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Original Contribution

The Effect of Attention Deficit/Hyperactivity Disorder on Physical Health Outcomes: A 2-Sample Mendelian Randomization Study

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Attention-deficit/hyperactivity disorder (ADHD) is associated with a broad range of physical health problems. Using different research designs to test whether ADHD has a causal role in these associations is important because comorbid health problems increase the serious social and economic impacts of ADHD. We used 2-sample Mendelian randomization (MR) to infer causal relationships between ADHD and previously implicated physical health conditions. Different MR methods were used to test the robustness and plausibility of our findings. Consistent findings underwent bidirectional and multivariable MR. We found evidence of ADHD having a causal effect on childhood obesity (odds ratio = 1.29, 95% confidence interval: 1.02, 1.63) and coronary artery disease (odds ratio = 1.11, 95% confidence interval: 1.03, 1.19) with consistent results across MR approaches. There was additional MR evidence for a bidirectional relationship between ADHD and childhood obesity. The relationship with coronary artery disease attenuated when controlling for childhood obesity. There was little evidence for inferring a causal effect on other cardiometabolic, autoimmune, allergic, and neurological diseases. Our findings strengthen the argument for effective treatment of children with ADHD, and suggest that clinicians who manage ADHD need to be aware of the risk of childhood obesity to reduce future risks of coronary artery disease.

ADHD; childhood obesity; coronary artery disease; Mendelian randomization

Abbreviations: ADHD, attention deficit hyperactivity disorder; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; GWAS, genome-wide association study; IVW, inverse variance weighted; MR, Mendelian randomization; MVMR, multivariable Mendelian randomization; SNP, single-nucleotide polymorphism.

Attention-deficit/hyperactivity disorder (ADHD) typically begins in early childhood and has a worldwide prevalence of approximately 5% in school-aged children (1, 2). Approximately 65% of children diagnosed with ADHD have symptoms and impairment that persist into adulthood (3), and ADHD can lead to educational, social, and occupational difficulties (4). The economic impact of ADHD is substantial, with the annual national excess costs for ADHD ranging from \$143 billion to \$266 billion in the United States; most of these costs are incurred in adulthood (5). A proportion of these costs is due to higher mortality and morbidity rates, although the reasons behind these associations are currently unclear (6, 7).

There is growing evidence from case-control and cohort studies that ADHD is associated with a broad range of phys-

ical health problems. These include obesity (8), type 2 diabetes mellitus, and hypertension (6)—known risk factors for cardiovascular disease. ADHD is associated with asthma (9); allergic rhinitis (10); and autoimmune conditions, including psoriasis and rheumatoid arthritis (11, 12); as well as childhood epilepsy (13) and migraine (14). Some of these reported associations withstand meta-analyses. However, conventional observational studies are problematic, because associations can arise due to selection bias, reverse causation, and residual confounding (15).

Alternative research designs are needed to infer causation; Mendelian randomization (MR) offers an approach by reducing bias from confounding and reverse causation (16). The rationale behind MR is that genetic variants that are robustly associated with an “exposure” (ADHD in this instance)

can be used as instrumental variables for that exposure. Theoretically, they are unconfounded indicators because they are determined randomly at conception and segregate to viable offspring independently of environmental influences (17, 18). Thus, provided certain assumptions are met, MR is akin to a randomized controlled trial where the intervention increases the likelihood of ADHD. In this study, we used a 2-sample MR design to estimate causal effects of ADHD (indexed by genetic instruments) on metabolic, cardiovascular, autoimmune, allergic, and neurological conditions. These conditions were selected if 1) they had been associated previously with ADHD through observational studies and 2) had publicly available summary statistics from large-scale genome-wide association studies (GWASs). When findings suggested a potentially causal effect, we further tested for possible bidirectional effects. ADHD typically arises early in development and thus precedes the onset of most physical health conditions in the children. However, bidirectional analyses could potentially detect dynastic effects, whereby genetic risk for physical health conditions in the mother causes increased risk of ADHD in the offspring (19).

METHODS

Genetic data: proxies for ADHD and physical health outcomes

Bidirectional MR analyses investigating causal effects used single-nucleotide polymorphisms (SNPs) as proxies for both ADHD (exposure) and physical health (outcomes). For ADHD, 13 SNPs were identified from a GWAS of individuals of European ancestry (19,099 cases and 34,194 control participants) (20) at $P < 1 \times 10^{-7}$ (Web Table 1) (available at <https://doi.org/10.1093/aje/kwaa273>). For physical health outcomes, SNPs were identified from GWAS summary statistics of European ancestry populations for cardiometabolic factors (e.g., body mass index (BMI) (21); childhood obesity (22); coronary artery disease (CAD) (23); myocardial infarction (23); hypertension (24); systolic blood pressure (24); type 2 diabetes mellitus (25)), neurological diseases (e.g., migraine (24), epilepsy (26)), autoimmune diseases (e.g., rheumatoid arthritis (27), inflammatory bowel disease (28)), allergic diseases (allergic rhinitis (24), asthma (29), eczema (30)), and lung cancer (31) (details of GWASs on the outcomes listed here can be found in Web Table 2). All outcome GWASs were independent of the ADHD GWAS (20). GWASs for CAD and myocardial infarction were derived from a mixed population sample with 77% White European participants (23). SNPs associated with ADHD were extracted from the respective outcome GWAS (Web Table 3) after removing palindromic sequences. Full details of SNP extraction and quality control are given in Web Appendix 1 and Web Table 3.

Investigating the causal role of ADHD on physical health outcomes

Two-sample MR was conducted to investigate the causal role of ADHD on physical health outcomes, using GWAS summary statistics to assess both SNP-exposure (i.e., ADHD)

and SNP-outcome (i.e., physical health) associations. This allows the estimation of an unconfounded causal effect between exposure and outcome, if certain assumptions (17) hold true: 1) The genetic variants are strongly associated with the exposure of interest; 2) the genetic variants are independent of confounders of the exposure-outcome association; and 3) the genetic variants do not affect the outcome except through the exposure (exclusion restriction criterion). If they affect the outcome through other pathways, this is called horizontal pleiotropy.

The SNP-exposure and SNP-outcome associations were assessed using 3 methods with different assumptions: inverse-variance weighted approach (IVW) (32), weighted median approach (33), and MR-Egger regression (34). The assumptions of different MR methods are summarized in Figure 1.

Odds ratios for associations between binary exposures and binary outcomes in 2-sample MR studies are interpreted as the odds ratio for outcome per unit increase in the log odds ratio of the exposure. When examining binary exposures in MR settings, causal inferences are valid for the continuous liability underlying the binary exposure (35). Thus, when we test for the causal effect of ADHD, we are essentially examining the effect of genetic liability for this exposure, which can be present in an individual even when they do not have an ADHD diagnosis. To avoid repetition, from this point, when we mention causal effects of a binary exposure, such as ADHD, we refer to genetic liability for this exposure.

We present MR P values that have not been corrected for multiple testing (while acknowledging the number of correlated phenotypes that have been tested) and focus on consistent results across MR methods to assess the strength of evidence favoring a causal effect.

Assessing instrument strength, heterogeneity, and outliers

Instrument strength (first MR assumption) was assessed using the F statistic ($F > 10$ suggests results should not suffer from weak instrument bias) (36). Heterogeneity in the MR effect estimates was assessed using Cochran's Q ; when heterogeneity was detected, we performed leave-one-out analysis to detect potential outliers. Heterogeneity in MR-Egger regression was assessed by I^2_{GX} (values $< 90\%$ suggest heterogeneity) (37); where heterogeneity was detected, simulation extrapolation adjusted MR-Egger regression was performed (R package SIMEX, version 1.7; R Foundation for Statistical Computing, Vienna, Austria) (37).

Investigating reverse causation: The causal role of physical health on ADHD

When a potentially causal effect of ADHD on a health outcome was detected, we investigated possible bidirectional effects by repeating the 2-sample MR analyses using independent genetic variants for the relevant physical outcomes as the exposure (childhood obesity, $P < 1 \times 10^{-6}$ (22); and CAD, $P < 5 \times 10^{-8}$ (23)) and ADHD as the outcome. Steiger filtering for SNPs was also used to examine

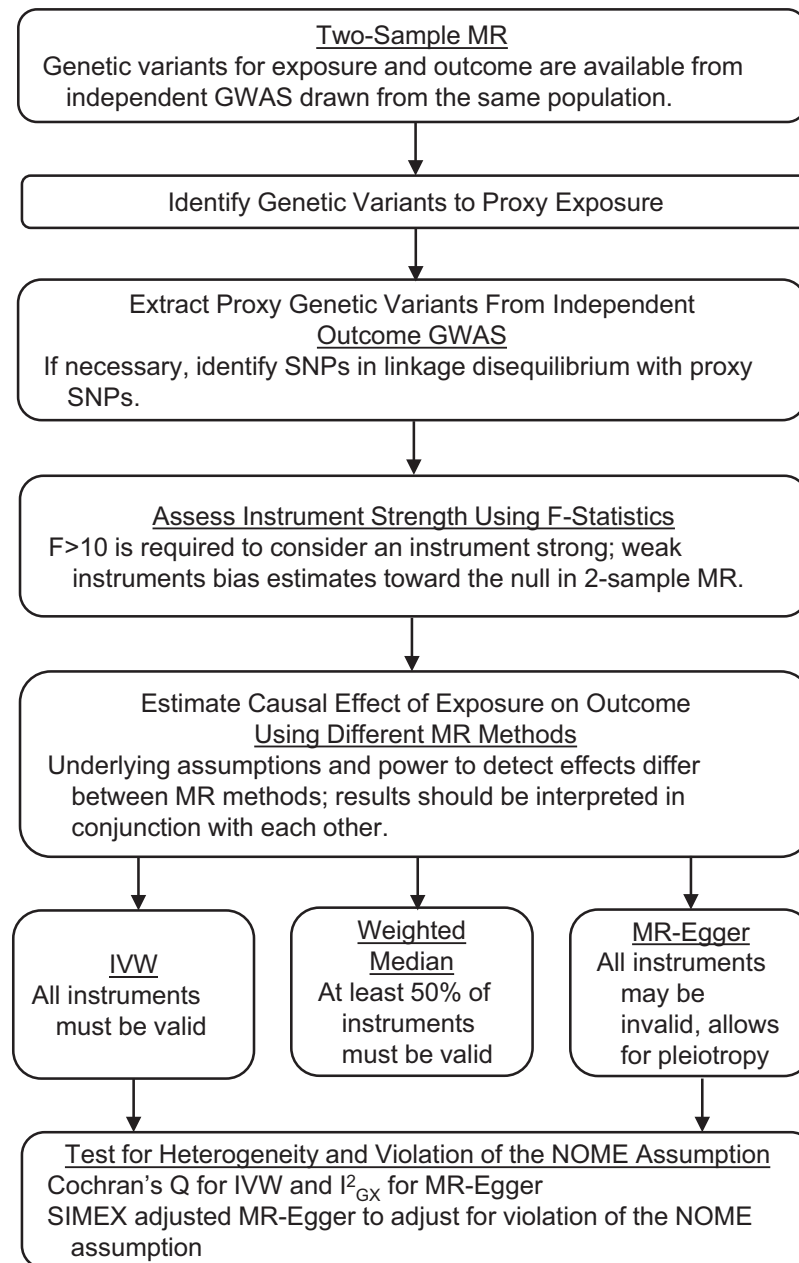


Figure 1. Flow chart of Mendelian randomization (MR) study design outlining MR sensitivity analyses performed, testing for instrument strength and heterogeneity. Abbreviations: GWAS; genome-wide association study; IVW, inverse variance weighted; NOME, no measurement error; SIMEX, simulation extrapolation; SNP, single-nucleotide polymorphism.

whether the instrument SNPs were better predictors of the outcome rather than the exposure, which could indicate reverse causation (38).

Investigating possible mediators of the association between ADHD and physical health outcomes

Multivariable MR (MVMR) analyses were conducted to assess 2 potential mediators of the association between

ADHD and CAD: childhood obesity (22) and lifetime smoking heaviness (39) on CAD. MVMR is an extension of MR that can be used to estimate the causal effects of multiple exposures on 1 outcome simultaneously and requires an additional assumption that each instrument must be conditionally independent of the outcome given all exposures and confounders. MVMR is explained in more detail elsewhere (40).

All steps of the 2-sample MR we performed are summarized in Figure 1. Analyses were conducted using the

Table 1. Two-Sample Mendelian Randomization for Attention-Deficit/Hyperactivity Disorder and Physical Health Outcomes, Using Inverse Variant Weighting

Disease	No. of SNPs	OR ^{a,b}	95% CI
BMI	10	0.03	−0.01, 0.08
Childhood obesity	9	1.29	1.02, 1.63
Coronary artery disease	11	1.11	1.03, 1.19
Myocardial infarction	11	1.06	0.97, 1.16
Hypertension	11	1.05	0.97, 1.13
Systolic blood pressure	11	−0.01	−0.05, 0.03
Type 2 diabetes mellitus	11	1.09	1.00, 1.20
Migraine	12	0.94	0.84, 1.05
Epilepsy	9	1.01	1.00, 1.02
Rheumatoid arthritis	10	1.02	0.87, 1.19
Inflammatory bowel disease	11	0.99	0.86, 1.15
Allergic rhinitis	11	0.92	0.80, 1.07
Asthma	8	1.16	0.93, 1.45
Eczema	11	0.94	0.82, 1.07
Lung cancer	10	1.10	0.96, 1.27

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; SNP, single-nucleotide polymorphism.

^a Odds ratios for binary outcomes are to be interpreted as a change in the log odds ratio of the outcome per unit increase in the log odds ratio of ADHD.

^b β Values are reported for the continuous outcomes BMI and systolic blood pressure.

TwoSampleMR package, version 0.4.14, for R, version 3.4.1.

RESULTS

Investigating the causal role of ADHD on physical health outcomes

MR results using the IVW approach are shown in [Table 1](#). There was evidence of a causal effect of ADHD on childhood obesity (odds ratio (OR) = 1.29 per log odds increase in ADHD genetic liability, 95% confidence interval (CI): 1.02, 1.63) and CAD (OR = 1.11 per log odds increase in ADHD genetic liability, 95% CI: 1.03, 1.19) using IVW. Both the weighted median estimator and MR-Egger regression showed effects consistently in the same direction as IVW, although with wider confidence intervals, as expected ([Figure 2](#), [Web Table 4](#)).

There was little evidence of a causal effect of ADHD on BMI, myocardial infarction, hypertension, systolic blood pressure, type 2 diabetes mellitus, migraine, epilepsy, autoimmune and allergic diseases, and lung cancer. There was evidence of a causal effect from MR-Egger regression (OR = 1.93, 95% CI, 1.08, 3.45) for inflammatory bowel disease ([Web Table 4](#)).

Assessing heterogeneity

Good instrument strength was indicated by the *F* statistics calculated for all the genetic variants used as instruments

([Web Table 5](#)). Heterogeneity in IVW was detected for BMI, hypertension, systolic blood pressure, and allergic rhinitis ([Web Table 5](#)). None of the leave-one-out plots identified any outlying SNPs (see [Web Figures 1–4](#)). There was no evidence that the MR-Egger intercept differed from the null for any of the heterogeneous tests, suggesting that the detected heterogeneity was unlikely to be due to bias from directional horizontal pleiotropy ([Web Table 6](#)).

Based on these initial findings, there was some evidence of a causal effect of ADHD on childhood obesity, CAD, and inflammatory bowel disease. Hence, these 3 outcomes underwent additional sensitivity analyses ([Web Appendix 2](#)). Evidence of a causal effect was detected through simulation extrapolation-adjusted MR-Egger regression for childhood obesity and CAD; hence, we also investigated possible bidirectional effects. We did not detect evidence of a causal effect for inflammatory bowel disease through simulation extrapolation adjusted MR-Egger regression (see [Web Appendix 2](#), [Web Table 7](#)), which suggested pleiotropic effects; hence, it was not taken forward for further analyses.

Investigating reverse causation: the casual role of physical health on ADHD

We performed bidirectional MR to examine the effect of CAD and childhood obesity on ADHD ([Table 2](#)). There was little evidence of a causal effect of CAD on ADHD with an IVW estimate of 0.98 (95% CI: 0.92, 1.04). However, there was some evidence of a causal effect of childhood obesity

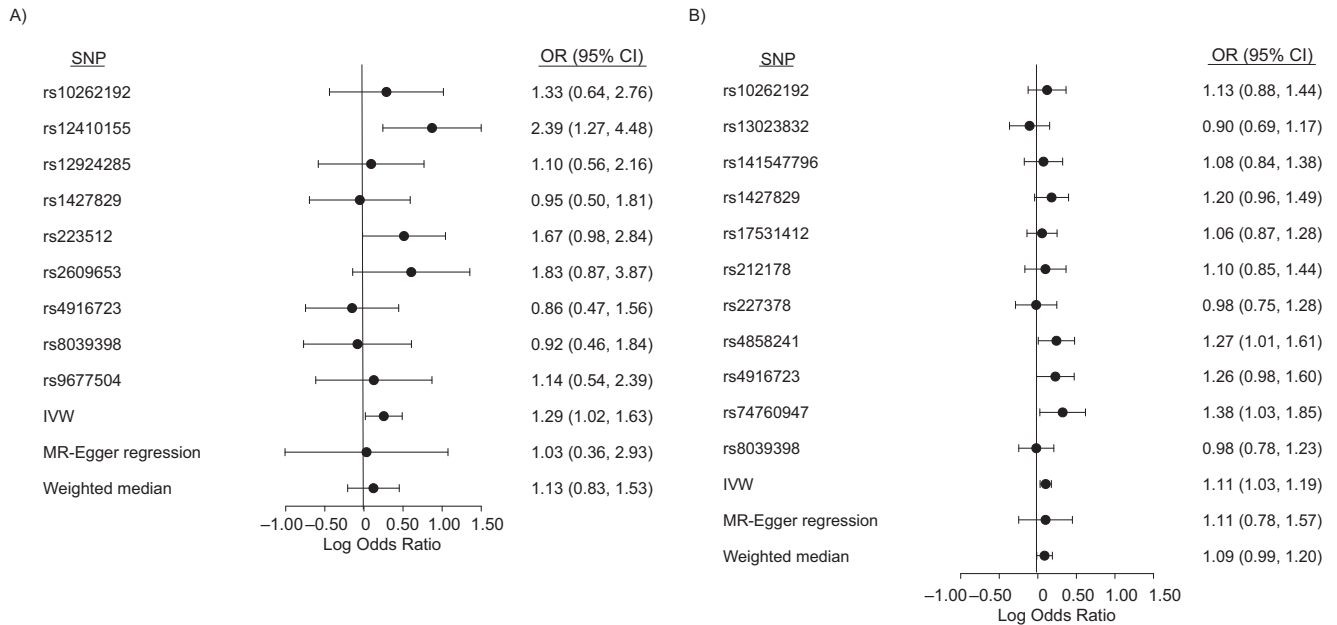


Figure 2. Effect estimates of single variants for attention-deficit hyperactivity disorder on A) childhood obesity and B) coronary artery disease, using inverse variant weighted regression (IVW), weighted median, and MR-Egger approaches. Estimates are shown as odds ratios (ORs) \pm 95% confidence intervals (CIs). SNP, single-nucleotide polymorphism.

on ADHD with an IVW odds ratio of 1.15 (95% CI: 1.05, 1.25) and weighted median odds ratio of 1.10 (95% CI: 1.01, 1.20). MR-Egger regression estimates were directionally consistent and there was little evidence of heterogeneity or horizontal pleiotropy (Web Table 8).

Steiger filtering did not indicate reverse causation, because all the genetic instruments for ADHD explained more variance in ADHD than in CAD or childhood obesity. In addition, none of the 13 SNPs that were used as instruments for ADHD (Web Table 1) were in linkage disequilibrium with any of the 8 SNPs associated with childhood obesity ($P < 5 \times 10^{-6}$) (22), suggesting there was no overlap between genetic instruments for ADHD and childhood obesity.

Investigating possible mediators of the association between ADHD and physical health outcomes, using MVMR

Because obesity and smoking are established risk factors for CAD (41) that are strongly associated with ADHD (6, 42), they are possible mediators of the association between ADHD and CAD. When genetic variants for ADHD and childhood obesity were simultaneously entered in the MVMR model, the direct causal effect of ADHD on CAD was attenuated to 1.06 (95% CI: 0.95, 1.17) compared with univariable MR, whereas the effect of childhood obesity on CAD remained stable (OR = 1.14, 95% CI: 1.08, 1.20) (Web Table 9). One explanation for the difference in the potentially

Table 2. Bidirectional MR With Causal Estimates for Childhood Obesity and Coronary Artery Disease on Attention-Deficit/Hyperactivity Disorder Using Inverse Variant Weighting, Weighted Medians, and MR-Egger Regression

Disease	No. of SNPs	IVW		Weighted Median		MR-Egger Regression	
		OR ^a	95% CI	OR ^a	95% CI	OR ^a	95% CI
Childhood obesity	7	1.15	1.05, 1.25	1.10	1.01, 1.20	1.16	0.60, 2.25
Coronary artery disease	37	0.98	0.92, 1.04	0.96	0.88, 1.05	0.91	0.79, 1.06

Abbreviations: CI, confidence interval; IVW, inverse variant weighted; MR, Mendelian randomization; OR, odds ratio; SNP, single-nucleotide polymorphism.

^a Odds ratios for binary outcomes should be interpreted as a change in the log odds ratio of the outcome per unit increase in the log odds ratio of the exposure.

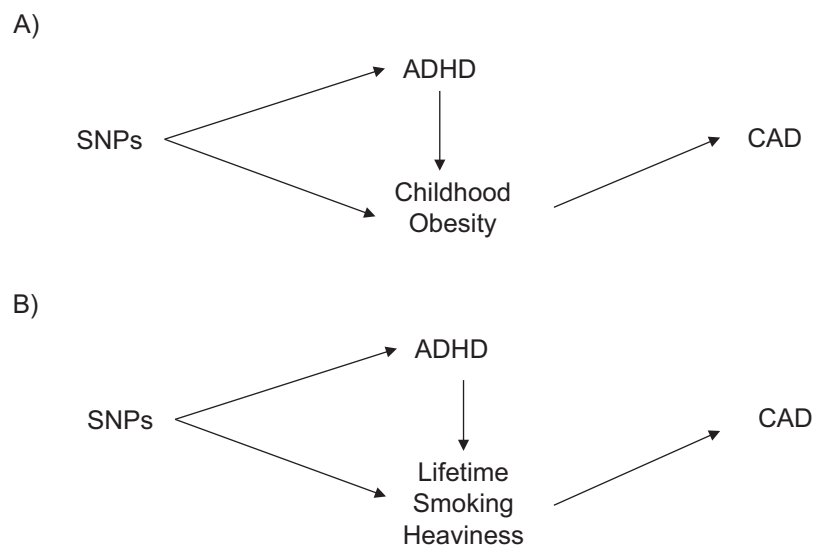


Figure 3. Relationships among A) attention-deficit hyperactivity disorder (ADHD), childhood obesity and coronary artery disease (CAD) and B) among ADHD, childhood obesity, and lifetime smoking heaviness according to results obtained by 3-sample (univariable) Mendelian randomization (MR) and multivariable Mendelian randomization. A) ADHD affects CAD through its effect on childhood obesity, rather than through a direct effect on CAD. B) ADHD affects CAD directly and not only through its effect on lifetime smoking heaviness. Abbreviations: SNP, single nucleotide polymorphism.

causal effects of ADHD on CAD between univariable 2-sample MR and MVMR is that ADHD contributes to CAD through its effect on childhood obesity, rather than through a direct effect on CAD. Thus, there was support for a mediating role of childhood obesity on CAD as illustrated in Figure 3A. The adjusted F statistic was >10 , indicating good instrument strength (Web Table 9).

The (univariable) causal effect of ADHD on lifetime smoking heaviness was 1.07 (95% CI: 1.04, 1.10). When genetic variants for ADHD and lifetime smoking heaviness were simultaneously entered in the MVMR model, the direct causal effect of ADHD on CAD remained stable (OR = 1.10, 95% CI: 1.00, 1.21), whereas the effect of lifetime smoking heaviness on CAD was attenuated (OR = 1.38, 95% CI: 0.99, 1.92) (Web Table 10). As shown in Figure 3B, this indicates that ADHD potentially affects CAD directly and not only through its effect on lifetime smoking heaviness. However, the adjusted F statistic was <10 (Web Table 10), which indicates low instrument strength and which suggested genetic overlap between ADHD and lifetime smoking heaviness; hence, we could not disentangle the effects of ADHD and smoking heaviness on CAD.

DISCUSSION

In this study, we used a 2-sample MR approach to test putative causal effects of ADHD on physical health outcomes, using genetic variants as instrumental variables as proxies for ADHD. We found evidence consistent with a causal effect of ADHD on CAD and evidence for a bidirectional association between ADHD and childhood obesity. There was little evidence of ADHD causal effects on neuro-

logical, autoimmune and allergic diseases, or lung cancer. MVMR results suggested that the causal effect of ADHD on CAD is (at least partially) mediated by childhood obesity.

As reported previously, in observational studies (6, 20, 43), ADHD has been associated with unhealthy lifestyle and risk behaviors. Patients with ADHD are more likely to smoke (42), be overweight (6, 44), and lead a sedentary life (45), and these are all known risk factors for CAD (41). Our results show, indeed, that the effect on CAD was attenuated when we simultaneously assessed the effects of ADHD and childhood obesity on CAD, suggesting childhood obesity may be a potential mediator. Therefore, it seems that at least some of the “impact” of ADHD that confers risk for CAD occurs early in life (i.e., childhood), so if interventions were to target this association, they would need to begin early. We did not identify evidence of causal effect of ADHD on adult BMI, which could indicate that these effects might be more pronounced during childhood when ADHD symptoms are at their peak.

Many studies have shown associations between ADHD and obesity in adolescents and adulthood (44, 46, 47). Motor hyperactivity is a hallmark of ADHD and, therefore, it may appear counterintuitive that patients with ADHD have a higher risk for obesity (48). However, observational studies have shown that those with ADHD have been reported to spend more time watching television (49), have lower levels of physical activity, and increased dysregulation of eating behavior (48).

Bidirectional MR for ADHD and childhood obesity suggested possible effects in both directions, in line with a previous MR study. Maternal effects have been discussed in depth by Martins-Silva et al. (19), who found a causal association

of BMI on ADHD using 2-sample MR. Although, typically, ADHD onset is thought to precede childhood obesity, bidirectional analyses could potentially detect dynastic effects, whereby parental genetic risks for physical health conditions cause increased risk of ADHD in the offspring.

When we simultaneously assessed the effects of ADHD and lifetime smoking heaviness on CAD using MVMR, our results suggested an effect of ADHD on CAD independent of lifetime smoking heaviness. However, the adjusted F statistic was <10 , indicating genetic overlap between ADHD and lifetime smoking heaviness. This is not altogether surprising, because smoking initiation (a core component of the lifetime smoking instrument) is highly correlated with impulsivity and risk taking (39). High genetic correlations between ADHD and smoking initiation have been reported elsewhere (50). Ideally, we would have used smoking heaviness for this analysis, rather than smoking initiation, to better capture the level of tobacco exposure. However, smoking heaviness requires stratification by smoking status, which was not possible using ADHD and CAD summary statistics. Therefore, we emphasize that this exploration of smoking as a possible mediator should be interpreted with caution, because we could not disentangle the effect of ADHD and smoking heaviness on CAD, and should be followed up using smoking heaviness if suitable individual level data become available.

We observed limited evidence supporting a causal role of ADHD on neurological, autoimmune, and allergic diseases. One explanation for this might be that there is no causal effect, and associations found in observational studies are better explained by other factors, such as unmeasured confounding. Another explanation is that these null findings might have arisen due to some of the study limitations, such as instrument validity, population stratification, and low power of MR compared to conventional study designs, which are discussed in more detail in later paragraphs.

Limitations

The latest ADHD GWAS was the first to identify genetic variants that are significantly associated with ADHD, but these variants still only explain little variation in the ADHD phenotype (20).

We relaxed the P -value threshold for SNP inclusion ($P < 1 \times 10^{-7}$) from the ADHD GWAS to increase the number of instruments so that sensitivity analyses, such as MR-Egger regression, could be performed (3 included SNPs were not genome-wide significant). Because relaxing the threshold for SNP inclusion increases the risk of potential sources of bias, such as pleiotropy or heterogeneity, we deemed increasing the P value threshold further would not to be beneficial. Results of our sensitivity analyses suggested there was substantial heterogeneity in MR-Egger regression, which was a marker of measurement error in the instruments. This indicated that there might not have been enough power to detect causal associations, because weak instruments bias associations toward the null in 2-sample MR studies (36). In addition, the age of the participants in the ADHD GWAS would be different from that of some of the outcome GWASs used to extract the instruments.

However, genetic instruments are associated with lifetime exposure to a phenotype (in this case, ADHD) even when identified in childhood. ADHD symptoms tend to persist into adulthood in 65% of children diagnosed with the condition (3). Even when ADHD symptoms do not persist into adulthood, childhood ADHD symptoms can potentially have long-lasting effects on physical health later in life (51).

Because of the high correlation between the outcomes tested, we also did not apply a formal correction for multiple testing but focused on consistent results across sensitivity analyses. However, none of our results passed a Bonferroni-corrected multiple testing burden of $P < 0.0025$ (0.05/15), which is likely to be too conservative in this context, and could still possibly be chance findings. Furthermore, although there was little statistical evidence for horizontal pleiotropy, the underlying biological pathways leading to ADHD are unknown for most of the genetic variants and, therefore, the possibility of pleiotropic effects of these variants cannot be discounted. Because in these analyses we used a 2-sample MR framework, which is based on publicly available data, we were not able to test whether the genetic variants used as instruments are independent of potential confounders of the observed exposure to outcome associations. Confounding may also arise due to population stratification (i.e., GWAS sample was not representative of the underlying population or GWAS samples were from mixed populations) (52), assortative mating (i.e., traits are not inherited independently and a consequent violation of the MR assumption that genetic variants are allocated randomly at conception) (53), or selection bias in the GWAS used, all of which might affect both positive and negative findings of our analyses. Furthermore, estimated 2-sample MR odds ratios for associations of binary exposures with binary outcomes can be biased and should only be interpreted in terms of direction and strength of association (35).

In conclusion, using 2-sample MR, we found evidence in favor of a causal effect of ADHD on CAD that is potentially mediated by childhood obesity. Additional research focusing on long-term follow-up of the physical health of children with either a high number of ADHD symptoms or an ADHD diagnosis is required to elucidate these relationships. Our findings strengthen the argument for early and effective treatment of ADHD symptoms in children because the symptoms may also have an impact on later physical health.

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