194	39	-0.07	0.94	0.143
Weighted median	37	-0.20	0.82	0.106	39	-0.02	0.98	0.206
Weighted mode	37	-0.18	0.83	0.386	39	-0.07	0.94	0.131
<i>Anxiety (Case-control)</i>								
MR Egger	39	-0.72	0.49	0.449	3	-0.60	0.55	0.733
Simple mode	39	0.98	2.65	0.044	3	-0.05	0.95	0.419
Weighted median	39	0.67	1.95	0.005	3	-0.02	0.98	0.498
Weighted mode	39	0.91	2.48	0.050	3	-0.04	0.96	0.435
<i>Anxiety (Continuous)</i>								
MR Egger	39	-0.18	-	0.225	6	0.08	1.08	0.857
Simple mode	39	0.13	-	0.141	6	0.09	1.09	0.631
Weighted median	39	0.06	-	0.107	6	0.04	1.04	0.727
Weighted mode	39	0.13	-	0.132	6	0.07	1.07	0.690
<i>Attention-deficit/hyperactivity disorder</i>								
MR Egger	37	-0.22	0.80	0.495	102	-0.04	0.96	0.554
Simple mode	37	0.03	1.03	0.872	102	-0.02	0.98	0.743
Weighted median	37	0.04	1.04	0.628	102	0.03	1.03	0.060
Weighted mode	37	0.00	1.00	0.989	102	0.00	1.00	0.937
<i>Autism</i>								
MR Egger	37	0.21	1.23	0.576	21	-0.06	0.95	0.719
Simple mode	37	0.16	1.17	0.539	21	0.05	1.05	0.362
Weighted median	37	0.11	1.12	0.337	21	0.03	1.03	0.231
Weighted mode	37	0.15	1.16	0.526	21	0.04	1.04	0.391
<i>Bipolar disorder</i>								
MR Egger	37	0.05	1.05	0.865	187	0.08	1.08	0.095
Simple mode	37	-0.21	0.81	0.290	187	-0.02	0.98	0.668
Weighted median	37	-0.19	0.83	0.027	187	-0.01	0.99	0.499
Weighted mode	37	-0.28	0.76	0.130	187	-0.01	0.99	0.789
<i>Intelligence</i>								
MR Egger	42	0.05	-	0.698	487	0.01	1.01	0.948
Simple mode	42	-0.02	-	0.807	487	-0.19	0.83	0.070
Weighted median	42	-0.01	-	0.649	487	-0.10	0.91	0.000
Weighted mode	42	0.00	-	0.972	487	-0.11	0.89	0.260
<i>Depression</i>								
MR Egger	36	-0.02	0.98	0.945	174	-0.04	0.96	0.765
Simple mode	36	0.06	1.06	0.491	174	-0.01	0.99	0.951
Weighted median	36	-0.01	0.99	0.874	174	-0.01	0.99	0.795
Weighted mode	36	0.06	1.06	0.421	174	-0.02	0.98	0.869
<i>Obsessive-compulsive disorder</i>								
MR Egger	37	1.06	2.88	0.260	7	0.01	1.01	0.894
Simple mode	37	0.56	1.75	0.400	7	-0.03	0.97	0.347
Weighted median	37	0.29	1.34	0.305	7	-0.03	0.98	0.177
Weighted mode	37	0.55	1.73	0.403	7	-0.03	0.97	0.324
<i>Schizophrenia</i>								
MR Egger	37	0.23	1.26	0.601	489	-0.04	0.97	0.237
Simple mode	37	-0.23	0.80	0.312	489	0.00	1.00	0.939
Weighted median	37	-0.07	0.93	0.404	489	0.00	1.00	0.735
Weighted mode	37	0.15	1.17	0.476	489	0.00	1.00	0.925
<i>Suicide attempts</i>								
MR Egger	36	0.23	1.26	0.529	29	0.04	1.04	0.658
Simple mode	36	-0.05	0.95	0.799	29	0.02	1.02	0.783
Weighted median	36	0.01	1.01	0.948	29	0.01	1.01	0.844
Weighted mode	36	-0.05	0.95	0.797	29	0.02	1.02	0.783
<i>Tic-disorders (Tourette Syndrome)</i>								
MR Egger	37	-0.28	0.75	0.647	9	0.00	1.00	0.993
Simple mode	37	-0.24	0.78	0.600	9	0.02	1.02	0.682
Weighted median	37	-0.19	0.83	0.366	9	0.01	1.01	0.589
Weighted mode	37	-0.22	0.81	0.593	9	0.02	1.02	0.571
Focal epilepsy								
<i>Anorexia Nervosa</i>								
MR Egger	25	-0.32	0.73	0.462	39	0.02	1.02	0.855
Simple mode	25	-0.19	0.83	0.373	39	-0.03	0.97	0.597
Weighted median	25	-0.08	0.92	0.490	39	-0.02	0.98	0.381
Weighted mode	25	-0.17	0.85	0.466	39	-0.02	0.98	0.709
<i>Anxiety (Case-control)</i>								
MR Egger	26	-1.07	0.34	0.301	3	0.41	1.51	0.841
Simple mode	26	-0.59	0.55	0.284	3	-0.03	0.97	0.622
Weighted median	26	-0.16	0.86	0.523	3	-0.01	0.99	0.816
Weighted mode	26	-0.57	0.57	0.334	3	-0.03	0.97	0.628

<i>Anxiety (Continuous)</i>								
MR Egger	26	-0.20	-	0.256	6	-0.25	0.78	0.638
Simple mode	26	-0.02	-	0.802	6	0.16	1.17	0.530
Weighted median	26	0.00	-	0.960	6	-0.04	0.96	0.762
Weighted mode	26	-0.03	-	0.679	6	-0.16	0.85	0.445
<i>Attention-deficit/hyperactivity disorder</i>								
MR Egger	25	0.36	1.43	0.369	102	-0.05	0.95	0.509
Simple mode	25	0.19	1.21	0.327	102	0.07	1.08	0.172
Weighted median	25	0.01	1.01	0.885	102	0.03	1.03	0.094
Weighted mode	25	0.16	1.18	0.380	102	0.06	1.07	0.181
<i>Autism</i>								
MR Egger	25	-0.16	0.85	0.738	21	-0.09	0.91	0.577
Simple mode	25	-0.24	0.79	0.346	21	0.04	1.04	0.546
Weighted median	25	-0.19	0.82	0.123	21	0.01	1.01	0.845
Weighted mode	25	-0.19	0.83	0.470	21	-0.04	0.96	0.488
<i>Bipolar disorder</i>								
MR Egger	25	0.38	1.46	0.468	187	0.06	1.06	0.250
Simple mode	25	-0.20	0.82	0.225	187	-0.01	0.99	0.772
Weighted median	25	-0.14	0.87	0.098	187	-0.01	0.99	0.685
Weighted mode	25	-0.19	0.83	0.234	187	-0.01	0.99	0.745
<i>Intelligence</i>								
MR Egger	28	0.01	-	0.930	487	-0.04	0.97	0.743
Simple mode	28	-0.01	-	0.829	487	-0.14	0.87	0.232
Weighted median	28	-0.01	-	0.683	487	-0.12	0.88	0.000
Weighted mode	28	-0.01	-	0.820	487	-0.14	0.87	0.182
<i>Depression</i>								
MR Egger	25	0.00	1.00	0.991	174	-0.04	0.96	0.790
Simple mode	25	0.07	1.08	0.349	174	-0.05	0.96	0.688
Weighted median	25	0.06	1.07	0.095	174	-0.02	0.98	0.612
Weighted mode	25	0.07	1.08	0.288	174	-0.05	0.96	0.648
<i>Obsessive-compulsive disorder</i>								
MR Egger	25	-1.21	0.30	0.245	7	-0.01	0.99	0.910
Simple mode	25	0.40	1.49	0.569	7	-0.05	0.95	0.186
Weighted median	25	0.16	1.18	0.581	7	-0.03	0.97	0.192
Weighted mode	25	0.37	1.45	0.559	7	-0.01	0.99	0.689
<i>Schizophrenia</i>								
MR Egger	25	0.19	1.21	0.636	489	-0.01	0.99	0.659
Simple mode	25	-0.15	0.86	0.280	489	-0.01	0.99	0.825
Weighted median	25	-0.06	0.94	0.435	489	0.00	1.00	0.874
Weighted mode	25	-0.05	0.95	0.685	489	0.00	1.00	0.934
<i>Suicide attempts</i>								
MR Egger	24	0.20	1.22	0.771	29	0.06	1.06	0.576
Simple mode	24	0.15	1.16	0.447	29	0.06	1.07	0.423
Weighted median	24	0.04	1.04	0.686	29	0.04	1.04	0.286
Weighted mode	24	0.12	1.13	0.513	29	0.06	1.06	0.445
<i>Tic-disorders (Tourette Syndrome)</i>								
MR Egger	25	0.33	1.39	0.662	9	0.02	1.02	0.865
Simple mode	25	0.22	1.24	0.633	9	0.00	1.00	0.970
Weighted median	25	0.21	1.23	0.307	9	0.00	1.00	0.988
Weighted mode	25	0.19	1.21	0.677	9	0.00	1.00	0.969
<i>Generalized epilepsy</i>								
<i>Anorexia Nervosa</i>								
MR Egger	67	0.16	1.17	0.511	39	-0.05	0.95	0.787
Simple mode	67	0.03	1.03	0.813	39	-0.03	0.97	0.721
Weighted median	67	0.05	1.05	0.356	39	-0.02	0.98	0.605
Weighted mode	67	0.05	1.05	0.733	39	-0.03	0.97	0.723
<i>Anxiety (Case-control)</i>								
MR Egger	78	-0.38	0.68	0.279	3	-1.73	0.18	0.355
Simple mode	78	0.03	1.04	0.888	3	0.00	1.00	0.995
Weighted median	78	0.06	1.06	0.540	3	-0.01	0.99	0.875
Weighted mode	78	0.10	1.10	0.640	3	0.00	1.00	0.997
<i>Anxiety (Continuous)</i>								
MR Egger	78	-0.08	-	0.201	6	0.93	2.52	0.243
Simple mode	78	-0.01	-	0.696	6	0.17	1.18	0.517
Weighted median	78	-0.02	-	0.366	6	0.16	1.18	0.402
Weighted mode	78	-0.01	-	0.663	6	0.18	1.20	0.473
<i>Attention-deficit/hyperactivity disorder</i>								
MR Egger	67	0.19	1.21	0.213	102	0.00	1.00	0.987
Simple mode	67	-0.08	0.92	0.495	102	0.05	1.05	0.505
Weighted median	67	0.03	1.04	0.392	102	0.05	1.05	0.066
Weighted mode	67	-0.09	0.91	0.453	102	0.04	1.04	0.569
<i>Autism</i>								
MR Egger	67	0.08	1.08	0.690	21	-0.03	0.97	0.896
Simple mode	67	-0.03	0.98	0.858	21	0.05	1.05	0.596
Weighted median	67	-0.01	0.99	0.905	21	0.04	1.04	0.402
Weighted mode	67	-0.02	0.98	0.905	21	0.04	1.04	0.578

<i>Bipolar disorder</i>								
MR Egger	67	-0.16	0.85	0.338	187	0.11	1.12	0.219
Simple mode	67	-0.07	0.93	0.472	187	-0.04	0.96	0.633
Weighted median	67	-0.03	0.97	0.502	187	-0.04	0.96	0.116
Weighted mode	67	-0.07	0.94	0.481	187	-0.04	0.96	0.646
<i>Intelligence</i>								
MR Egger	80	-0.03	-	0.654	487	-0.05	0.95	0.796
Simple mode	80	-0.03	-	0.408	487	-0.54	0.58	0.005
Weighted median	80	0.00	-	0.750	487	-0.10	0.91	0.033
Weighted mode	80	-0.01	-	0.712	487	-0.55	0.58	0.003
<i>Depression</i>								
MR Egger	66	0.00	1.00	0.986	174	-0.10	0.91	0.679
Simple mode	66	-0.04	0.96	0.347	174	-0.13	0.88	0.429
Weighted median	66	-0.01	0.99	0.551	174	-0.11	0.89	0.027
Weighted mode	66	-0.03	0.97	0.413	174	-0.13	0.88	0.359
<i>Obsessive-compulsive disorder</i>								
MR Egger	67	0.49	1.63	0.213	7	0.05	1.06	0.611
Simple mode	67	-0.14	0.87	0.636	7	-0.07	0.93	0.204
Weighted median	67	-0.12	0.89	0.339	7	-0.04	0.96	0.222
Weighted mode	67	-0.14	0.87	0.582	7	-0.06	0.94	0.215
<i>Schizophrenia</i>								
MR Egger	67	-0.14	0.87	0.471	489	-0.08	0.92	0.136
Simple mode	67	0.08	1.09	0.381	489	-0.09	0.92	0.199
Weighted median	67	0.02	1.02	0.626	489	-0.01	0.99	0.354
Weighted mode	67	0.06	1.06	0.470	489	-0.06	0.94	0.319
<i>Suicide attempts</i>								
MR Egger	65	-0.02	0.98	0.896	29	-0.10	0.91	0.491
Simple mode	65	0.00	1.00	0.955	29	-0.07	0.93	0.464
Weighted median	65	0.01	1.01	0.894	29	-0.05	0.95	0.287
Weighted mode	65	0.00	1.00	0.979	29	-0.07	0.94	0.458
<i>Tic-disorders (Tourette Syndrome)</i>								
MR Egger	67	0.36	1.43	0.279	9	-0.05	0.95	0.884
Simple mode	67	0.07	1.07	0.791	9	-0.09	0.91	0.118
Weighted median	67	0.01	1.01	0.923	9	-0.05	0.95	0.170
Weighted mode	67	-0.13	0.88	0.606	9	-0.09	0.91	0.177

Supplement References

1. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol*. 2015;44(2):512-25.