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ASSESSING CAUSALITY IN THE ASSOCIATION BETWEEN ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND OBESITY: A MENDELIAN RANDOMIZATION STUDY

Attention-deficit/hyperactivity disorder and obesity

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ABSTRACT

Background/Objectives: Attention Deficit Hyperactivity Disorder (ADHD), one of the most common neurodevelopmental disorders in childhood and adolescence, is associated with obesity in observational studies. However, it is unclear whether ADHD contributes to, results from or is merely correlated with obesity. This study evaluates the presence and direction of a causal effect between ADHD and obesity. **Subjects/Methods:** We performed a bidirectional two-sample Mendelian randomization using summary data from consortia of genome-wide association studies to investigate if ADHD (N=55 374) has a causal effect on body mass index (BMI) in childhood (N= 35 668) and adulhood (N=322 154 to 500 000), and vice-versa. The main analysis was performed using the Inverse Variance Weighted (IVW) method. As sensitivity analyses, we used other Mendelian randomization methods that are more robust to horizontal pleiotropy (i.e. MR-Egger, weighted mode and penalized weighted median estimators), as well as stratified the analysis by the putative mechanisms of genetic instruments (i.e. pathways involved or not in neurological processes). **Results:** The IVW method indicated a positive causal effect of BMI on ADHD: β=0.324 (95%CI 0.198 to 0.449, p<0.001; expressed as change in ln(odds ratio) of ADHD per each additional SD unit of BMI). IVW estimates were directionally consistent with other methods. On the other hand, we did not find consistent evidence for a causal effect of ADHD genetic liability on BMI. **Conclusions:** The results suggested that higher BMI increases the risk of developing ADHD, but not the other way around.

INTRODUCTION

Obesity and Attention Deficit Hyperactivity Disorder (ADHD) are common clinical conditions. Obesity has become a worldwide epidemic [1], implicated in the etiology of cardiovascular and metabolic diseases [2]. ADHD may increase the risk of important conditions, including professional and educational disadvantages [3], substance use disorders [4], and involvement in criminal offenses [5], car accidents [6] and injuries [7]. Studies in diverse settings have reported an association between ADHD and obesity [8-11]. A recent meta-analysis including 42 studies worldwide and a total of 728 126 participants (48 161 ADHD cases) estimated a pooled odds ratio for obesity of 1.3 (95%CI: 1.16 to 1.46) in children/adolescents and adults with ADHD compared to non-affected individuals [12]. There is also robust evidence of a positive genetic correlation between ADHD and BMI from different approaches, such as LD score regression [13], genetic markers for BMI [14] and polygenic risk scores for ADHD risk [15].

Despite the well-established phenotypic and genetic correlation between ADHD risk and BMI, the causal relationship between these two traits remain unknown. It has been hypothesized that ADHD may contribute to obesity due to impulsivity and inattention symptoms, which could lead to over-consumption or difficulties to follow a regular eating pattern [12, 16-18]. Alternatively, ADHD might be a consequence of obesity[19, 20]. Few studies have explored this possibility and mechanisms are not clear, although obesity-induced sleeping problems, inflammation, and chronic hyperglycemia have been hypothesized as potential mechanisms [19, 21, 22]. It is also possible that the association between ADHD and obesity may arise due to non-causal mechanisms, such as confounding, where a common factor may contribute to the development of both conditions [22].

Due to the observational nature of most studies on the association between ADHD and obesity, the current evidence on this topic may be distorted due to biases such as residual confounding. Therefore it is important to re-assess this association using different approaches that are more robust to this type of bias under a triangulation perspective [23]. One of such methods is Mendelian randomization is a method that uses genetic variants associated with modifiable exposures as instrumental variables (IVs), aiming to assess causality between the exposures and the outcomes. Valid causal inference using Mendelian randomization requires that (i) relevance: the IV is strongly associated with the exposure of interest; (ii) independence: the IV is independent of the confounding factors between outcome and exposure; and (iii) exclusion restriction: the effect of IV on outcome is fully mediated by the exposure [24].

A previous Mendelian randomization study has assessed the effect of BMI on several psychiatric disorders, which was not supportive of the notion that higher BMI increases the risk of developing bipolar disorder and schizophrenia, although there was a suggestive causal effect on major depression [25]. To the best of our knowledge, no previous Mendelian randomization study has investigated the relationship between ADHD and BMI. In this study, we used Mendelian randomization to assess the presence and direction of a causal effect between obesity and ADHD.

METHODS

Study design

We performed a bidirectional two-sample Mendelian randomization analysis using summary data from genome-wide association studies (GWAS) consortia to

investigate whether obesity is a cause or a consequence of ADHD, or if these two traits are correlated due to factors other than a causal relationship between obesity and ADHD (e.g. confounding). Genetic variants identified from the ADHD GWAS were looked up in the BMI GWAS to estimate the causal effect of ADHD on obesity and associations were also ascertained in the opposite direction.

Data sources

Data on the association between genetic polymorphisms and the phenotypes of interest was extracted from publicly available datasets of summary association results from four GWAS consortia.

The Psychiatric Genomics Consortium (PGC)

Summary association results for ADHD were extracted from a GWAS conducted by the PGC [13]. The study was composed of 20 183 ADHD cases and 35 191 controls, including children and adults iPSYCH study, and 11 European, North American and Chinese studies [13]. Both family and case-control studies were included. European ancestry individuals comprised 96.25% of the sample. The genome-wide association analysis was conducted in each cohort using logistic regression, assuming additive genetics effects. Ancestry-informative principal components calculated using genome-wide genotyping data were included as covariates to minimize bias due to population stratification, along with relevant study-specific covariates where applicable. Variants with imputation quality score (INFO) <0.8 or minor allele frequency (MAF)

<0.01 were excluded. Twelve independent (r^2< 0.1) genetic variants strongly associated with ADHD ($P<5\times10^{-8}$) were identified. Further details can be found elsewhere [13].

The Early Growth Genetics (EGG) consortium

The EGG discovery phase consisted of 20 studies including 35 668 children of European ancestry (from 2 to 10 years of age). Syndromic cases of obesity were excluded. Sex- and age-adjusted standard deviation scores were created for BMI at the latest time point available (oldest age) for each cohort if multiple measurements existed. The association estimates were obtained through linear regression, assuming an additive genetic model. The data used here includes the results from the discovery phase.

In total, 18 loci reached genome-wide significance ($P<5\times10^{-8}$) in the EGG joint discovery and replication analyses. More details can be obtained in [26]. We estimate that up to 4.2% of PGC participants might have been included in EGG consortium (Supplementary Table 2).

For replication purposes we have used two other largely independent summary association results for BMI in adults, described below.

The Genetic Investigation of Anthropometric Traits (GIANT)

Summary association results for BMI were extracted from the GIANT consortium [27]. The pooled sample included 322 154 and 17 072 adults of European and non-European ancestry, respectively, from GWAS and Metabochip studies. Here, we considered the 77 independent (500 kilo-bases apart) genetic variants that reached

genome-wide significance in the sex-combined analysis exclusively for individuals of European ancestry sample [27].

The UK Biobank

UK Biobank is a national prospective cohort that recruited more than 500 000 men and women from across the United Kingdom, with aged 40 to 69 years between 2006 to 2010. The association analysis with BMI was performed using 10.8 million Single Nucleotide Polymorphisms (SNPs), assuming additive genetic effects and excluding variants with MAF<0.01 and INFO<0.8. For this study, we used publicly available summary association results for BMI [28]. Details on sample and SNP quality control can be found in UK Biobank documentation [29, 30].

Genetic Instruments

As genetic instruments for ADHD or BMI, we selected independent (as defined by each study) genetic instruments strongly associated ($P<5\times10^{-8}$) with ADHD and BMI, respectively, as described above. When the selected (index) genetic instrument was not available in the outcome GWAS, we replaced it by a proxy variant ($R^2>0.80$) when possible, using the European population from 1000 genomes (phase 3 version 5) [31] as reference pannel. Proxies of ADHD instruments were identified using the SNP Annotator (SNiPA) v3.2 and LDlink tools [32, 33]. For proxies of BMI instruments, we used the R package Two-sample MR [34].

From the 12 genetic instruments selected as instruments for ADHD, we were able to find nine (four index and five proxies) in EGG, ten (six index and four proxy) in

GIANT, and nine (seven index and two proxy) in UK Biobank datasets of summary GWAS results (Supplementary Table 1).

From the 18 polymorphisms selected as instruments for BMI in childhood from EGG, 16 were identified in the ADHD dataset of summary GWAS results. From the 77 genetic instruments selected as BMI instruments in adulthood from GIANT [27], 72 were found in the ADHD dataset. No other large ADHD GWAS was available to for replication.

Mendelian randomization analysis

We estimated the effect of BMI on ADHD (and vice-versa) using the Inverse Weighted Variance (IVW) estimator, which consists of a linear regression of the instrument-outcome association estimates on the instrument-exposure association estimates, weighted by the inverse of the variance of the instrument-outcome association estimates. The intercept of this regression is constrained at zero, which corresponds to the assumption that the genetic instruments can only affect the outcome through the exposure or that horizontal pleiotropic effects are balanced [35].

Sensitivity analyses

To assess the robustness of the primary analysis, we used other Mendelian randomization estimators that are more robust to horizontal pleiotropy than the IVW estimator: MR-Egger regression, Penalized Weighted Median (PMW) and the weighted mode-based estimator (MBE).

The MR-Egger regression consistently estimates the causal effect even if all genetic instruments violate the exclusion restriction assumption, as long as the Instrument Strength Independent of Direct Effect (InSIDE) assumption holds. InSIDE requires that the strength of the instrument (i.e., the association between the instrument and the exposure) is not correlated with the direct effect of the instrument on the outcome (i.e., the effect of the instrument on the outcome via horizontal pleiotropy) [36]. The PMW method gives consistent estimates even if up to (but not including) half of the weight in the analysis comes from valid instruments, where each instrument that contributes to high heterogeneity (i.e., that yields a causal effect estimate substantially different than the most of the remaining instruments) is downweighted (penalized) [37]. The weighted MBE requires the ZEro Modal Pleiotropy Assumption (ZEMPA) holds. ZEMPA postulates that the most common (i.e., the mode) horizontal pleiotropic effect is zero, which allows consistent causal effect estimation even if most instruments are invalid. The weighted version of ZEMPA can be interpreted as postulating that the homogeneous subset of instruments with the largest sum of weights comprises only valid instruments [38].

Additional sensitivity analyses were performed by stratifying the BMI genetic instruments from GIANT according to the functional class of the protein encoded by the mapped gene, as identified by Locke *et al.,* (2015) [27]. More specifically, the instruments were classified into two classes: instruments likely to directly regulate neurophysiological processes versus other instruments. The neural pathways included the categories labelled in the original publication as Neuronal Developmental processes, Neurotransmission, Neuronal Expression and Hypothalamic expression and regulatory function. The other pathways included those not described as a neuro-related process, such as lipid biosynthesis and metabolism, bone development, mitochondrial,

endocytosis/exocytosis, tumorigenesis, immune system and limb development. The genetic instruments used in each dataset are fully described in the supplementary table 3. Similar methodology was already used to estimate the causal effect of BMI in other psychiatric disorders [25].

We have also performed a leave-one-out analysis to identify potentially overly influential instruments by removing 1 variant at a time and recalculating the IVW estimate.

The analyses were performed using the R (https://www.r-project.org/) package Two-sample MR package [39].

RESULTS

Effect of ADHD susceptibility on BMI

Results for the effect of ADHD susceptibility on BMI are expressed as change in BMI standard deviation (SD) units per each additional unit the ln(odds ratio) of ADHD, that is the natural logarithm of the odds ratio. The negative estimates indicate a negative (inverse) association; positive estimate indicates a positive association; a point estimate equal to zero indicates no association.

Overall, the evidence ADHD genetic liability causally affects BMI was inconsistent across data sources and methods. In the main analyses (IVW), we found some evidence that higher ADHD liability increases BMI in EGG (β=0.095, 95% CI: 0.011 to 0.179, p=0.025) and UK Biobank (β=0.074, 95% CI: 0.027 to 0.118, p=0.002), but not in GIANT (β=0.023, 95% CI: -0.018 to 0.065, p=0.280) (Figure 1a; Figure 1c; Figure 1b, Supplementary Table 4). In sensitivity analyses using methods that are more robust to pleiotropic instruments, we observed similar results for penalized weighted

median and weighted mode, but inconsistent results for MR-Egger (Supplementary Table 4). MR-Egger estimates were in the opposite direction to IVW estimates in UK Biobank (β= -0.059, 95% CI: -0.248 to 0.129, p=0.554) and GIANT (β= -0.065, 95% CI: -0.255 to 0.124, p=0.518) (Figure 1c; Supplementary Figure 1c; Supplementary Table 4).

The MR-Egger intercept yielded no strong indication of unbalanced horizontal pleiotropy (β= -0.008, 95% CI: -0.043 to 0.028, p=0.691; β=0.013, 95% CI: -0.005 to 0.030, p=0.200; and β=0.008, 95% CI: -0.009 to 0.026, p=0.375, for EGG, UK Biobank and GIANT respectively). The leave-one-out analyses yielded no strong indication that there were influential instruments (Supplementary Figure 2a; Supplementary Figure 2b; Supplementary Figure 2c).

Effect of BMI on ADHD susceptibility

Results for the effect of BMI on ADHD susceptibility are expressed as change in ln(odds ratio) of ADHD per each additional SD unit of BMI. The negative estimates indicate a negative (inverse) association; positive estimate indicates a positive association; a point estimate equal to zero indicates no association.

We observed consistent evidence of a positive effect of BMI on ADHD both when using instruments identified in the EGG childhood BMI GWAS (β=0.324, 95%CI: 0.198 to 0.449, p<0.001), and when using instruments identified in the GIANT adulthood BMI GWAS (β=0.402, 95%CI: 0.228 to 0.575, p<0.001), using the IVW method (Figure 2a; Figure 2b; Supplementary Table 4; Supplementary Figure 3a; Supplementary Figure 3b). Similar results were obtained across the other Mendelian randomization methods (i.e. MR-Egger, penalized weighted median and weighted

mode) (Supplementary Table 4; Supplementary Figure 3a; Supplementary Figure 3b). The MR-Egger interpret did not provide strong indication of unbalanced horizontal pleiotropy (β= -0.009, 95%CI: -0.051 to 0.032, p=0.664 and β= -0.005, 95%CI: -0.019 to 0.008, p=0.438 for EGG and GIANT respectively). The leave-one-out analyses provided not strong indication that there were influential instruments (Supplementary Figure 4a; Supplementary Figure 4b).

Effect of BMI on ADHD susceptibility: subgroup analyses by biological pathway

To further explore the positive effect of BMI on ADHD risk suggested by our Mendelian randomization analyses, we performed additional sensitivity analysis in which the genetic instruments associated with BMI were classified as related to neurological or other pathways, as classified by Locke *et al.* (2015) [27] and used by Hartwig *et al.* (2016) [25] (Supplementary Table 3). The rationale for this analysis is based on the GIANT BMI GWAS results [27], which observed an important enrichment of neurological pathways in the genetic etiology of BMI. Then, it is possible that the positive association between high BMI and ADHD is led by genetic instruments involved in neural mechanisms that affect both BMI and ADHD independently [25]. However, results were similar when stratifying the genetic instruments in this way. The IVW effect estimates were 0.377 (95%CI 0.082 to 0.673, p= 0.012) for instruments involved in neurological pathways, compared to 0.415 (95%CI 0.199 to 0.631, p< 0.001) for other instruments per 1 SD increase in BMI (Figure 3b; Figure 3a; Supplementary Table 5). In sensitivity analyses using other Mendelian randomization methods, point estimates were even larger for instruments not implicated in neurological pathways (Figure 3b; Figure 3a; Supplementary Table 5; Supplementary

Figure 5b; Supplementary Figure 5a, Supplementary Figure 5b). The leave-one-out analysis provided no strong indication that there were influential instruments (Supplementary Figure 6a; Supplementary Figure 6b).

DISCUSSION

In the present study, we assessed causality in the association between ADHD and BMI using bidirectional two-sample Mendelian randomization. In the analyses with BMI as the exposure and ADHD as the outcome, our findings indicated a causal effect of higher BMI on higher ADHD risk. This result was robust to several sensitivity analyses exploring bias due to horizontal pleiotropy in different ways. For ADHD genetic liability as the exposure and BMI as the outcome, the main analysis suggested a causal effect of higher ADHD liability on higher BMI. However, this finding did not replicate across different datasets and were inconsistent across different Mendelian randomization estimators.

A recent systematic review and meta-analysis of 42 studies with clinical and population-based samples reported an association between obesity and ADHD in children/adolescents and adults [12]. Longitudinal studies indicate that ADHD in childhood is associated with higher BMI and obesity risk in adulthood, suggesting that ADHD precedes BMI [16-18, 40]. This has led to hypotheses where ADHD triggers weight gain by deregulating eating behavior in several ways: (i) impulsivity would contribute to deficient inhibitory and delay aversion and, consequently, over-consumption [41], (ii) inattention would facilitate adhering to unhealthy dietary patterns [41-44], (iii) organizational and attention difficulties would trigger compensatory mechanisms leading to compulsive eating and reduced caloric expenditure [45, 46].

However, disentangling the direction of causal effects between conditions of high complexity and long latency is challenging in classical observational settings, including those of longitudinal design, due to issues of residual confounding and reverse causality. In our study, we used genetic instruments for both BMI and ADHD risk as proxies for exposure to these phenotypes in order to avoid issues with reverse causality (since germ-line genotypes precede phenotypes) and residual confounding (as genetic instruments tend not to be related to classical confounding factors) [47]. In contrast to the aforementioned large meta-analysis, we did not find robust evidence for an effect of ADHD liability on BMI. On the other hand, we did find consistent evidence for a risk-increasing effect of higher BMI on ADHD.

The mechanisms potentially involved in this direction are unknown and require further investigation. Sleep disruption has been suggested by the most recent systematic review and meta-analysis as a possible contributor for this association between obesity and ADHD [21, 22]. It is mainly based on the reports of higher frequency of short sleep duration, Delayed Sleep Phase Syndrome (SDPS) [21], and late circadian rhythm among both individuals with obesity and with ADHD [48]. According to this hypothesis, the discontinuation of sleep in obese individuals would lead to symptoms of ADHD [21, 22, 49, 50]. However, evidence supporting this is too incipient and whether sleep disruption could be a plausible mediator of the relation between BMI and ADHD, especially among children, remains to be elucidated.

Another possible mechanism is the proinflammatory state induced by obesity [51], which may be a risk factor for ADHD [52] . In addition, chronic hyperglycemia may impair learning and memory processing [52], most commonly through affecting the frontal and hippocampal regions responsible for attention, cognition and motor planning.

Changes in these areas can lead to inattention, loss of emotions and behavioral inhibition, which may explain the risk of developing ADHD symptoms later [52].

The strengths of our study include the large sample size, the use of bidirectional Mendelian randomization to estimate the effect between the phenotypes in both directions, and the use of extensive sensitivity analyses to evaluate robustness of our results to horizontal pleiotropy. Some limitations of this study should also be considered. As any other causal inference method, Mendelian randomization relies on assumptions, some of which are untestable. Assumption (i) – the relevance assumption – states that genetic instruments should be strongly associated with the exposure of interest. This is the only IV assumption that is fully testable. To avoid including weak instruments, we only selected independent genetic instruments that were strongly associated with the exposure ($P<5.0\times10^{-8}$) in large datasets (N= 55 374 for ADHD instruments and N=339 226 for BMI instruments).

Assumption (ii) – the independence assumption – refers to the fact that genetic instruments should not be related to confounding factors of the exposure-outcome association. Although genetic instruments are generally uncorrelated with classical confounding factors [47], assumption (ii) could be violated in case of population stratification where there are subgroups within the study population that have different frequencies of the alleles of interest and which concomitantly have different risk of having the outcome. To minimize population stratification bias, we restricted our analyses to only or predominantly European populations and used data from genome-wide association studies that strictly accounted for population structure (Supplementary Table 3).

Assumption (iii) – the exclusion restriction – states that genetic instruments should only affect the outcome through the exposure. This would be violated due to

horizontal pleiotropy, where the genetic instruments affect both the exposure and the outcome through independent pathways. It is impossible to empirically rule out that horizontal pleiotropy is driving the results. However, our results were consistent across a series of sensitivity analyses using different Mendelian randomization methods that rely on different assumptions about horizontal pleiotropy, thus strengthening causal inference [53]. These analyses revealed a consistent effect of BMI on ADHD, but inconsistent results in the opposite direction. We also stratified our analysis according to the putative pathway regulated by the mapped genes for each genetic variant (neuronal or other pathways) as one would expect that, if the association between BMI and ADHD was explained by a common shared neurological mechanism (e.g. dopaminergic pathways, reward system and satiety), results would be inflated for the stratum of instruments assigned to neuronal pathways compared to results for the other stratum. However, estimates were comparable suggesting that this is unlikely to explain our findings.

The fact that we have found stronger evidence for an effect of high BMI on ADHD risk than for an effect in the opposite directions should be interpret with caution since many more genetic instruments were available to test the effect of BMI (N = 77 variants) than the effect of ADHD liability (N = 12 variants). Therefore, we cannot completely rule out the possibility that we were underpowered to detect modest effects of ADHD liability on BMI.

Genetic instruments tend to reflect lifelong differences in phenotypes and, therefore, Mendelian randomization studies cannot identify whether there is a critical timing for the effect of the exposure. Therefore, even though we investigated the effect of BMI at different life stages (childhood and adulthood), it should be noted that BMI is genetically correlated across these stages. Therefore, it is possible that the effect that we

see for adulthood BMI might be in fact capturing an effect of BMI early in life or vice-versa. Similarly, as maternal and offspring genotypes are correlated, the estimated effects of own BMI on ADHD risk could be reflecting the effect of in utero exposure to high maternal BMI.

To the best of our knowledge, this is the first Mendelian randomization study to probe the bidirectional relation between BMI and ADHD. We found consistent evidence for an effect of high BMI on ADHD risk that was replicated in independent samples and robust to sensitivity analyses and inconsistent evidence for an effect in the opposite direction contrasting with findings from conventional observational studies. Further studies are needed to confirm these findings and to clarify potential mechanisms underlying this effect.

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Conflict of interest:

L.A.R. has been a member of the speakers' bureau/advisory board and/or acted as a consultant for Eli-Lilly, Janssen-Cilag, Medice, Novartis and Shire in the last three years. He receives authorship royalties from Oxford Press and ArtMed. He has also received travel awards from Shire for his participation in the 2018 APA meetings and

from Novartis to take part of the 2016 AACAP meeting. The ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by him received unrestricted educational and research support from the following pharmaceutical companies in the last three years: Janssen - Cilag, Novartis, and Shire.

Supplementary information is available at (International Journal of Obesity)'s website.

Figure Legends

Figure 1. Causal relationship between ADHD as exposure and BMI considering different datasets. Forest plots showing the effect of genetically enhanced ADHD (PGC) on BMI considering EGG data (n = 9 genetic instruments) (A); GIANT (n = 10 genetic instruments) (B); and UK Biobank (n = 9 genetic instruments) (C). The results are shown for three effect estimates of MR tests. Forest plots show each genetic variant with the 95% confidence interval of the estimate of weighted mode, MR-Egger, penalized weighted median and inverse weighted variance results.

Figure 2. Causal relationship between BMI as exposure ADHD considering different datasets. Forest plots showing the effect of genetically enhanced BMI (EGG) on ADHD (PGC) (n=16 genetic instruments) (A); and BMI (GIANT) on ADHD (PGC) (n=72 genetic instruments) (B). The results are shown for three effect estimates of MR tests. Forest plots show each genetic variant with the 95% confidence interval of the estimate of weighted mode, MR-Egger, penalized weighted median and inverse weighted variance results.

Figure 3. Causal relationship considering functional pathways derived from BMI instrumental variables as exposure. Forest plots showing the effect of genetically enhanced BMI (GIANT) as exposure and ADHD (PGC) for neurological pathways (n=42 genetic instruments) (A); and for other pathways (n=30 genetic instruments) (B). Forest plots show each genetic variant with the 95% confidence interval of the estimate of weighted mode, MR-Egger, penalized weighted median and inverse weighted variance results.

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