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Attention-Deficit/Hyperactivity Disorder and Major Depressive Disorder: Evidence From Multiple Genetically Informed Designs

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ABSTRACT

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) and major depressive disorder (MDD) are two highly prevalent disorders that frequently co-occur. Prior evidence from genetic and cohort studies supports an association between ADHD and MDD. However, the direction and mechanisms underlying their association remain unclear. As onset of ADHD occurs in early life, it has been hypothesized that ADHD may cause MDD.

METHODS: We examined the association of ADHD with MDD using 3 different genetically informed methods to disentangle causality from confounding: 1) a nationwide longitudinal register-based full sibling comparison (N = 1,018,489) adjusting for shared familial confounding; 2) a prospective co-twin control study comprising 16,477 twins (5084 monozygotic and 11,393 dizygotic); and 3) a two-sample Mendelian randomization analysis using the largest available ADHD (N = 225,534) and MDD (N = 500,199) genome-wide association study summary statistics, adjusting for correlated and uncorrelated horizontal pleiotropy.

RESULTS: Sibling and twin comparisons indicated that individuals with ADHD have an increased risk for subsequent development of MDD (hazard ratio = 4.12 [95% CI 3.62–4.69]) after adjusting for shared genetic and familial factors and that ADHD scores endorsed by parents are positively associated with subsequent MDD scores at ages 15 and 18 years (b = 0.07 [95% CI 0.05–0.08] and b = 0.09 [95% CI 0.08–0.11], respectively). Mendelian randomization analyses showed that genetic liability for ADHD is causally related to MDD (odds ratio = 1.15 [95% CI 1.08–1.23]).

CONCLUSIONS: Our study provides consistent results across 3 different genetically informative approaches, strengthening the hypothesis that ADHD is causally related to MDD.

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Attention-deficit/hyperactivity disorder (ADHD) and major depressive disorder (MDD) are highly prevalent psychiatric disorders with some overlap in symptoms (1). ADHD is diagnosed in 5% to 10% of youths and 2% to 5% of adults (2), while MDD has a lifetime prevalence of 12% of adolescents and 16% of adults (3,4). Although ADHD is a childhood-onset disorder and onset of MDD usually occurs later in life, it is well established that these conditions frequently co-occur (5,6). Previous research has indicated a strong genetic overlap between ADHD and MDD, with an estimated genetic correlation of r_g = 0.42 (7,8), and large-scale genomic structural equation modeling studies show that MDD loads on two factors: one that represents neurodevelopmental conditions, including ADHD, and one that represents internalizing disorders (9).

The concurrent presence of ADHD and MDD is associated with elevated levels of psychiatric and somatic comorbidities, which negatively impacts the prognosis of individuals with these conditions. Children and adolescents with comorbid ADHD and MDD tend to have more severe and more persistent symptoms and poorer response to pharmacotherapy for MDD and ADHD compared with individuals with either condition alone (10–14). The paucity of evidence-based interventions for children and adolescents with these conditions together is of particular concern given the high health care economic burden of each disorder alone (15,16) that is greatly exceeded in ADHD with comorbid MDD (17). In contrast to the well-established co-occurrence of ADHD and MDD, a detailed understanding of the longitudinal pathway from ADHD to MDD is currently lacking.

There are only a few prospective studies of ADHD and MDD (12,18–22). Among those, some studies have found that genetic liability for ADHD is associated with both depression diagnosis and symptoms (12,20,21). Using a population-based cohort, Gundel *et al.* (19) found a more than 6-fold increased risk of developing MDD within the first year of ADHD diagnosis. Similarly, in a prospective cohort in the United Kingdom, Powell *et al.* (22) showed that women with ADHD had twice the risk of developing subsequent MDD by age 25. However, these studies did not account for unmeasured confounding factors, including genetic and environmental factors shared among family members. This is a critical limitation given the previously reported genetic association between ADHD and MDD. To

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date, two Mendelian randomization (MR) studies have tested a causal hypothesis for the association between ADHD and MDD (18,23). Both studies found that ADHD genetic liability was associated with an increased risk of depression. One of these studies found that this association was weaker when using the largest available broadly defined depression genome-wide association study (GWAS) that identified 102 risk loci (24), with evidence of horizontal pleiotropy. Riglin *et al.* (18) also complemented the MR evidence with a longitudinal birth cohort with converging findings across the two study designs. However, the longitudinal analyses did not account for unmeasured familial confounding, and MR analyses in both studies used weak genetic instruments for ADHD. Instruments for ADHD included 12 genome-wide significant hits (7) compared with the most recent available ADHD GWAS that identified 27 risk loci. This is an important limitation, as the use of weak genetic instruments may lead to bias in the estimates of the causal effect (25) and may be underpowered to provide reliable estimates of a causal effect of the exposure on the outcome. Another limitation of using weak instruments in MR is that it may be subject to confounding by other factors. For example, if the genetic variant is also associated with other exposures or confounders, this could affect the estimates of the causal effect. Finally, the use of weak instruments may lead to low statistical power, increasing the likelihood of a type II error (i.e., failing to detect a true effect). This can limit the ability to draw robust conclusions from the analysis. Similarly, not controlling for correlated or uncorrelated horizontal pleiotropy is another source of bias through confounding by the other traits or outcomes affected by the genetic variant or through collider stratification bias (26).

In this study, we assessed the relationship between ADHD and MDD using 3 genetically informed designs to better disentangle causality from confounding. The integration of evidence from different methods addressing the same research question (i.e., triangulating evidence) not only can identify different sources of potential bias, but also can ultimately strengthen the certainty of the conclusions in etiological epidemiology (27–29). First, using a longitudinal nationwide register-based cohort sibling design, we assessed the relationship between ADHD and depression while controlling for unmeasured familial factors shared by siblings (i.e., shared genetic and environmental factors). Second, we investigated the relationship between ADHD symptoms at age 9 years and subsequent depression symptoms in adolescence at ages 15 and 18 years using validated standardized questionnaires in a prospective co-twin control comparison including monozygotic (MZ) and dizygotic (DZ) twins, allowing us to perform a more stringent control for genetic and shared environmental factors. Lastly, we performed a two-sample MR to quantify whether genetic liability to ADHD is causally associated with depression accounting for pleiotropic effects (both correlated and uncorrelated horizontal pleiotropy), using summary-level statistics from the largest, most recent GWASs to date of ADHD (30) and MDD (24).

METHODS AND MATERIALS

The study received ethical approval from the Regional Ethical Review Board in Stockholm, Sweden and followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) (31) and Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization (STROBE-MR) (32) guidelines. The requirement for informed consent was waived because the study was register based, and data on the included individuals were de-identified. The investigation conforms to the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Sibling Cohort

Study Population. Our study cohort was identified using several Swedish population registries linked by the unique personal identification number assigned to every individual registered in Sweden, including the Total Population Register, Medical Birth Register, Death Register, Prescribed Drug Register (PDR), National Patient Register (NPR), and Multigeneration Register. From the Total Population Register, we identified all individuals born and living in Sweden between 1992 and 2007, excluding individuals who died or emigrated before age 5, individuals with unidentifiable biological parents, stillbirths, and individuals with congenital malformations. All individuals were linked to their full siblings using the Multigeneration Register (1,018,489 individuals within 456,160 clusters of full siblings). The cohort was followed from age 5 years until a recorded diagnosis of depression, death, emigration, or the end of the study period (December 31, 2013).

Exposure and Outcome. Depression was defined by at least one depression diagnosis in the NPR (inpatient and specialized outpatient services) from age 5 years onward (ICD-9 codes 296B, 300E, and 311; ICD-10 codes F32 and F33). ADHD was defined by either receiving at least one ADHD diagnosis in the NPR from age 3 years onward (ICD-9 code 314; ICD-10 code F90) or a prescription of any approved ADHD medication in the PDR within the study period (Anatomical Therapeutic Chemical codes N06BA04, N06BA01, N06BA02, N06BA09, and N06BA12).

Covariates. Using information from the Total Population Register and Swedish Longitudinal Integrated Database for Health Insurance and Labor Market Studies, we included sex and birth year as covariates in the analyses given that the administrative prevalence of both ADHD and depression are different in males and females and has changed over time. Further, the highest parental education of either parent at the year of birth of each sibling was included as a proxy for socioeconomic status.

Statistical Analysis. Incidence rates of depression with 95% CIs in individuals with and without ADHD were calculated fitting a Poisson generalized linear model using a log link function. To investigate the relationship between ADHD and subsequent depression, we fitted a set of Cox proportional hazards models with attained age as the underlying time scale. First, we fitted an unadjusted model including ADHD as a time-varying covariate. In adjusted models, we first adjusted for genetic and environmental factors shared by siblings by

performing a sibling-stratified Cox proportional hazards model. Next, estimates were further adjusted for sex, birth year, and parental education. Estimates were stratified by sex to determine sex differences in the association between ADHD and MDD. Lastly, to address the potential influence of ADHD medications on the association between ADHD and MDD, analyses were stratified based on individuals with an ADHD diagnosis and no recorded prescription of ADHD medications in the PDR versus individuals with one or more prescriptions in the PDR. Estimates are presented as hazard ratios (HRs) with 95% CIs.

Child and Adolescent Twin Study in Sweden

Study Population. Our twin cohort was based on data from the CATSS (Child and Adolescent Twin Study in Sweden). CATSS is an ongoing, longitudinal nationwide cohort. All Swedish twins and their parents are invited to participate when the twins turn 9 (12-year-olds were also included in the first wave) since July 2004 [details can be found in Anckarsäter *et al.* (33)]. We selected all MZ and DZ twins whose parents completed the Autism-Tics, ADHD and Other Comorbidities inventory at age 9 and who also had at least one completed parent-reported or self-rated questionnaire for depression symptoms at ages 15 or 18 years (N = 16,477; 11,393 DZ, 5,084 MZ).

Exposure and Outcome. At age 9, the Autism-Tics, ADHD and Other Comorbidities inventory (34) was administered to parents of the twins via telephone. This scale comprises 19 items closely corresponding to DSM-IV criteria for ADHD. Depression symptoms were captured at ages 15 and 18 years using different scales and raters. At age 15, both twins and parents provided information about internalizing symptoms using the Strengths and Difficulties Questionnaire (35). The Strengths and Difficulties Questionnaire is a 25-item questionnaire that includes 5 subscales. In this study, we used the emotional problems subscale, which contains 5 Likert-type items. At age 18, the twins completed information on 11 Likert-type items on depression using the Center for Epidemiologic Studies Depression Scale (Iowa form) (36), and their parents completed the Adult Behavior Checklist/18-59 (anxious/depressed scale) (37). All scales showed adequate internal consistency in our cohort (α = 0.92, α = 0.71, α = 0.70, α = 0.87, α = 0.88, respectively).

Statistical Analysis. Factor scores were used given that different raters and questionnaires were used and the difference in factor loadings for each item that do not justify sum scoring (38). For each scale, factor scores were estimated using Markov chain Monte Carlo Bayesian estimation to compute the posterior median for each factor score using 600 imputed plausible values (39). Factor scores were estimated in a confirmatory factor analysis model with all depression latent factors (i.e., different rater and questionnaire) allowed to correlate. ADHD factor scores were calculated in a separate confirmatory factor analysis model. Item scores were treated as ordinal (40) and were estimated using the probit link. Bayesian estimation was performed using a Gibbs sampler using 4 independent chains with 10,000 iterations each. Model convergence was assessed using the Gelman-Rubin convergence statistic. Results using robust maximum likelihood are presented in the Supplement. Factor scores were calculated using Mplus 8.3 (41).

We tested the within-twin pair association between ADHD symptoms at age 9 years and subsequent depression symptoms in adolescence at ages 15 and 18 years fitting a conditional linear regression, with each twin pair treated as a separate stratum, using generalized estimating equations. Importantly, the within-twin pair association is adjusted for shared genetic and environmental factors, allowing us to get an association that is closer to the causal effect than between-twin comparisons. We performed analyses for MZ twins and same-sex DZ twins. Specifically, we adjusted 100% of genetic and environmental factors shared by MZ twins, and 50% of segregating genetic effects and the shared environmental factors in DZ twins. Because of well-established sex differences of ADHD in childhood, with higher rates of ADHD in males and higher rates of MDD in females through ages, opposite-sexed DZ twin pairs were removed from the analyses. Analyses were performed with the R package drgee (42). All analyses were performed using R version 4.2.2 (43).

Mendelian Randomization

Genetic Correlations. To explore the shared genetic component of ADHD and depression, the genetic correlation was calculated using linkage disequilibrium score regression and precomputed European linkage disequilibrium scores from the 1000 Genomes Project Phase 3 downloaded from https://github.com/bulik/ldsc.

Univariate Mendelian Randomization. To assess the potential causal effect of liability to ADHD on depression, we extracted summary-level data from the largest, most recent GWASs with European ancestry for ADHD (N = 225,534; 38,691 cases and 186,843 controls) (30) and MDD (N = 500,199 excluding 23andMe; 170,756 cases and 329,443 controls) (24). Single nucleotide polymorphisms (SNPs) were extracted from each GWAS using the genome-wide significance threshold ($p < 5 \times 10^{-8}$), and linkage disequilibrium clumping was performed on the instrument using an r^2 cutoff of 0.001 and a clumping window of 10,000 kb. The direction of the effects and reference alleles were harmonized between ADHD and depression GWASs. When SNPs were missing in the outcome GWAS, a proxy SNP with high linkage disequilibrium (r^2 = 0.8 within 250 kb) was used. Palindromic SNPs with a minor allele frequency < 0.3 were aligned, whereas those with minor allele frequency ≥ 0.3 were excluded from the analyses.

MR analyses were first performed using the inverse variance weighted approach. Given that the inverse variance weighted method can result in biased estimates in the presence of horizontal pleiotropy, we further performed 5 different MR approaches to assess potential violations of MR assumptions: 1) robust MR-Egger, 2) weighted median, 3) MR pleiotropy residual sum and outlier, 4) Bayesian weighted MR (44), and 5) causal analysis using summary effect estimates (45) (CAUSE). While methods such as MR-Egger and weighted median can detect uncorrelated horizontal pleiotropy, these methods

cannot detect correlated pleiotropy resulting in spurious associations. Moreover, Egger fails when many weak horizontal pleiotropic effects exist or a few but large pleiotropic effects exist (44). In contrast, Bayesian weighted MR accounts for the uncertainty of estimated weak effects and horizontal pleiotropy, and CAUSE was used to account for uncorrelated and correlated horizontal pleiotropy. False discovery rate *p*-value adjustments were performed to account for multiple comparisons. Although it is well established that onset of ADHD precedes MDD, MR Steiger directionality test (46) was used to investigate the direction of association between ADHD and MDD. Finally, we performed leave-one-out analysis to evaluate the presence of influential outliers. MR was performed in R version 4.2.2 (43) using the TwoSampleMR (version 0.5.6) and CAUSE (version 1.2.0.335) packages (45,47).

Given recent concerns regarding the low specificity of how MDD is defined in large GWASs (48), analyses were repeated including two different GWASs that used a more strict definition of MDD, requiring a combination of structured interviews and electronic health records (excluding self-reported diagnosis from the UK Biobank and 23andMe) (N = 138,884) (49) or a DSM-IV diagnosis (N = 18,759) (50).

RESULTS

Sibling and Co-twin Analyses

Our sibling cohort comprised 1,018,489 individuals with a median age at the end of follow-up of 14 years (interquartile range, 10–18 years; range, 6–21 years), of whom 495,931 (49%) were females and 522,558 (51%) were males. Among those, 35,968 (3.53%) were diagnosed with ADHD and 12,176 (1.20%) were diagnosed with depression after age 5 years, with a median (interquartile range) age at diagnosis of 11.8 (9.31–14.8) and 16.6 (14.9–18.1) years, respectively. The median follow-up time was 8.80 years with a total follow-up time including 8.6 million person-years.

The incidence rate of depression was 12.07 (95% CI 11.83–12.3) events per 10,000 person-years in individuals without ADHD and 62.37 (95% CI 59.81–65.04) events per 10,000 person-years in individuals with ADHD. At the population level, individuals with ADHD had a 7-fold increased risk of subsequent depression compared with individuals without ADHD (HR = 7.40 [95% CI 7.06–7.75]). When adjusting for shared unmeasured familial confounders in sibling-stratified analyses, the risk was attenuated but remained elevated (HR = 4.12 [95% CI 3.62–4.69]). This relationship slightly increased after further adjusting for birth year, sex, and achieved parental education (HR = 4.72 [95% CI 4.12–5.40]), with a similar magnitude of the association between males and females (HR = 3.94 [95% CI 3.03–5.11] and HR = 4.31 [95% CI 3.29–5.65], respectively) (Table 1). Similar estimates were obtained when stratifying individuals based on the identification of individuals with ADHD through the NPR versus the PDR (Table S2).

The twin cohort comprised 16,477 twins (5084 MZ and 11,393 DZ) born between 1992 and 2004, of whom 8799 (53%) were females and 7678 (47%) were males. When examining the unadjusted relationship between ADHD factor scores at age 9 years and subsequent depression factor scores at ages 15 and 18 years, we observed a positive relationship between ADHD and depression factor scores across raters (i.e., self-rated and parental rating) and zygosity. Table 2 shows all estimates for overall, MZ, and DZ twins at ages 15 and 18 using parent and self-rated factor scores. Among MZ twins, ADHD factor scores endorsed by parents were associated with higher MDD factor scores at ages 15 (b = 0.07 [95% CI 0.05–0.08]) and 18 years (b = 0.09 [95% CI 0.08–0.11]). When adjusting for shared unmeasured familial confounding, we observed an attenuation of these associations, but they remained statistically significant (b = 0.03 [95% CI 0.01–0.05] and b = 0.06 [95% CI 0.03–0.08], respectively).

Table 1. Association Between ADHD and Depression in the Cohort of Full Siblings, *N* = 1,018,489

Model	HR (95% CI)
Unadjusted	7.40 (7.06–7.75)
Adjusted[a]	4.12 (3.62–4.69)
Fully Adjusted[b]	4.72 (4.12–5.40)
Males[c]	3.94 (3.03–5.11)
Females[c]	4.31 (3.29–5.65)

ADHD, attention-deficit/hyperactivity disorder; HR, hazard ratio.

[a]Estimates adjusted for shared familial confounding factors.

[b]Estimates adjusted for shared familial confounding factors, birth year, sex, and parental education.

[c]Estimates adjusted for shared familial confounding factors, birth year, and parental education.

Mendelian Randomization

Genetic Correlations. We found moderately strong genetic correlations between depression and ADHD (r_g = 0.52, SE = 0.03, $p = 2 \times 10^{-79}$).

Univariate MR Analyses. We found evidence of a causal effect of genetic liability for ADHD on depression (odds ratio [OR] = 1.15 [95% CI 1.08–1.23]) using inverse variance weighting. Weighted median, Bayesian weighted MR, MR pleiotropy residual sum and outlier, and CAUSE provided consistent estimates in the same direction and magnitude (Figure 1). We found no evidence of uncorrelated horizontal pleiotropy using MR-Egger intercept (OR = 1.01 [95% CI 0.99–1.03], p = .235). Cochran Q statistic showed heterogeneity of the effects in the included variants for ADHD liability and depression (Q = 127.36, $p = 4.66 \times 10^{-16}$); however, leave-one-out sensitivity analyses did not highlight that the effect was driven by any particular SNP (Figure 2). Results from the two-sample MR analyses assessing the causal relationship between ADHD and depression are shown in Table 3. The Steiger directionality test supported the hypothesis that ADHD genetic liability causes MDD is the correct causal direction ($p = 3 \times 10^{-141}$). Analyses using a stricter MDD definition showed similar conclusions, with a slight increase in the coefficients (OR = 1.26 [95% CI 1.16–1.37] and OR = 1.31 [95% CI 1.13–1.54]).

DISCUSSION

This study used three different genetically informed designs (a longitudinal nationwide sibling comparison analysis, a prospective co-twin control analysis, and a two-sample Mendelian

Table 2. Association Between ADHD Factor Scores and Depression Factor Scores at Ages 15 and 18 in the Twin Cohort, *N* = 16,477

			Parent			Twin		
Model	Sex	Age, Years	Unadjusted *b* (95% CI)	Adjusted *b* (95% CI)[a]	*p* Value	Unadjusted *b* (95% CI)	Adjusted *b* (95% CI)[a]	*p* Value
Overall	Same sex	15	0.07 (0.06 to 0.08)	0.03 (0.02 to 0.04)	<.001	0.03 (0.02 to 0.04)	0.01 (0.002 to 0.03)	.028
		18	0.09 (0.08 to 0.11)	0.05 (0.03 to 0.07)	<.001	0.03 (0.02 to 0.04)	0.02 (0.003 to 0.03)	.018
MZ	Overall	15	0.07 (0.05 to 0.08)	0.03 (0.01 to 0.05)	.001	0.03 (0.02 to 0.04)	0.01 (−0.003 to 0.03)	.105
		18	0.09 (0.08 to 0.11)	0.06 (0.03 to 0.08)	<.001	0.03 (0.01 to 0.04)	0.01 (−0.004 to 0.03)	.130
DZ	Same sex	15	0.07 (0.06 to 0.09)	0.03 (0.01 to 0.05)	.011	0.03 (0.01 to 0.04)	0.02 (−0.004 to 0.04)	.104
		18	0.09 (0.07 to 0.11)	0.04 (0.01 to 0.07)	.009	0.03 (0.01 to 0.04)	0.03 (0.003 to 0.05)	.030

ADHD, attention-deficit/hyperactivity disorder; DZ, dizygotic; MZ, monozygotic.
[a]Estimates adjusted for shared familial confounding factors.

randomization) to assess the relationship between ADHD and MDD. We found support from all three designs converging to suggest that ADHD has a causal effect on the development of subsequent depression. Results from the longitudinal nationwide sibling comparison design showed that siblings with ADHD had a 4-fold increased risk for subsequent depression compared with their siblings without ADHD, with no differences between males and females. Results from the co-twin control study revealed that ADHD factor scores were positively associated with depression scores later in life at ages 15 and 18 years, supporting the interpretation that ADHD has a causal effect on MDD. Similarly, MR analyses indicated evidence for a causal relationship between ADHD genetic liability and depression.

By integrating evidence from different genetically informative methods and representative population samples, we provide a more robust basis for the hypothesis of a causal relationship between ADHD and MDD. The result from the population-based sibling analyses suggests an attenuation of the ADHD-MDD relationship when adjusting for unmeasured familial confounding. This indicates that traditional observational approaches not adjusting for familial factors may result in biased estimations. Further, in line with previous research (51), we found no evidence suggesting that ADHD medication influences the observed relationship between ADHD and depression based on analyses stratified by ADHD medication status. In within-twin pair comparisons we observed a similar pattern of results. Within MZ twins, adjusting for 100% of the genetic and shared familial confounding attenuated the association between ADHD factor scores and MDD factor scores, highlighting again the importance of shared familial factors. The association remained statistically significant, suggesting a causal link between ADHD and subsequent MDD that cannot be entirely explained by shared genetic and environmental factors. Instead, this highlights the importance of environmental factors not shared by family members underlying this association.

Future research should prioritize the identification of specific environmental factors that may mediate the development of depression in individuals with ADHD. Several potential mediating pathways warrant further investigation. First, factors such as differential treatment by parents, traumatic experiences, compromised peer relationships, and unique life events not shared between twins or siblings may increase the vulnerability to depression (11,52–55). Second, chronic

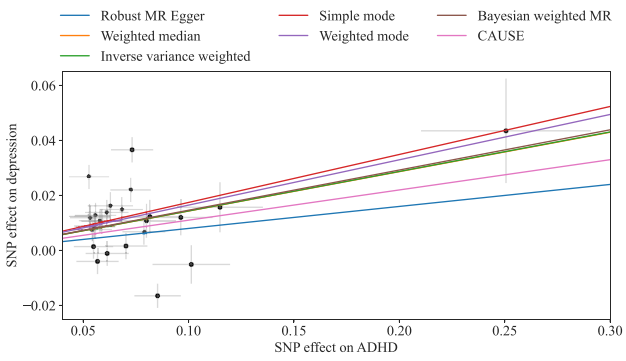

Figure 1. Scatterplot of single nucleotide polymorphism (SNP) effects on attention-deficit/hyperactivity disorder (ADHD) and major depressive disorder. The slope of each line represents the estimated Mendelian randomization (MR) effect per method. CAUSE, causal analysis using summary effect estimates.

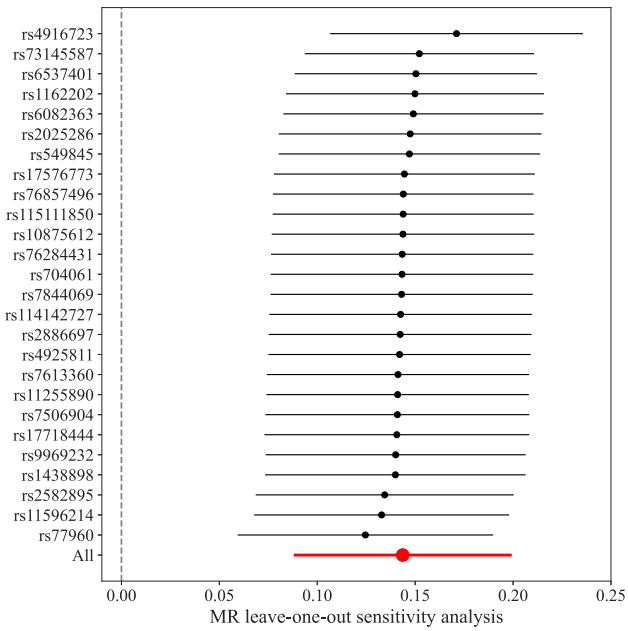

Figure 2. Leave-one-out sensitivity analysis. MR, Mendelian randomization.

Table 3. Results From Two-Sample MR Assessing Causal Relationships Between ADHD and Depression

Method	No. SNPs	*b*	SE	*p* Value	OR	Lower Bound	Upper Bound	Heterogeneity		Pleiotropy Test	
								Q	*p* Value	Egger Intercept	Egger *p*
Main Analyses											
MR-Egger robust	26	0.08	0.09	.389	1.08	0.91	1.28	127.36	4.66×10^{-16}	0.01	.349
Weighted median	26	0.14	0.03	<.001	1.15	1.10	1.21	–	–	–	–
Inverse variance weighted	26	0.14	0.03	<.001	1.15	1.08	1.23	135.21	4.24×10^{-17}	–	–
Simple mode	26	0.18	0.04	<.001	1.19	1.09	1.30	–	–	–	–
Weighted mode	26	0.17	0.05	<.001	1.18	1.08	1.29	–	–	–	–
Bayesian weighted	26	0.15	0.03	<.001	1.16	1.09	1.23	–	–	–	–
MR-PRESSO	26	0.14	0.02	<.001	1.15	1.10	1.20	–	–	–	–
CAUSE	26	0.17	0.01	–	1.19	1.08	1.31	0.06	–	–	–
Sensitivity Analyses											
Inverse variance weighted (MDD definition 2)	26	0.23	0.04	<.001	1.26	1.16	1.37	–	–	–	–
Inverse variance weighted (MDD definition 3)	23	0.27	0.08	<.001	1.31	1.13	1.54	–	–	–	–

ADHD, attention-deficit/hyperactivity disorder; CAUSE, causal analysis using summary effect estimates; MDD, major depressive disorder; MR, Mendelian randomization; PRESSO, pleiotropy residual sum and outlier; SNP, single nucleotide polymorphism; OR, odds ratio.

stressors, including academic underachievement and occupational difficulties resulting from ADHD-related challenges, can undermine self-esteem, exacerbate emotional dysregulation, foster a sense of isolation and diminished self-worth, and generate feelings of frustration and failure (56–58), thereby increasing the likelihood of depression. Lastly, experiences related to substance misuse as well as other psychiatric and somatic comorbidities may impact development of depression (59–61) through various mechanisms, such as altering brain chemistry or affecting social support networks (62,63). Exploring these pathways can provide valuable insights into the complex relationship between ADHD and depression, informing targeted interventions to mitigate depression risk in individuals with ADHD.

The present article has several strengths. First, the longitudinal nature of our register-based sibling comparison study allowed us to establish the temporal relationship between ADHD and MDD in a cohort of more than 1 million individuals. Shared unmeasured familial confounding was adjusted in sibling analyses, and recall biases are not a concern when using electronic health records. Second, twin comparisons used standardized, well-validated scales from twins and their parents at ages 9, 15, and 18 years. Moreover, twin comparisons allowed us to perform a more stringent control for familial confounding by using MZ twin pairs. Third, we used the largest, most recent GWAS on ADHD with more than double the identified risk loci (27 GWAS hits) compared with a prior GWAS included in the two previous MR studies of ADHD and MDD (18). The MR findings in the current study showed consistent results across 8 different methods. In contrast to a previous study (18) that found weak evidence for a causal relationship between ADHD liability and MDD using a broad definition of depression (OR = 1.06 [95% CI 0.98–1.15]), our study revealed a stronger association (OR = 1.19 [95% CI 1.08–1.31]) than previously reported by including the largest to date GWAS on ADHD (30).

Conclusions from this study should be interpreted within the context of some potential limitations. Although register data allowed us to establish temporal relationships between ADHD and MDD, timing of diagnoses in registers is not necessarily accurate, as it is possible that there is a delay from onset to getting diagnosed and treated. ADHD diagnoses in the sibling comparisons were identified using inpatient and outpatient services. As such, misclassification is possible, potentially attenuating the association between ADHD and MDD. Misclassification of individuals with MDD is also plausible given that individuals with MDD after age 18 years are most likely managed in primary care services. However, by including inpatient and outpatient services, we were able to capture the more severe cases. Another important limitation is the relatively low response rates in CATSS participants at ages 15 and 18—61% and 59%, respectively. Further, selection bias is possible if individuals/families affected by ADHD and/or depression are less likely to participate in survey studies. Another limitation is that population-based studies using symptom questionnaires (CATSS) cannot differentiate ADHD from depression as accurately as clinical assessments by clinicians. This may result in inflated associations between ADHD and depression. The study primarily focuses on a young/adolescent population, with the sibling cohort limited to individuals up to age 21 and the twin cohort assessing associations at ages 9 and 15 to 18. It is crucial to acknowledge that the mechanism underlying MDD can vary across developmental stages (64). Generalizing these findings to adult populations should be done cautiously, considering that MDD symptoms in adults may differ from symptoms in adolescents. Future research in adults is necessary for a comprehensive understanding of the ADHD-MDD association across the life span. Finally, MR analyses are also susceptible to bias due to the confounding effect of population stratification that occurs secondary to differences in ancestral populations from which different genotypes come, together with other factors such as

pleiotropy, unmeasured and unknown confounding, linkage disequilibrium, and ethnic differences in allele frequencies.

In conclusion, findings from 3 genetically informed methods converge to suggest a possible causal relationship between ADHD and depression. Understanding the potential causal mechanisms linking ADHD and MDD underscores the need for effective treatment of ADHD. Further, this understanding can inform assessment and management of individuals with ADHD, reducing their risk for developing MDD. Consequently, such proactive measures can lead to improved outcomes and overall well-being for individuals affected by ADHD.

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MG-A had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. MG-A and HL were responsible for study concept and design. MG-A performed the statistical analysis. All authors were responsible for acquisition, analysis, and interpretation of data. MG-A wrote the original draft of the manuscript. All authors critically revised the manuscript for important intellectual content. HL and DD supervised the study.

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