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Understanding the causal relationships of attention-deficit/hyperactivity disorder with mental disorders and suicide attempt: a network Mendelian randomisation study

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ABSTRACT

Background Attention-deficit/hyperactivity disorder (ADHD) is a lifespan neurodevelopmental condition resulting from complex interactions between genetic and environmental risk factors. There is evidence that ADHD is associated with other mental disorders, but it remains unclear whether and in what way a causal relationship exists.

Objective To investigate the direct and indirect causal paths between ADHD and seven common mental disorders.

Methods Two-sample network Mendelian randomisation analysis was performed to identify psychiatric disorders causally related to ADHD. Total and direct effects were estimated in an univariable and multivariable setting, respectively. Robustness of results was ensured in three ways: a range of pleiotropy-robust methods, an iterative approach identifying and excluding outliers, and use of up to two genome-wide association studies per outcome to replicate results and calculate subsequently pooled meta-estimates.

Results Genetic liability to ADHD was independently associated with the risk of anorexia nervosa (OR 1.28 (95% CI 1.11 to 1.47); p=0.001). A bidirectional association was found with major depressive disorder (OR 1.09 (95% CI 1.03 to 1.15); p=0.003 in the forward direction and OR 1.76 (95% CI 1.50 to 2.06); $p=4\times10^{-12}$ in the reverse direction). Moreover, after adjustment for major depression disorder, a direct association with both suicide attempt (OR 1.30 (95% CI 1.16 to 1.547); $p=2\times10^{-5}$) and post-traumatic stress disorder (OR 1.18 (95% CI 1.05 to 1.33); p=0.007) was observed. There was no evidence of a relationship with anxiety, bipolar disorder or schizophrenia.

Conclusions This study suggests that ADHD is an independent risk factor for a number of common psychiatric disorders.

Clinical implications The risk of comorbid psychiatric disorders in individuals with ADHD needs to be considered both in diagnosis and treatment.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Despite growing evidence from observational studies, the question of whether and in what way ADHD is causally related to other psychiatric disorders has remained unanswered.

WHAT THIS STUDY ADDS

⇒ Under consideration of mediation effects, this network Mendelian randomisation study found that ADHD increases the risk of major depression, post-traumatic stress syndrome, anorexia nervosa and suicide attempt.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study opens new insights into the paths between psychiatric disorders. Thus, in clinical practice, patients with ADHD should be monitored for the psychiatric disorders included in this study and preventive measures should be initiated if necessary.

BACKGROUND

Attention-deficit/hyperactivity disorder (ADHD) is a lifespan neurodevelopmental condition characterised by the presence of inattentive and/or hyperactive/impulsive symptoms in children and adolescents that extends to adulthood in up to 65%.[1] Consequently, individuals with ADHD exhibit deficits in executive function, emotional regulation and motivation.[2] Worldwide, the prevalence of ADHD is estimated to be 5.3% in children/adolescents and 2.5% in adults.[3] Epidemiological studies show that ADHD in childhood is more common in boys than in girls,[4] but in adults there seems to be an equal gender distribution.[5] Prospective studies including children with the disease observed a decline of symptoms with increasing age. Therapeutic approaches consist mainly of pharmacological and psychological treatments, but to date there is no single or universal treatment for this disorder.[6]

The aetiology of ADHD is not fully understood. The disorder is thought to result from complex interactions between genetic and environmental risk factors. Furthermore, prenatal and perinatal factors have been discussed as contributing causes.[1] However, genetic factors seem to play the most important role, as the heritability rate is 70–80%.[7]

There are a number of observational studies showing that ADHD is associated with non-mental diseases across the lifespan (eg, neurological disorders, endocrine and metabolic diseases,

and autoimmune diseases).[8] In addition, there is evidence that ADHD is related to other mental disorders; in particular, ADHD appears to be associated with mood and anxiety disorders.[9 10] In a very recent meta-analysis by Nourredine *et al*, ADHD in childhood was found to be associated with a higher risk of later psychotic disorders.[11] However, whether there is a causal link between ADHD and other mental disorders remains unknown because, in observational studies, confounding and reverse causation cannot be excluded.

OBJECTIVE

In this study we explored whether there is a causal relationship between ADHD and other mental disorders—namely, major depressive disorder (MDD), bipolar disorder, anxiety disorder, schizophrenia, post-traumatic stress disorder (PTSD), anorexia nervosa (AN) and at least one suicide attempt by two-sample network Mendelian randomisation (MR) analysis.

METHODS

Study design

To understand the cause–effect relationships between ADHD and psychiatric disorders, our study based on the MR approach consisted of several steps. The MR framework uses genetic variants in an instrumental variable setting to test for a causal effect of an exposure on an outcome. Where possible, we extended this study design with a meta-analysis combining MRs of two different cohorts per phenotype. Our stepwise network design is shown in online supplemental method 1 and can be described as follows.

As a first step, our aim was to find out which of the seven mentioned disorders were basically related to ADHD by calculating total effects (ie, any path between ADHD and the respective outcome) applying univariable MR. In a second step, we performed further univariable MR analyses to identify ADHD-related disorders that could potentially act as confounders or mediators due to the effects detected in the first stage. Finally, we calculated the so-called direct effects and extracted in this way the effects that could be attributed directly to ADHD using multivariable MR.

Data collection

In this comprehensive MR study we used a range of datasets to obtain the best possible evidence. Regarding the sample sizes and a clear case definition based on diagnoses by psychiatrists (ICD10 and DSM), we used genome-wide association studies (GWASs) from the iPSYCH project and the Psychiatric Genomics Consortium (PGC) in the main analyses. Phenotypes from PGC including combined diagnoses or substance use disorders were not considered in this study. If available, we replicated the results using summary statistics from the FinnGen[12] project and calculated meta-analysis estimates applying random-effects models for these outcomes. Phenotype and cohort descriptions are shown in online supplemental method 2 and summarised in table 1.

All datasets were restricted to individuals from European ancestry of both sexes. Where available, genetic variants with an imputation info score <0.8 or a minor allele frequency <0.01 were excluded from the analyses. More detailed information can be found in the respective GWASs.[13–20]

Instrument selection

As relevant genetic variants we chose single nucleotide polymorphisms (SNPs) associated with the respective exposure based on the genome-wide association threshold of $p=5\times10^{-8}$. To ensure independence of instruments, SNPs in linkage disequilibrium (LD) within a 10 000 kb window and a r^2 threshold of 0.001 were pruned using PLINK clumping. If a genetic variant was missing from the outcome dataset, we searched for proxies that were in LD with $r^2 \geq 0.8$ using the 1000 Genomes database. After the harmonisation process, in which we attempted to infer forward strand alleles using allele frequencies, we excluded palindromic SNPs with a minor allele frequency >0.42.

Statistical analyses

Univariable MR

To estimate the lifetime causal effects and investigate potential outliers responsible for horizontal pleiotropy, we iteratively applied the radial regression framework. In each iteration step we performed the inverse-variance weighted (IVW) regression with second order weights as the main method, and excluded variants based on the Cochran's *Q* and Rueckers *Q* statistics, considering a significance threshold of 0.01. The robustness of estimates was assessed by applying a range of pleiotropy robust methods in the context of sensitivity analyses. These included the weighted mean, weighted median, MR-RAPS (many weak instrument analysis) and MR-PRESSO (outlier corrected estimates) methods. Directional and widespread horizontal pleiotropy was tested using the MR-Egger test and the MR-PRESSO global test (based on the residual sum of squares) and tests of the heterogeneity statistics (*Q* statistics), respectively. To assess whether the assumption that an exposure causes an outcome is valid, the MR-Steiger test was applied.

Meta-analyses

With the exception of the phenotypes suicide attempt and MDD, for which we were not able to find further non-overlapping GWASs, we performed a meta-analysis based on two MR studies

Table 1 Description of outcome datasets and the number of genetic instruments used before and after outlier correction

Chracteristic	Schizophrenia[18]		Anorexia nervosa[19]		PTSD[17]		Anxiety[15]		Bipolar disorder[16]		MDD[14]	Suicide[20]
Cases	39 910	5760	16 992	1233	23 185	1312	4584	2593	41 917	5091	170 756	6024
Controls	60 558	249 610	55 525	10 169	151 309	235 546	19 225	235 546	371 549	228 817	329 443	44 240
Potential instruments*	9	9	11	9	11	9	9	9	9	9	9	10
Remaining Instruments†	6	9	10	7	11	9	9	9	8	9	7	9
Consortia	PGC	FinnGen	PGC‡	FinnGen	PGC	FinnGen	iPSYCH	FinnGen	PGC§	FinnGen	PGC	iPSYCH

*Before outlier correction.
†After outlier correction.
‡And ANGI, UKB, GCAN, WTCCC3, CHOP, PFCG.
§Statistics were received for iPSYCH, deCODE, Estonian Biobank, HUNT and UK Biobank cohorts.
.MDD, major depressive disorder; PTSD, post-traumatic stress disorder.

per outcome. Using the results from our MR analyses, we calculated pooled estimates by performing IVW random effects models to account for between-study heterogeneity. Weights, heterogeneity statistics and comparison of fixed and random effects models of meta-analyses per outcome are shown in online supplemental figure 1.

Network and multivariable MR

To assess potential confounding and mediation mechanisms, we modelled the reverse directions with ADHD as outcome and estimated the causal effects of ADHD-related psychiatric disorders on each other by performing multiple univariable MR analyses in the context of a network MR.[21] This means that, as shown in online supplemental figure 1, we tested the network consisting of all possible paths and their directions between ADHD and related mental disorders (found in the first step) for notable associations in specific univariable MR analyses (ie, each arrow represents one MR analysis). In this way, we aimed to identify phenotypes that either mediate an association or bias it in the sense of horizontal pleiotropy. After finding mental disorders potentially responsible for horizontal pleiotropy, we used multivariable MR analyses to calculate the direct effects of ADHD on one of the associated outcomes. In this context, we estimated the effects that could be directly attributed to the ADHD rather than to another mental disorder, allowing the genetic instruments to be associated with multiple phenotypes. Where appropriate, we assessed mediation mechanisms considering also bidirectional relationships on the log scale using the product-of-coefficient method[22] (see online supplemental method 3). More details about the multivariable MR can be found elsewhere.[23] The robust IVW method with multiplicative random effects was used as the principal approach, while the weighted median, MR-Egger and MR-Lasso served as sensitivity analyses within multivariable MR. Multivariable heterogeneity statistics and the MR-Egger intercept were calculated to quantify and test for horizontal and directional pleiotropy, respectively.

Regarding multiple testing issues based on seven null hypotheses (outcomes), a Bonferroni adjusted threshold of 0.007 was considered as a type I error for the analyses. ORs presented can be interpreted as the average change in the respective outcome per 2.72-fold increase in the prevalence of the exposure.[24]

All analyses were performed using the open source statistical software R (v4.1.2). For MR we used mainly the packages TwoSampleMR (v0.5.6), MendelianRandomization (v0.6.0), RadialMR (v1.0), mr.raps (v0.2) and MRPRESSO (v1.0). Figures were created with ggplot2 (v3.3.5).

Reporting follows the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization: The STROBE-MR Statement.

RESULTS

Univariable MR: total effects

Starting with 9–11 potential genetic instruments for ADHD (see online supplemental table 1), the number of SNPs was reduced to 6–11 during the outlier assessment (see online supplemental table 2), depending on the respective outcome (table 1).

Results based on MR and subsequent meta-analyses revealed positive associations between the genetic liability to ADHD and the risk of a suicide attempt (OR 1.34 (95% CI 1.16 to 1.55); $p=8\times10^{-5}$), AN (OR 1.28 (95% CI 1.11 to 1.47); p=0.001), PTSD (OR 1.20 (95% CI 1.08 to 1.34); p=0.001) and MDD (OR 1.09 (95% CI 1.03 to 1.15); p=0.003) (figure 1). No notable associations were observed with anxiety, bipolar disorder and

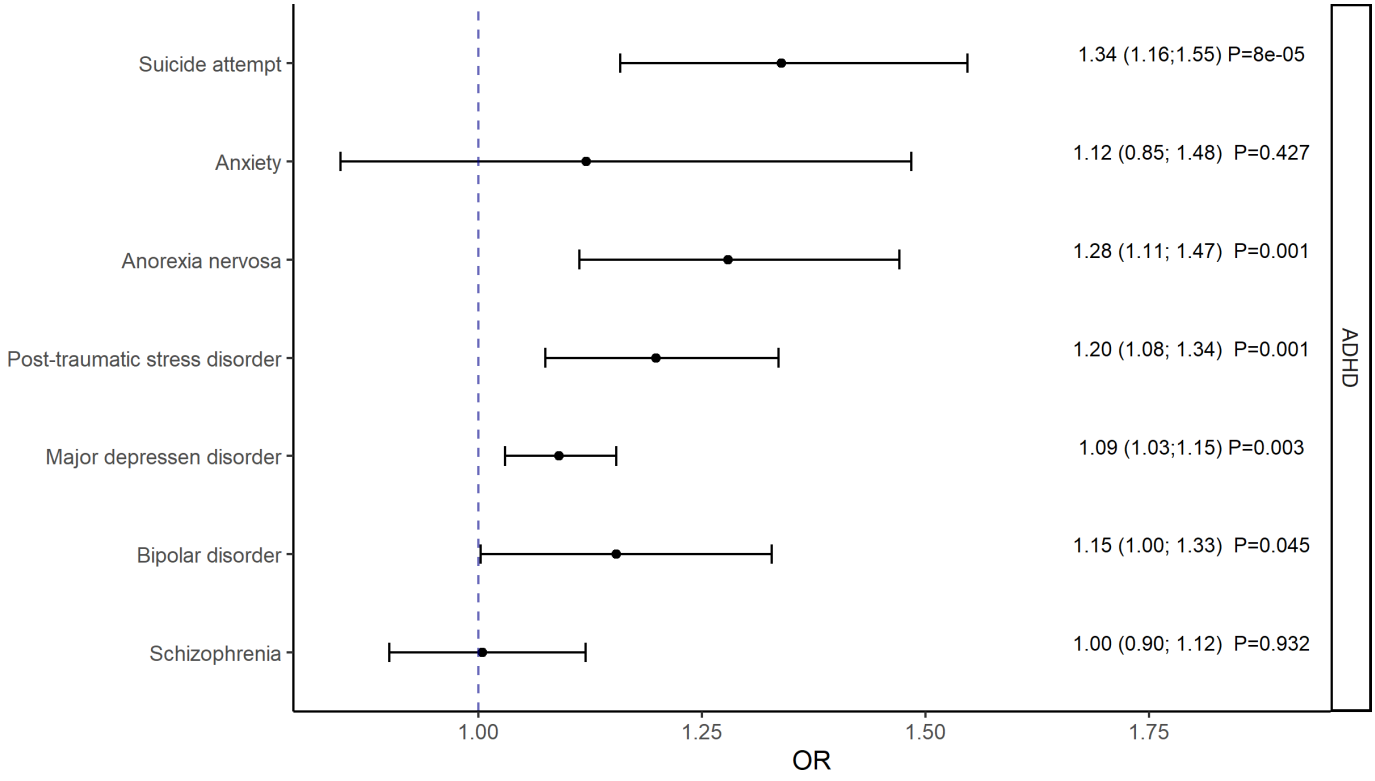

Figure 1 Effect estimates in the form of odds ratios (ORs) and 95% confidence intervals representing the impact of attention-deficit/hyperactivity disorder on the risk of psychiatric outcomes. Estimates derived from meta-analyses based on two Mendelian randomisation studies per outcome (except suicide and major depression disorder). The results should be interpreted based on the Bonferroni corrected threshold of 0.007.

schizophrenia. All of these estimates, except MDD and suicide attempt, resulted from meta-analyses shown in online supplemental figure 1.

Looking at the study-specific MR sensitivity analyses, all findings were supported by the pleiotropy-robust approaches, which led to consistent point estimates, suggesting robust results (see online supplemental figure 2). Comparing the first iterations before outlier exclusion and the outlier-corrected final models, most effect estimates were consistent in terms of direction and magnitude. The only exception was the positive association between ADHD and schizophrenia, which disappeared completely when the identified outliers were removed.

No directional pleiotropy was detected in any of the final MR models regarding the MR-Egger intercept test. Despite the unadjusted p values of the PRESSO global test and the Cochran's *Q* statistic (0.03 and 0.02) in the model with AN (see online supplemental table 3), there was no evidence of SNPs driving the effect or of substantial heterogeneity in the plots (leave-one-out analysis, funnel plot and the scatter plot showing genetic associations).

Network MR

To fully understand the paths regarding our findings described above, we aimed to investigate potential bidirectional and indirect effects of ADHD-related psychiatric disorders from our analyses (ie, MDD, PTSD, AN and at least one suicide attempt) on each other. Since an analysis of PTSD and the phenotypes from the FinnGen cohort was not possible due to lack of instruments, we were only able to use MDD and AN as candidates in the network MR.

In this context, genetic liability to MDD was observed to be positively associated with the risk of PTSD (OR 1.84 (95% CI 1.59 to 2.14); $p=8\times10^{-16}$) and suicide attempt (OR 1.61 (95% CI 1.25 to 2.08); $p=3\times10^{-4}$) but not with AN (OR 1.50 (95% CI 0.96 to 2.33); p=0.073) (figure 2). In addition, modelling the relation of MDD to ADHD yielded an OR of 1.76 (95% CI 1.50 to 2.06) ($p=4\times10^{-12}$), implying a bidirectional association (figure 2). The modelling directions were supported by the MR-Steiger tests (see online supplemental table 4). In contrast, no associations could be found with AN as exposure and MDD, PTSD and suicide attempt as outcomes (figure 2). Again, the estimates with PTSD and AN as outcomes were pooled using meta-analyses, which are shown in online supplemental figure 3. All results were supported by the study-specific sensitivity analyses (see online supplemental figure 4 and online supplemental figure 5).

Multivariable MR: direct effects

With regard to these results, we used multivariable MR to assess whether and to what extent the relationships between ADHD and both PTSD and suicide attempt are affected by MDD. After adjustment for MDD, ADHD was still positively related to PTSD (OR 1.18 (95% CI 1.05 to 1.33); p=0.007) and suicide attempt (OR 1.30 (95% CI 1.16 to 1.47); $p=2\times10^{-5}$) as shown in figure 3. MDD was also directly related to PTSD (OR 1.67 (95% CI 1.37 to 2.02); $p=2\times10^{-7}$) and suicide attempt (OR 1.42 (5% CI 1.08 to 1.87); p=0.011), suggesting that the associations between ADHD and both psychiatric outcomes were mediated by MDD (figure 3). Considering the bidirectional association with ADHD, MDD mediated 21.1% of the proportion of the AHDH–PTSD association (indirect effect: OR 1.05) and 10.3% of the ADHD–suicide attempt association (indirect effect: OR 1.03).

All multivariable results were consistently confirmed by sensitivity analyses, with no evidence of pleiotropy considering the tests due to the multivariable MR-Egger intercept and the *Q* statistic (see online supplemental figure 6, online supplemental table 5).

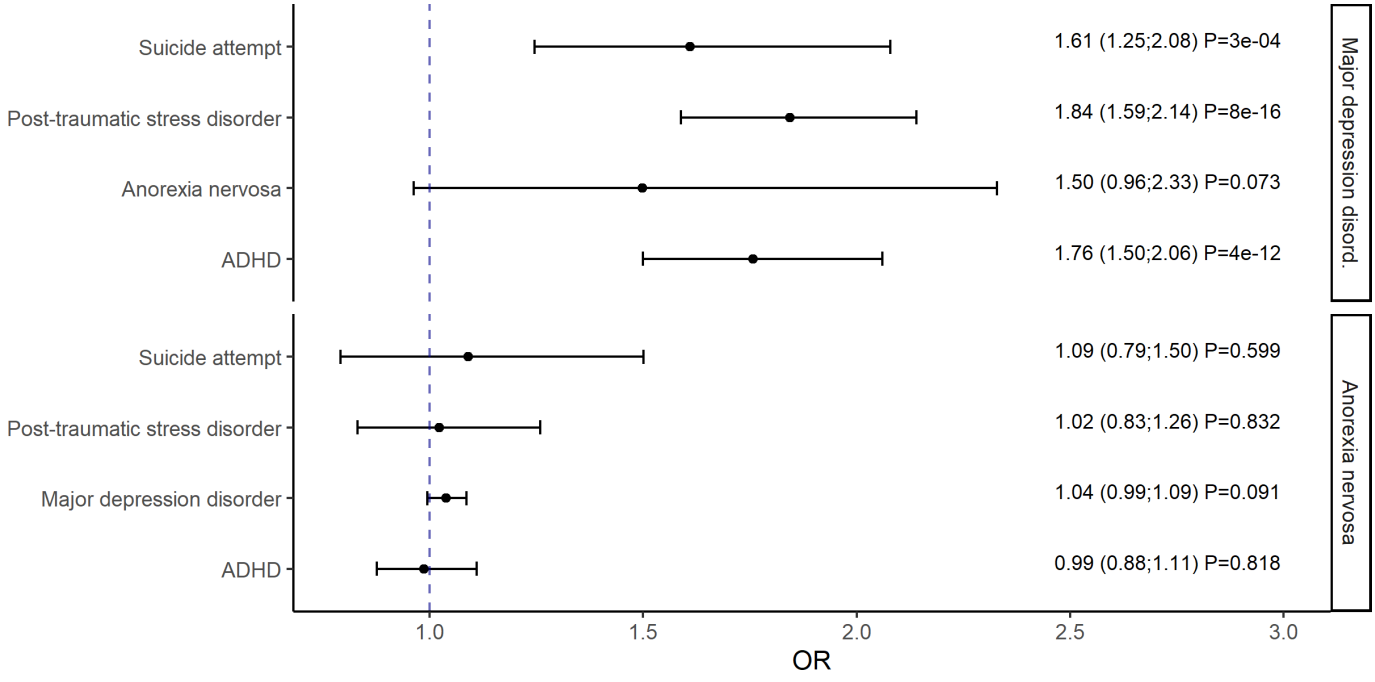

Figure 2 Results from network Mendelian randomisation analyses testing causal effects of major depression disorder or anorexia nervosa on the risk of psychiatric outcomes. Estimates are given in the form of odds ratios (ORs) and 95% confidence intervals. Estimates derived from meta-analyses based on two Mendelian randomisation studies per phenotype (except the outcomes suicide and major depression disorder). Results should be interpreted based on the Bonferroni corrected threshold of 0.007.

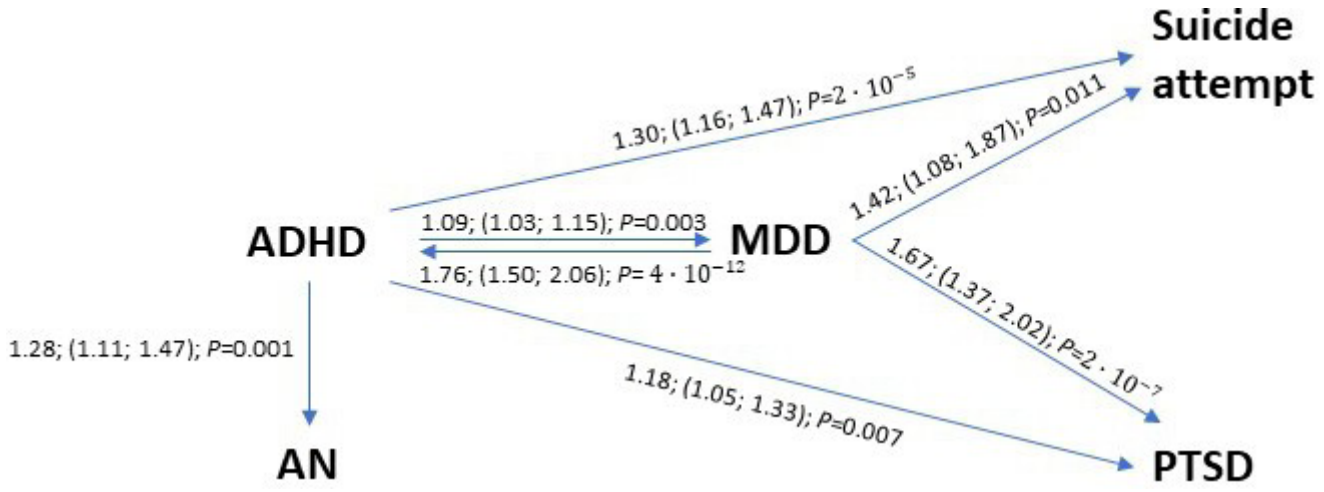

Figure 3 Summary of the findings of this study based on two-sample Mendelian randomisation (MR) analyses. Effect estimates of the associations between ADHD and both suicide attempt and PTSD resulted from multivariable MR analyses after adjusting for MDD. Estimates are given in the form of odds ratios (ORs) and 95% confidence intervals. ADHD, attention-deficit/hyperactivity disorder; AN, anorexia nervosa; MDD, major depressive disorder; PTSD, post-traumatic stress disorder.

DISCUSSION

In this two-sample network MR analysis we evaluated the causal links between ADHD and a range of psychiatric disorders. We identified an impact of ADHD on PTSD, suicide attempt and AN and a bidirectional association between ADHD and MDD. Regarding the bidirectional relationship between ADHD and MDD, a common underlying pathophysiological pathway can be hypothesised, so that both mental disorders may separately and jointly increase the risk of suicide attempts or PTSD. In this context, however, the increased risk of AN can be attributed entirely to ADHD. There was no evidence for a causal link between ADHD and bipolar disorders, anxiety or schizophrenia.

ADHD and MDD

A number of studies consistently found that approximately 35–50% of adults with ADHD experience one or more major depressive episodes during their lifetime; this percentage is significantly higher than the risk for a major depressive episode in the general population (approximately 15%). Data from family studies suggest a familial association and shared genetic risk between ADHD and depression.[25 26] The present finding that ADHD is associated with MDD underlines previous results from observational[27 28] and a recent MR analysis.[29] Imaging studies have shown that patients with ADHD exhibit alterations in prefrontal cortex (PFC) circuits and demonstrate weaker activation of the PFC when attempting to regulate attention and behaviour. The PFC requires optimal levels of norepinephrine and dopamine for proper functioning. Genetic studies have consistently found alterations in genes involved in catecholamine transmission in patients with ADHD.[30] The monoamine hypothesis of depression postulates that depression is caused by decreased modulatory function of serotonin, norepinephrine or dopamine in the brain.[31] Based on the biological aspects of depression and ADHD, the two disorders might share similar pathophysiological brain regions including decreased activity in the PFC,[32 33] amygdala and hippocampus regions.[34–37] Anhedonia, the neurobiology of which is complex and involves disruption of pathways regulating reward and motivation,[38] represents a major feature of both MDD and ADHD.[37] The activity of various components of the limbic–cortical–striatal–pallidal–thalamic pathway correlates with hedonic tone in healthy individuals and is altered in patients with MDD and ADHD.

Note that the observed bidirectional relationship between ADHD and MDD should be seen with caution. ADHD often develops at an early age, which is why the majority of cases considered in the GWAS were diagnosed in childhood (14 878 in childhood vs 6961 in adulthood).[39] MR estimates the mean lifetime effect and is not able to model effects that occur within a specific time period. Thus, the reverse direction may be biased.

ADHD and PTSD

PTSD is a mental and behavioural disorder that can be triggered by a traumatic life event. Classic symptoms include hyperarousal, avoidance and intrusion. Prior investigations have suggested that ADHD is a risk factor for PTSD.[40 41] In part, studies have questioned whether ADHD and PTSD are really two different disorders.[42] However, it is now believed that the two disorders must be considered as two distinct conditions despite sharing common risk factors.[43] Both ADHD and PTSD exhibit genetic transmission[44 45] but, with a few exceptions, the onset of ADHD significantly precedes the onset of PTSD, suggesting that ADHD is an antecedent risk factor for the development of PTSD. Our results support a positive relationship between ADHD and the risk of PTSD, which are in accordance with a longitudinal observational study[46] and a systematic review and meta-analysis.[40]

ADHD and AN

We also found evidence for a causal link between ADHD and eating disorders, in this case with AN. This finding supports prior results from systematic reviews and a meta-analysis showing a higher risk of eating disorders in individuals with ADHD.[47] In the meta-analysis by Nazar *et al*, the pooled OR of diagnosing any eating disorder in ADHD was 3.82 (95% CI 2.34 to 6.24), and for diagnosing AN in ADHD patients the OR was 4.28 (95% CI 2.24 to 8.16). Both ADHD and eating disorders share neurocognitive deficits; patients with the diseases have difficulties in shifting, action sequences, working memory and inhibitory control.[48] Several theories address possible explanations for the association of ADHD with eating disorders. A recent systematic review examining mechanisms underlying comorbid AN and

ADHD suggests that emotion dysregulation may mediate the relationship between these two disorders.[49]

ADHD and suicide attempt

The present study showed that ADHD is related to at least one suicide attempt. Although some previous studies postulated that ADHD was not associated with an increased risk of suicide attempt or completion,[50–53] an increased risk of suicide with ADHD has recently been suggested.[54] A recent systematic review and meta-analysis investigating the relationship between ADHD and suicidal spectrum behaviours including 57 observational studies reported significant associations between ADHD and suicidal attempts (OR 2.37, 95% CI 1.64 to 3.43).[55] One potential explanation for these findings is that ADHD and suicidal behaviour share common genetic factors that may reflect genetic variants associated with impulsivity, a trait that is highly heritable.[56] Impulsivity is a core component of ADHD and closely associated with suicidal behaviour.[57]

ADHD and schizophrenia

Contrary to the previously reported association found by Nourredine *et al*, we could not confirm a link between ADHD and schizophrenia after outlier removal. Their systematic review and meta-analysis summarised 12 observational studies including 1.85 million participants. Five longitudinal studies were included for the meta-analysis with the outcome schizophrenia yielding an OR of 4.59 (95% CI 3.83 to 5.50) for participants with childhood ADHD.[11] However, regarding the overall quality of the studies included in the meta-analysis, a high risk of bias in different areas in several studies was observed.

ADHD and anxiety

Furthermore, we found no evidence for a relationship between ADHD and general anxiety disorder. With a prevalence of about 25–50%, anxiety disorders represent one of the most common comorbidities in patients with ADHD.[58] Epidemiological and clinical studies have indicated a high comorbidity of anxiety disorders in children and adolescents[59] as well as in adult patients with ADHD.[27 60] In longitudinal studies, patients with ADHD were found to develop a higher level of anxiety disorders compared with controls.[61 62]

ADHD and bipolar disorders

After adjustment for multiple testing, our results regarding the risk of bipolar disorders in patients with ADHD could not clearly confirm the findings from a recent systematic review and meta-analysis including six studies which reported a higher risk of bipolar disorder in individuals with ADHD compared with healthy controls (risk ratio 8.97, 95% CI 4.26 to 18.87).[63] Another systematic review and meta-analysis including 71 studies with 646 766 participants from 18 countries found that one in 13 adults with ADHD was also diagnosed with bipolar disorder.[10]

Implications

The present MR study extends existing research by examining the causal association between ADHD and common psychiatric disorders. There is little doubt that ADHD and other mental disorders share common pathophysiological causes, but the exact causative mechanisms have not yet been fully elucidated.[30 36 64] Also, prenatal and perinatal factors are discussed as possible underlying risk factors.[65] A further important issue in this connection is that children with ADHD are often treated with psychostimulant drugs which could have an effect on the development of further mental disorders later in life.[11] Furthermore, systemic inflammation could in part explain the joint occurrence of ADHD and other mental disorders.[66]

Due to the association between ADHD and PTSD, clinicians who treat patients with ADHD should be alert to the fact that their patients with this diagnosis are at a higher risk of developing PTSD later in life. Thus, early and effective treatment of ADHD may reduce the risk and a subsequently more severe course of PTSD.[45]

Strengths and limitations

The strengths of our study, which is less prone to unmeasured confounding and reverse causality than observational studies, include robustness of the results based on an iterative approach focusing on outliers, up to two datasets per outcome, and a range of sensitivity analyses in both the univariable and multivariable design.

The results of our MR analyses partially confirmed most, but not all, of the previously reported associations in a hypothesis-free context. For example, we could not maintain the association between ADHD and schizophrenia after removing outliers. This may be due to the various limitations of observational studies, such as unobserved confounding, reverse causality, publication and selection bias or the limitations of MR. As with any statistical method, it is important to remember that absence of evidence is not equivalent to evidence of absence. MR examines lifelong effects, but some causal factors for the onset of mental disorders may have more acute effects. Further investigations are necessary to address these unresolved issues. Another limitation of MR arises from horizontal pleiotropy—that is, one and the same gene may be associated with different phenotypic traits. The genetic architecture of psychiatric phenotypes is highly polygenic and pleiotropic[67] and often the biological function of their associated genetic variants is unknown. However, we were able to confirm our results by using different approaches such as network MR in an iterative way, a series of sensitivity analyses, and multivariable MR accounting for potential confounding and mediation effects. It is therefore unlikely that the observed relationships of ADHD with MDD, AN, suicide attempts and PTSD were apparent only because of horizontal pleiotropy. Furthermore, caution should be taken when interpreting the magnitude of calculated effect estimates and mediation effects since MR does not provide accurate point estimates in case of binary exposures.[22] For this reason, the estimators presented should be viewed as tests of causality or mediation rather than true causal effects. Finally, the results are based on data from individuals of European descent, so generalisability to other ethnicities is limited.

CONCLUSIONS

The present findings are important for clinicians treating patients with ADHD because they provide a guide as to the mental comorbidities on which to focus preventively and therapeutically during the course of the disease. ADHD serves as an early indicator of other mental disorders due to shared psychopathologies. Therefore, it is necessary to monitor patients with ADHD for early signs of mental comorbidities. In addition, an increased risk of AN in patients with ADHD must be considered. This would allow for early treatment tailored to the patient.

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Contributors CM participated in data collection, supervised the project and drafted the Background and Discussion sections. DF performed the statistical analyses, created all tables and plots and drafted the Methods and Results sections. Both authors participated in the design of the study, investigation and interpretation of results. CM and DF act as guarantors for the study.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable since the study is based on summary-level data. In all original studies, ethical approval and participant consent to participate had been obtained

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. This study is based on freely available summary-level data. Datasets used in the main analyses can be obtained from iPSYCH (https://ipsych.dk/en) project and PGC (https://www.med.unc.edu/pgc), respectively.[13–20] Data used in the replication analyses are available at the FinnGen project (https://www.finngen.fi/en).[12]

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REFERENCES

1 Thapar A, Cooper M. Attention deficit hyperactivity disorder. *Lancet* 2016;387:1240–50.
2 Asherson P, Buitelaar J, Faraone SV, *et al*. Adult attention-deficit hyperactivity disorder: key conceptual issues. *Lancet Psychiatry* 2016;3:568–78.
3 Posner J, Polanczyk GV, Sonuga-Barke E. Attention-deficit hyperactivity disorder. *Lancet* 2020;395:450–62.
4 Sandberg S. *Hyperactivity and attention disorders of childhood*. *Cambridge Child and Adolescent Psychiatry*. 11 July 2002.
5 Kooij SJJ, Bejerot S, Blackwell A, *et al*. European consensus statement on diagnosis and treatment of adult ADHD: the European Network Adult ADHD. *BMC Psychiatry* 2010;10:67.
6 National Institute for Health and Care Excellence. Attention deficit hyperactivity disorder: diagnosis and management; 2019. Available: https://www.nice.org.uk/guidance/ng87
7 Faraone SV, Perlis RH, Doyle AE, *et al*. Molecular genetics of attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2005;57:1313–23.
8 Kittel-Schneider S, Arteaga-Henriquez G, Vasquez AA, *et al*. Non-mental diseases associated with ADHD across the lifespan: Fidgety Philipp and Pippi Longstocking at risk of multimorbidity? *Neurosci Biobehav Rev* 2022;132:1157–80.
9 Sandstrom A, Perroud N, Alda M, *et al*. Prevalence of attention-deficit/hyperactivity disorder in people with mood disorders: a systematic review and meta-analysis. *Acta Psychiatr Scand* 2021;143:380–91.
10 Schiweck C, Arteaga-Henriquez G, Aichholzer M, *et al*. Comorbidity of ADHD and adult bipolar disorder: a systematic review and meta-analysis. *Neurosci Biobehav Rev* 2021;124:100–23.
11 Nourredine M, Gering A, Fourneret P, *et al*. Association of attention-deficit/hyperactivity disorder in childhood and adolescence with the risk of subsequent psychotic disorder: a systematic review and meta-analysis. *JAMA Psychiatry* 2021;78:519–29.
12 Kurki MI, Karjalainen J, Palta P, *et al*. FinnGen: unique genetic insights from combining isolated population and national health register data. *Genetic and Genomic Medicine* [Preprint] 2022.
13 Demontis D, Walters RK, Martin J, *et al*. Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat Genet* 2019;51:63–75.
14 Howard DM, Adams MJ, Clarke T-K, *et al*. Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nat Neurosci* 2019;22:343–52.
15 Meier SM, Trontti K, Purves KL, *et al*. Genetic variants associated with anxiety and stress-related disorders: a genome-wide association study and mouse-model study. *JAMA Psychiatry* 2019;76:924–32.
16 Mullins N, Forstner AJ, O'Connell KS, *et al*. Genome-wide association study of more than 40,000 bipolar disorder cases provides new insights into the underlying biology. *Nat Genet* 2021;53:817–29.
17 Nievergelt CM, Maihofer AX, Klengel T, *et al*. Largest genome-wide association study for PTSD identifies genetic risk loci in European and African ancestries and implicates novel biological pathways. *bioRxiv* [Preprint] 2018.
18 Trubetskoy V, Pardiñas AF, Qi T, *et al*. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature* 2022;604:502–8.
19 Watson HJ, Yilmaz Z, Thornton LM, *et al*. Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. *Nat Genet* 2019;51:1207–14.
20 Erlangsen A, Appadurai V, Wang Y, *et al*. Genetics of suicide attempts in individuals with and without mental disorders: a population-based genome-wide association study. *Mol Psychiatry* 2020;25:2410–21.
21 Burgess S, Daniel RM, Butterworth AS, *et al*. Network Mendelian randomization: using genetic variants as instrumental variables to investigate mediation in causal pathways. *Int J Epidemiol* 2015;44:484–95.
22 Sanderson E. Multivariable Mendelian randomization and mediation. *Cold Spring Harb Perspect Med* 2021;11.
23 Burgess S, Dudbridge F, Thompson SG. Multivariable Mendelian randomization: the use of pleiotropic genetic variants to estimate causal effects *Am J Epidemiol* 2015;181:290–1.
24 Burgess S, Labrecque JA. Mendelian randomization with a binary exposure variable: interpretation and presentation of causal estimates. *Eur J Epidemiol* 2018;33:947–52.
25 Lee PH, Doyle AE, Li X, *et al*. Genetic association of attention-deficit/hyperactivity disorder and major depression with suicidal Ideation and attempts in children: the Adolescent Brain Cognitive Development study. *Biol Psychiatry* 2022;92:236–45.
26 Doherty JL, Owen MJ. Genomic insights into the overlap between psychiatric disorders: implications for research and clinical practice. *Genome Med* 2014;6:29.
27 Kessler RC, Adler L, Barkley R, *et al*. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey replication. *Am J Psychiatry* 2006;163:716–23.
28 Spencer T, Biederman J, Wilens T, *et al*. A large, double-blind, randomized clinical trial of methylphenidate in the treatment of adults with attention-deficit/hyperactivity disorder. *Biological Psychiatry* 2005;57:456–63.
29 Soler Artigas M, Sánchez-Mora C, Rovira P, *et al*. Mendelian randomization analysis for attention deficit/hyperactivity disorder: studying a broad range of exposures and outcomes. *Int J Epidemiol* 2023;52:386–402.
30 Wu T, Liu X, Cheng F, *et al*. Dorsolateral prefrontal cortex dysfunction caused by a go/no-go task in children with attention-deficit hyperactivity disorder: a functional near-infrared spectroscopy study. *Front Neurosci* 2023;17.
31 Krishnan V, Nestler EJ. The molecular neurobiology of depression. *Nature* 2008;455:894–902.
32 Arnsten AFT. The emerging neurobiology of attention deficit hyperactivity disorder: the key role of the prefrontal association cortex. *J Pediatr* 2009;154:I–S43.
33 Treadway MT, Waskom ML, Dillon DG, *et al*. Illness progression, recent stress, and morphometry of hippocampal subfields and medial prefrontal cortex in major depression. *Biol Psychiatry* 2015;77:285–94.
34 Frodl T, Stauber J, Schaaff N, *et al*. Amygdala reduction in patients with ADHD compared with major depression and healthy volunteers. *Acta Psychiatr Scand* 2010;121:111–8.
35 Onnink AMH, Zwiers MP, Hoogman M, *et al*. Brain alterations in adult ADHD: effects of gender, treatment and comorbid depression. *Eur Neuropsychopharmacol* 2014;24:397–409.
36 Viering T, Naaijen J, van Rooij D, *et al*. Amygdala reactivity and ventromedial Prefrontal cortex coupling in the processing of emotional face stimuli in attention-deficit/hyperactivity disorder. *Eur Child Adolesc Psychiatry* 2022;31:1895–907.
37 Meinzer MC, Pettit JW, Leventhal AM, *et al*. Explaining the covariance between attention-deficit hyperactivity disorder symptoms and depressive symptoms: the role of hedonic responsivity. *J Clin Psychol* 2012;68:1111–21.
38 Cooper JA, Arulpragasam AR, Treadway MT. Anhedonia in depression: biological mechanisms and computational models. *Curr Opin Behav Sci* 2018;22:128–35.
39 Rajagopal VM, Duan J, Vilar-Ribó L, *et al*. Differences in the genetic architecture of common and rare variants in childhood, persistent and late-diagnosed attention-deficit hyperactivity disorder. *Nat Genet* 2022;54:1117–24.
40 Spencer AE, Faraone SV, Bogucki OE, *et al*. Examining the association between posttraumatic stress disorder and attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *J Clin Psychiatry* 2016;77:72–83.
41 Adler LA, Kunz M, Chua HC, *et al*. Attention-deficit/hyperactivity disorder in adult patients with posttraumatic stress disorder (PTSD): is ADHD a vulnerability factor *J Atten Disord* 2004;8:11–6.

42 Szymanski K, Sapanski L, Conway F. Association or diagnostic confusion? A clinical perspective. *J Infant Child Adolescent Psychotherapy* 2011;10:51–9.
43 Antshel KM, Kaul P, Biederman J, *et al*. Posttraumatic stress disorder in adult attention-deficit/hyperactivity disorder: clinical features and familial transmission. *J Clin Psychiatry* 2013;74:e197–204.
44 Sartor CE, Grant JD, Lynskey MT, *et al*. Common heritable contributions to low-risk trauma, high-risk trauma, posttraumatic stress disorder, and major depression. *Arch Gen Psychiatry* 2012;69:293–9.
45 Biederman J, Petty CR, Spencer TJ, *et al*. Examining the nature of the comorbidity between pediatric attention deficit/hyperactivity disorder and post-traumatic stress disorder. *Acta Psychiatr Scand* 2013;128:78–87.
46 Howlett JR, Campbell-Sills L, Jain S, *et al*. Attention deficit hyperactivity disorder and risk of posttraumatic stress and related disorders: a prospective longitudinal evaluation in U.S. Army soldiers. *J Trauma Stress* 2018;31:909–18.
47 Nazar BP, Bernardes C, Peachey G, *et al*. The risk of eating disorders comorbid with attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *Int J Eat Disord* 2016;49:1045–57.
48 Juarascio AS, Manasse SM, Espel HM, *et al*. Could training executive function improve treatment outcomes for eating disorders? *Appetite* 2015;90:187–93.
49 El Archi S, Cortese S, Ballon N, *et al*. Negative affectivity and emotion dysregulation as mediators between ADHD and disordered eating: a systematic review. *Nutrients* 2020;12.
50 Conejero I, Jaussent I, Lopez R, *et al*. Association of symptoms of attention deficit-hyperactivity disorder and impulsive-aggression with severity of suicidal behavior in adult attempters. *Sci Rep* 2019;9:4593.
51 Giupponi G, Giordano G, Maniscalco I, *et al*. Suicide risk in attention-deficit/hyperactivity disorder. *Psychiatr Danub* 2018;30:2–10.
52 Brent DA, Johnson B, Bartle S, *et al*. Personality disorder, tendency to impulsive violence, and suicidal behavior in adolescents. *J Am Acad Child Adolesc Psychiatry* 1993;32:69–75.
53 Brent DA, Perper JA, Moritz G, *et al*. Psychiatric risk factors for adolescent suicide: a case-control study. *J Am Acad Child Adolesc Psychiatry* 1993;32:521–9.
54 Curtis L. Suicide risk is high, but often overlooked, in autistic spectrum disorder populations. *J Child Psychol Psychiatry* 2022;63:1089–91.
55 Septier M, Stordeur C, Zhang J, *et al*. Association between suicidal spectrum behaviors and attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *Neurosci Biobehav Rev* 2019;103:109–18.
56 Fazel S, Långström N, Hjern A, *et al*. Schizophrenia, substance abuse, and violent crime. *JAMA* 2009;301:2016–23.
57 Agosti V, Chen Y, Levin FR. Does attention deficit hyperactivity disorder increase the risk of suicide attempts? *J Affect Disord* 2011;133:595–9.
58 Pallanti S, Salerno L. The burden of adult ADHD in comorbid psychiatric and neurological disorders. In: *The burden of adult ADHD in comorbid psychiatric and neurological disorders. 1st ed*. Cham: Springer, 2020.
59 Yüce M, Zoroglu SS, Ceylan MF, *et al*. Psychiatric comorbidity distribution and diversities in children and adolescents with attention deficit/hyperactivity disorder: a study from Turkey. *Neuropsychiatr Dis Treat* 2013;9:1791–9.
60 Choi W-S, Woo YS, Wang S-M, *et al*. The prevalence of psychiatric comorbidities in adult ADHD compared with non-ADHD populations: a systematic literature review. *PLoS One* 2022;17.
61 Tai Y-M, Gau C-S, Gau SS-F, *et al*. Prediction of ADHD to anxiety disorders: an 11-year national insurance data analysis in Taiwan. *J Atten Disord* 2013;17:660–9.
62 Biederman J, Monuteaux MC, Mick E, *et al*. Young adult outcome of attention deficit hyperactivity disorder: a controlled 10-year follow-up study. *Psychol Med* 2006;36:167–79.
63 Brancati GE, Perugi G, Milone A, *et al*. Development of bipolar disorder in patients with attention-deficit/hyperactivity disorder: a systematic review and meta-analysis of prospective studies. *J Affect Disord* 2021;293:186–96.
64 Xie C, Xiang S, Shen C, *et al*. A shared neural basis underlying psychiatric comorbidity. *Nat Med* 2023;29:1232–42.
65 Davies C, Segre G, Estradé A, *et al*. Prenatal and perinatal risk and protective factors for psychosis: a systematic review and meta-analysis. *Lancet Psychiatry* 2020;7:399–410.
66 Chen X, Yao T, Cai J, *et al*. Systemic inflammatory regulators and 7 major psychiatric disorders: a two-sample Mendelian randomization study. *Prog Neuropsychopharmacol Biol Psychiatry* 2022;116.
67 Brainstorm Consortium . Analysis of shared heritability in common disorders of the brain. *Science* 2018;360:eaap8757.