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**Examining the contribution of birth weight to mental health, cognitive, and socioeconomic outcomes:  
A two-sample Mendelian randomization**

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## Abstract

**Background.** Low birth weight is associated with adult mental health, cognitive, and socioeconomic problems. However, the causal nature of these associations remains difficult to establish due to confounding.

**Aims.** We aimed to estimate the contribution of birth weight to adult mental health, cognitive, and socioeconomic outcomes using two-sample Mendelian randomization, an instrumental variable approach strengthening causal inference.

**Method.** We used 48 independent single-nucleotide polymorphisms as genetic instruments for birth weight (N of the genome-wide association study, 264 498), and considered mental health (attention-deficit hyperactivity disorder [ADHD], autism spectrum disorders, bipolar disorder, major depressive disorders, obsessive-compulsive disorder, post-traumatic stress disorder [PTSD], schizophrenia, suicide attempt), cognitive (intelligence), and socioeconomic (educational attainment, income, social deprivation) outcomes.

**Results.** We found evidence for a contribution of birth weight to ADHD (OR for 1 SD-unit decrease [ $\sim$ 464 grams] in birth weight, 1.29; CI, 1.03-1.62), PTSD (OR=1.69; CI=1.06-2.71), and suicide attempt (OR=1.39; CI=1.05-1.84), as well as for intelligence ( $\beta$ =-0.07; CI=-0.13; -0.02), and socioeconomic outcomes, ie, educational attainment ( $\beta$ =-0.05; CI=-0.09; -0.01), income ( $\beta$ =-0.08; CI=-0.15; -0.02), and social deprivation ( $\beta$ =0.08; CI=0.03; 0.13). However, no evidence was found for a contribution of birth weight to the other examined mental health outcomes. Results were consistent across a wide range of sensitivity analyses.

**Conclusions.** These findings support that birth weight could be an important element on the causal pathway to mental health, cognitive and socioeconomic outcomes.

## Introduction

Low birth weight (a global index of poor fetal development) has been associated with a range of mental health problems (including attention-deficit/hyperactivity disorder [ADHD], autism, bipolar disorder, depression, schizophrenia, suicide),<sup>1-8</sup> as well lower intelligence and socioeconomic status (see also **Supplementary material eIntroduction**).<sup>9-11</sup> These findings are consistent with the Developmental Origins of Health and Disease Hypothesis (DOHaD),<sup>12,13</sup> which states that adverse in-utero and perinatal experiences may have long-lasting effects on adult health. Yet, the causal nature of these associations remains unclear. Birth weight is influenced by a range of intrauterine exposures and maternal conditions and behaviors such as mental health and diet, exposure to tobacco and alcohol, toxins, pollution, and socioeconomic adversity.<sup>14-20</sup> Those factors are likely to confound the association between birth weight and mental health and socioeconomic outcomes, because such confounding factors may cause a change in both birth weight and outcomes. Clarifying whether birth weight is a causal risk factor for mental health, cognitive, and socioeconomic problems is important for understanding their etiology. In the impossibility to directly randomize birth weight to probe its causal role on later outcomes, the most robust evidence would come from quasi-experimental designs. Mendelian randomization (MR) is a methodology that strengthens causal inference on the association between an exposure and an outcome using genetic variants as instruments.<sup>21-23</sup> Genetic variants are randomly allocated at conception and relatively independent of environmental confounding factors, therefore this design mimics that of a randomized trial, in which treatment is randomly allocated and confounding factors do not depend on treatment allocation (see **Fig 1** and **Supplementary material eMethods** for details on MR assumptions).<sup>21,22</sup> A previous study attempted to use MR to investigate the role of birth weight on ADHD, major depressive disorder, and schizophrenia, showing no evidence for a causal role of birth weight.<sup>24</sup> However, a major limitation of this study was the inability to account for the confounding effect of maternal genotype, which can lead to incorrect MR estimates.<sup>25,26</sup> Maternal and individual (ie, offspring) genotypes are correlated, and any effect of intrauterine exposures or maternal behavior influenced by the mother's genetic makeup may also result in an association between the offspring's genotype and mental health outcomes (**Fig 1**). However, new data from a recently published genome-wide association study (GWAS) of birth weight<sup>26</sup> providing estimates of the association of SNPs with birth weight after adjustment for the correlation between maternal and individual genotypes, enable us, for the first time, to overcome this limitation. The present Mendelian

randomization study relies on summary statistics from the largest available GWAS to estimate the contribution of birth weight to mental health (including common psychiatric disorders and suicide attempt), cognitive (ie, intelligence), and socioeconomic outcomes (including educational attainment, income, and social deprivation).

## Method

### Data sources

This study relied on summary statistics from GWASs performed by international consortia (**Table 1**). Only GWASs of individuals of European ancestry were used, as genetic variants can be differently associated with a trait in different ancestry groups due to specific linkage disequilibrium structures.<sup>27</sup> All GWAS were adjusted for population stratification using ancestry-informed principal components, as well as for other main covariates (eg, age and sex; see details in cited publications). All phenotypes were primarily measured among adult individuals, and summary statistics were available for both sexes combined only. We used the largest available non-overlapping exposure and outcome GWASs whenever possible, i.e., for all outcomes except for ADHD, intelligence, and socioeconomic outcomes. However, this overlap is unlikely to bias the results (**Supplementary material eMethods**). Power analysis is presented in the online material (**Supplementary material eMethods**).

**Birth weight.** N=209 independent genome-wide significant single-nucleotide polymorphisms (SNPs) associated with birth weight were identified by the largest GWAS meta-analysis conducted by the EGG consortium and including the UK Biobank sample (N=264 498).<sup>26</sup> Among these GWAS significant variants, we selected 48 SNPs identified as having an effect on birth weight once adjusting for the correlated maternal effect on birth weight,<sup>25</sup> and maintaining statistical significance at  $P < 1 \times 10^{-5}$ . The mean  $F$  statistic for these SNPs was 36 (median, 28; range, 19-182; **Supplementary material eMethods**), suggesting that all SNPs were strong instruments according to the suggested threshold of  $F > 10$ .<sup>28</sup> Birth weight (which had mean of ~3407 and standard deviation of ~464) was z-score transformed separately in males and females in the studies participating in the GWAS meta-analysis, and adjusted for study-specific covariates, including gestational duration (when available).

**Outcomes.** We obtained the estimates of associations between the birth weight instrument SNPs and our outcomes from GWASs summary statistics. Whenever possible, instrument SNPs which were unavailable in

the GWAS summary statistics of the outcome phenotype, were replaced with overlapping proxy SNPs in linkage disequilibrium ( $r^2 > 0.80$ ) identified using the LDproxy online tool (<https://ldlink.nci.nih.gov/>). The following outcomes were considered: (1) mental health outcomes (all binary variables): ADHD,<sup>29</sup> autism spectrum disorder,<sup>30</sup> bipolar disorder,<sup>31</sup> major depressive disorders,<sup>32</sup> obsessive-compulsive disorder,<sup>33</sup> post-traumatic stress disorder (PTSD),<sup>34</sup> schizophrenia,<sup>35</sup> suicide attempt (i.e., hospital admission for a suicide attempt);<sup>36</sup> (2) cognitive outcome: intelligence (measured as the general factor of intelligence and primarily evaluating fluid domains of cognitive functioning);<sup>37</sup> (3) socioeconomic outcomes: educational attainment (measured as years of education),<sup>38</sup> household income (measured as total income before taxes using 5 income categories),<sup>39</sup> social deprivation (measured using the Townsend Social Deprivation Index)<sup>39</sup>. Details on phenotypes assessment can be found in the individual publications.

### **Data analysis**

We conducted a two-sample Mendelian randomization analyses in R<sup>40</sup> using the TwoSampleMR,<sup>41</sup> MendelianRandomization,<sup>42</sup> and MRPRESSO packages. In two-sample MR, causal estimates can be obtained using summary statistics from different samples (ie, GWAS), one for the instrument/SNP-exposure association, another for the instrument/SNP-outcome association. The 2 datasets were harmonized, and the positive strand alleles was inferred using allele frequencies for palindromes (minor allele frequency up to 0.4) whenever possible. Analyses including and excluding the remaining palindromic SNPs were conducted, yielding consistent results. Therefore, we reported results using the full set of SNPs. For each SNP, the ratio between the SNP-exposure and the SNP-outcome association (Wald test) was calculated. Then, Wald estimates for single SNPs were combined using random-effect inverse-variance weighting (IVW) meta-analysis as primary analysis. This method corresponds to a weighted regression of SNP-outcome effects on SNP-exposure effects, in which weights were based on a multiplicative random-effect model. Heterogeneity across the meta-analyzed estimates, which may be indicative of horizontal pleiotropy (ie, the fact that same SNPs influence multiple traits, so the association between instrument SNPs and outcome could not be entirely explained by the exposure, but act through alternative pathways, violating instrumental variable assumptions),<sup>22</sup> was quantified using the  $Q$  statistic (a significant test suggests pleiotropy). Additionally, a range of analyses were used to test the sensitivity of the IVW estimation: (i) MR-Egger regression,<sup>43</sup> which

relaxes the assumptions of Mendelian randomization allowing for unbalanced pleiotropic effects. A major drawback of MR-Egger is the low power of this test; however, consistency in the direction and the size of the effect between MR-Egger estimate and IVW estimate can support the validity of the IVW analysis. We also used the intercept of the MR-Egger regression to test for the presence of unbalanced pleiotropy (a significant test suggests unbalanced pleiotropy). (ii) Weighted median, which assumes that at least 50% of the total weight of the instrument comes from valid variants. It is more likely to give a valid causal estimate than MR-Egger or the IVW method because it is more consistent with the true causal effect in the presence of up to 50% invalid variants. (iii) Robust Adjusted Profile Score (RAPS),<sup>44</sup> which is an estimator that deals with weak instruments and is robust to pleiotropic effects. We also performed 3 additional analyses. First, MR-PRESSO (Pleiotropy Residual Sum and Outlier)<sup>45</sup> was used to detect and correct for outliers which may reflect bias due to pleiotropy. Second, leave-one-out analyses, in which the analyses were repeated by excluding one SNP instrument at a time, was performed to identify whether a single SNP was driving the association. Outlier SNPs were excluded from the analysis. Third, we searched the PhenoScanner database (a curated database of publicly available results from large-scale genetic association studies) for each SNP instrument (and those in linkage disequilibrium within  $r^2 \geq 0.80$ ) to see whether they have been associated ( $P < 1 \times 10^{-5}$ ) with traits likely to bias our analysis because of horizontal pleiotropy or because their association with confounders of the exposure-outcome association. In that case, these SNPs would be excluded in sensitivity analyses. Fourth, we conducted a Steiger filtering analyses to investigate whether the specified direction of the association (birth weight predicting mental health, cognitive, and social outcomes) is further supported.

Associations were considered statistically significant at  $P < .05$ . Additionally, to account for the possibility of false positive findings, we used False Discovery Rate, with  $q$ -value  $< .05$ .

### **Ethical approval**

This study is based on publicly available summary statistics from studies that already obtained ethical approval; therefore, a separate ethical approval was not required.

## Results

### Contribution of birth weight to mental health outcomes

We found evidence for a contribution of birth weight to ADHD, with an OR of 1.29 (CI, 1.03-1.62;  $P = .027$ ;  $q < .05$ ) per 1-SD unit decrease in birth weight (**Fig 2**). No evidence of horizontal pleiotropy was detected (MR-Egger intercept,  $P = .653$ ; **Supplementary material eTable 4**), but the  $Q$  statistic indicated presence of significant heterogeneity ( $P = .002$ ). However, the association was consistent across the MR methods used as sensitivity analyses (MR-RAPS OR, 1.27; CI, 1.01-1.61;  $P = .045$ ; weighted median OR, 1.34; CI, 1.00-1.81,  $P = .054$ ; MR-Egger OR, 2.11; CI, 1.31-3.34;  $P = .001$ ), and the MR-PRESSO and leave-one-out procedures did not detect any outlier. Similarly, we found evidence for a contribution of birth weight to PTSD (OR, 1.69; CI, 1.06-2.71,  $P = .029$ ;  $q < .05$ ), with consistent estimates across sensitivity analyses methods (MR-RAPS OR, 1.71; CI, 1.02-2.88;  $P = .044$ ; weighted median OR, 2.09; CI, 0.98-4.44,  $P = .056$ ; MR-Egger OR, 3.00; CI, 0.96-9.38;  $P = .050$ ), and no evidence for heterogeneity ( $Q$  statistic,  $P = .481$ ), unbalanced horizontal pleiotropy (MR-Egger intercept,  $P = .957$ ), and outliers influencing the results. We found no evidence supporting a contribution of birth weight to other psychiatric disorders, including autism spectrum disorders (OR, 1.03; CI, 0.85-1.24;  $P = .792$ ), bipolar disorder (OR, 0.93; CI, 0.77-1.13,  $P = .476$ ), major depressive disorder (OR, 1.00; CI, 0.90-1.12;  $P = .988$ ), obsessive-compulsive disorder (OR, 0.72; CI, 0.45-1.16,  $P = 0.175$ ), and schizophrenia (OR, 1.08; CI, 0.91-1.28,  $P = .386$ ). No unbalanced horizontal pleiotropy was detected for these outcomes; correcting for outlier SNPs detected for schizophrenia (rs1547669 and rs222857) did not alter the results. Furthermore, we found evidence supporting a contribution of birth weight to suicide attempt (OR, 1.39; CI, 1.05-1.84;  $P = .023$ ;  $q < .05$ ). Consistent results were found in sensitivity analyses (MR-RAPS OR, 1.50; CI, 1.11-2.02;  $P = .008$ ; weighted median OR, 1.82; CI, 1.21-2.76;  $P = .004$ ; MR-Egger OR, 1.34; CI, 0.56-3.23;  $P = .247$ ), and we did not find evidence for heterogeneity ( $Q$  statistic,  $P = .590$ ), unbalanced horizontal pleiotropy (MR-Egger intercept,  $P = .172$ ), and outliers.

### Contribution of birth weight to intelligence

We found evidence for a contribution of birth weight to intelligence ( $\beta$ , -0.07; CI, -0.13; -0.02,  $P = 0.010$ ;  $q = .001$ ; **Fig 3**) after exclusion of 1 outlier SNP (rs1482852; **Supplementary material eResults**). This result remained after correction for an additional outlier SNP detected by the MR-PRESSO procedure (rs4144829;  $\beta$ , -0.05; CI, -0.11; -0.01,  $P = 0.036$ ). We did not find evidence for unbalanced horizontal pleiotropy (MR-

Egger intercept,  $P = 0.123$ ), although there was significant heterogeneity according to the  $Q$  statistic ( $P < 0.001$ ).

### **Contribution of birth weight to socioeconomic outcomes**

We found evidence for a contribution of birth weight to educational attainment ( $\beta$ , -0.05; CI, -0.09; -0.01;  $P = 0.011$ ;  $q = .039$ ), income ( $\beta$ , -0.08; CI, -0.15; -0.02;  $P = 0.013$ ;  $q = .039$ ), and social deprivation ( $\beta$ , 0.08; CI, 0.03; 0.13;  $P = 0.001$ ;  $q = .006$ ; **Fig 3**). MR-PRESSO detected outlier SNPs only for educational attainment (rs112139215, rs1129156, rs11698914, rs222857, rs4144829, rs7402983, rs7968682, rs8756), but outlier correction did not alter the results ( $\beta$ , -0.08; CI, -0.08; -0.02,  $P = 0.005$ ). Educational attainment showed significant heterogeneity ( $Q$  statistic,  $P < 0.001$ ). For income, we found evidence of both significant heterogeneity ( $Q$  statistic,  $P = 0.011$ ) and unbalanced pleiotropy (MR-Egger intercept,  $P = 0.024$ ), but all sensitivity analyses yielded consistent results (weighted median:  $\beta$ , -0.09, CI, -0.17; -0.00;  $P = 0.041$ ; MR-Egger:  $\beta$ , -0.11; CI, -0.25; 0.04;  $P = 0.139$ ; MR-RAPS,  $\beta$ , -0.08; CI, -0.15; -0.02;  $P = 0.015$ ).

### **Additional sensitivity analyses**

Searching the PhenoScanner database for each SNP instrument revealed associations between these SNPs and other anthropometric (eg, height), metabolic (eg, basal metabolism), hypertensive (eg, blood pressure), and lipoprotein (eg, HDL) traits. It is unlikely that those traits could generate bias by violating instrumental variable assumptions. Steiger filtering analyses suggested that the genetic variants used were indeed instruments for the exposure rather than for the outcomes (**Supplementary material eResults**).

## **Discussion**

Using a genetically informed instrumental variable approach to strengthen causal inference, this study investigated the contribution of birth weight to common psychiatric disorders, suicide attempt, as well as cognitive and socioeconomic outcomes. We found evidence supporting a role of birth weight in the pathway leading to ADHD, PTSD, suicide attempt, intelligence, and socioeconomic outcomes (ie, educational attainment, income, and social deprivation), but not to the other examined mental health outcomes.

This study relied on a robust two-sample Mendelian randomization design, the largest available GWAS summary statistics, and multiple genetic instruments indexing birth weight. These features allowed our analyses to be well powered and to limit weak instrument bias.<sup>28</sup> Furthermore, an innovative

methodological feature is the use of genetic instruments adjusted for the correlated effect of maternal genotype. This approach has been previously applied to cardiometabolic outcomes,<sup>26</sup> but, to our knowledge, this is the first study relying on adjusted estimates to investigate the association of birth weight with mental health, cognitive, and socioeconomic outcomes. As recently shown,<sup>25,26</sup> failure to account for this confounding effect may create bias in the causal estimates.

Previous observational,<sup>46,47</sup> within-sibling<sup>7</sup> and twin<sup>48</sup> studies suggested an association between low birth weight and ADHD. Consistently, our results also suggest a potential causal role of birth weight in the etiology of ADHD.<sup>7,48</sup> Both ADHD and autism spectrum disorder are neurodevelopmental disorders with childhood onset, and both had been associated with low birth weight.<sup>7</sup> However, our study found evidence for potentially causal contribution of birth weight only to ADHD, suggesting that the contribution of birth weight might be specific to ADHD rather than common to neurodevelopmental disorders. This suggestion deserves further investigations, especially in light of a recent genetically informed (within sibling) study showing associations with both ADHD and autism, as well as with a common neurodevelopmental latent factor.<sup>7</sup> Future GWASs of autism, with larger sample size, will also provide the opportunity to re-test the association between birth weight and autism with a more powered analysis. We also found evidence supporting a potential causal role of birth weight on suicide attempt, consistent with a recent meta-analysis<sup>8</sup> but not with a within-sibling Swedish study who failed to report an association of birth weight with suicide attempt in early adulthood.<sup>49</sup> Differences between studies' populations (including age at suicide attempt assessment) and statistical power may explain these divergences. It is worth noting that we did not find evidence for a contribution of birth weight to depression, the psychiatric disorder that most strongly relates to suicide.<sup>50</sup> As suicide risk is the result of both specific factors and factors shared with major psychiatric disorders comorbid with suicide,<sup>51</sup> our finding points to birth weight as a factor causally contributing to suicide risk beyond factors also associated with depression. To further probe the role of birth weight in the etiology of suicide, our finding needs to be replicated using suicide mortality, rather than suicide attempt, as an outcome. This will be possible when large-scale GWASs for suicide mortality become available. Similarly, the documented association between birth weight and PTSD was in line with observational evidence on stress-related disorders,<sup>52</sup> but not with a within-sibling study.<sup>7</sup> However, the literature on this association is scarce, and additional studies are needed. Finally, our study could not support the contribution of birth weight to other

psychiatric disorders, including depression, bipolar disorder, obsessive-compulsive disorders, and schizophrenia. These findings, in line with other quasi-experimental studies<sup>7</sup>, are important, especially considering that available observational evidence was either contradictory (eg, for depression)<sup>5,53</sup> or suggested associations (eg, for schizophrenia).<sup>1</sup>

It is important to note that our study does not support a widespread contribution of birth weight to the general risk of psychopathology (i.e., P-factor), but rather specific contributions to ADHD, PTSD, and suicide attempt risk. However, future Mendelian randomization investigations designed to specifically address this hypothesis may be informative to clarify the potential contribution of birth weight on common versus specific psychopathology factors. This effort may be facilitated by reliance on continuously measured outcomes (i.e., considering liability to psychopathology as a continuum) rather than on dichotomous outcomes as in the present study.

Inconsistent observational evidence was also available for the association of birth weight with socioeconomic outcomes, with some studies showing adult negative outcomes for low birth weight children compared to normal birth weight children, while others showing no differences.<sup>9,10</sup> Our findings across various socioeconomic indices are consistent with a causal role of birth weight.

Finally, in line with observational studies showing lifelong negative cognitive consequences for children born with very low birth weight,<sup>11</sup> this study found evidence supporting that the contribution of birth weight to intelligence may be causal. Additionally, as previous studies mainly focused on children with very low birth weight, our findings add to the literature by replicating these results in a sample of children with birth weight mostly within the normal range. Taken together, available evidence on the association between birth weight and cognitive outcomes suggests that compensation effects of cognitive abilities for children born with low birth weight would not be able to fully counteract the negative effects of low birth weight.<sup>54</sup>

Future studies should attempt to clarify the putative causal mechanisms explaining these associations. It has been suggested that restricted fetal growth negatively impact brain development,<sup>55</sup> and that this might be a mechanism explaining part of the association between birth weight and mental health and socioeconomic outcomes. For example, a study found alterations in brain reactive system and white matter in very low birth weight children, which was associated with lowered fluid intelligence and heightened anxiety.<sup>55</sup> Future studies

using quasi-experimental designs should be conducted to establish whether brain development lays in the causal path between birth weight and psychosocial outcomes, as well as to identify the brain regions implicated, which may differ across outcomes. Similarly, environmental mechanisms should be identified, as they might be potential targets for interventions aiming to promote mental and socioeconomic wellbeing among low birth weight children.

### **Limitations**

First, the phenotypes considered in this study rely on the definitions and samples used in the original GWAS, which are often highly heterogeneous regarding the recruited population, the definition of the phenotype, and the assessment. Although this heterogeneity results from the need to use very large samples to identify small genetic effects, it may also influence our findings. However, studies such as those conducted in independent samples using polygenic scores derived from these GWAS seems to corroborate the validity of their phenotypes. Second, due to data availability, this study is limited to individuals of European ancestry. Third, because a large proportion of individuals included in the birth weight GWAS had birth weight within the normal range, the results of our analyses might not reflect the effect of extremely low/high birth weight on mental health, cognitive, and social adaptation. Additionally, our analyses assume a linear relation between birth weight and outcomes.<sup>26,49</sup> Fourth, we could not explore potential sex differences in the association between birth weight and mental health, as sex-specific GWAS summary statistics were not available. Fifth, although we conducted a large array of sensitivity analyses showing robustness of our findings, horizontal pleiotropy cannot be completely ruled out, as the biological action of most included SNPs is not fully understood yet. Sixth, most of the reported associations only concerned adult individuals, and they may differ during other developmental periods. Seventh, although our analyses took into account the correlated role of maternal genotype, residual confounding dynastic effect cannot be excluded, including those related to paternal effects.<sup>23</sup> Future studies including both maternal and paternal genotype, as well as studies based on within-family GWAS (currently not largely available but necessary to go beyond the assumptions of between-family Mendelian randomization designs)<sup>56</sup> are needed to corroborate our results.<sup>57</sup>

### **Conclusions**

This Mendelian randomization study supports that birth weight could be an important element on the causal pathway to mental health, cognitive and socioeconomic outcomes later in life. As low birth weight is a global

indicator of restricted fetal development, future studies should identify modifiable risk factors leading to low birth weight.

## **Statements**

### **Declaration of interest**

The authors declare no conflict of interest.

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### **Author contribution**

MO designed the study, performed data analyses, interpret the data, drafter the manuscript. JBP contributed to study designs, data analysis, data interpretation, and writing of the final manuscript. All authors contributed to data interpretation and writing of the manuscript

### **Data Availability**

This study is based on publicly available summary statistics.

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**Table 1. Summary of Genome-Wide Association Studies used in the analyses**

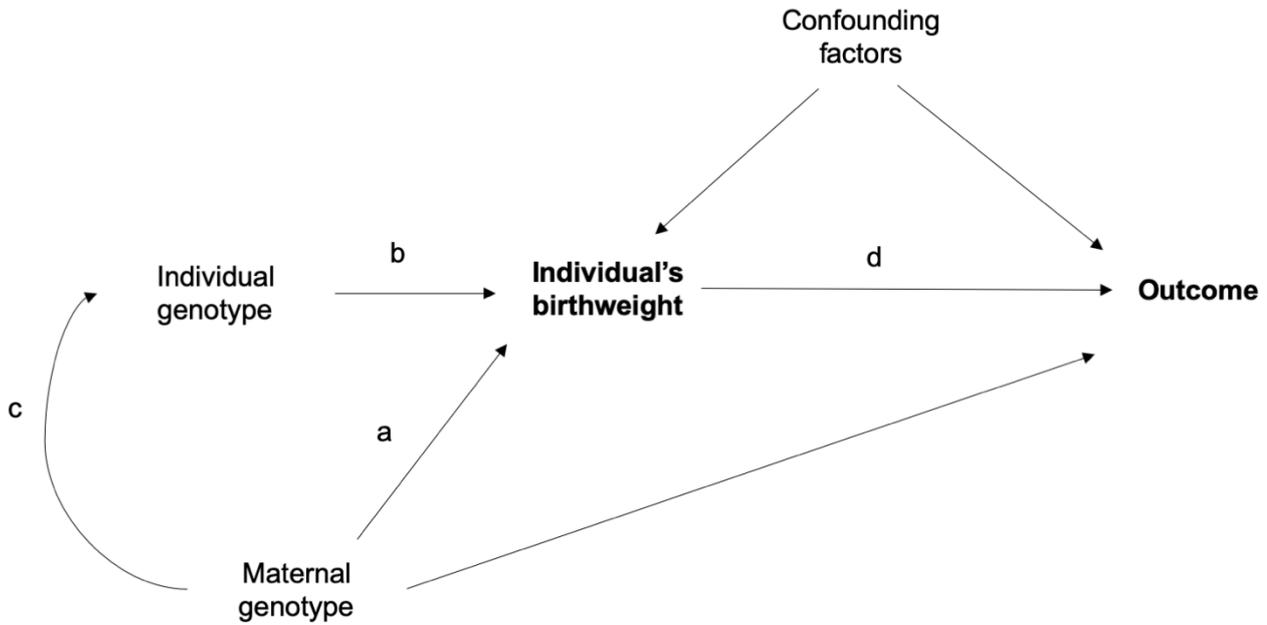
Phenotype	Source GWAS (Consortium)	Sample size			No. SNPs	Phenotype assessment
		N total	Cases	Controls		
Birth weight	EGG, UKB	264 498	-	-	48	Medical records, self-reports, midwife reports
ADHD	PGC, iPSYCH, EAGLE	53 293	19 099	34 194	42	Registry-based diagnoses, self-reports, diagnostic interviews
Autism Spectrum Disorder	PGC, iPSYCH	46 350	18 381	27 969	44	Registry-based diagnoses, clinical assessment
Bipolar Disorder	PGC	46 582	20 352	31 358	46	Diagnostic interviews, clinician-administered checklists, or medical records
Major Depressive Disorder	PGC	173 005	59 851	113 154	46	Register-based diagnoses, diagnostic interviews, questionnaires
Obsessive-Compulsive Disorder	IOCDF-GC, OCGAS	9725	2688	7037	42	DSM-IV diagnosis
Post-Traumatic Stress Disorder	PGC	9537	2424	7113	46	Diagnostic interviews, questionnaires
Schizophrenia	CLOZUK, PGC	105 318	40 675	64 643	44	Clinical assessment, diagnostic interviews
Suicide attempt	iPSYCH	50 264	6024	44 240	35	Register-based ascertainment
Intelligence	SSGAC	269 867	-	-	46	Neurocognitive tests
Educational attainment	SSGAC	1 131 881	-	-	46	Self-report
Income	UKB	96 900	-	-	47	Self-report
Social Deprivation	UKB	112 005	-	-	47	Townsend deprivation index

ADHD, Attention-Deficit/Hyperactivity Disorder; EGG, Early Growth Genetics consortium; CHARGE; Cohorts for Heart and Aging Research in Genomic Epidemiology consortium; PGC, Psychiatric Genomics Consortium; iPSYCH, Lundbeck Foundation Initiative for Integrative Psychiatric Research; IOCDF-GC, International Obsessive Compulsive Disorder Foundation Genetics Collaborative; OCG-AS, OCD Collaborative Genetics Association Studies; EAGLE, Early Life-course & Genetic Epidemiology Consortium; SSGAC, Social Science Genetic Association Consortium; UKB, UK Biobank; COGENT, Cognitive Genomics Consortium; SNP, Single Nucleotide Polymorphism; GWAS, genome-wide association study.

The Townsend deprivation index is a measure of material deprivation incorporating information on unemployment, non-car ownership, non-home ownership, and household overcrowding (higher values indicate higher social deprivation).

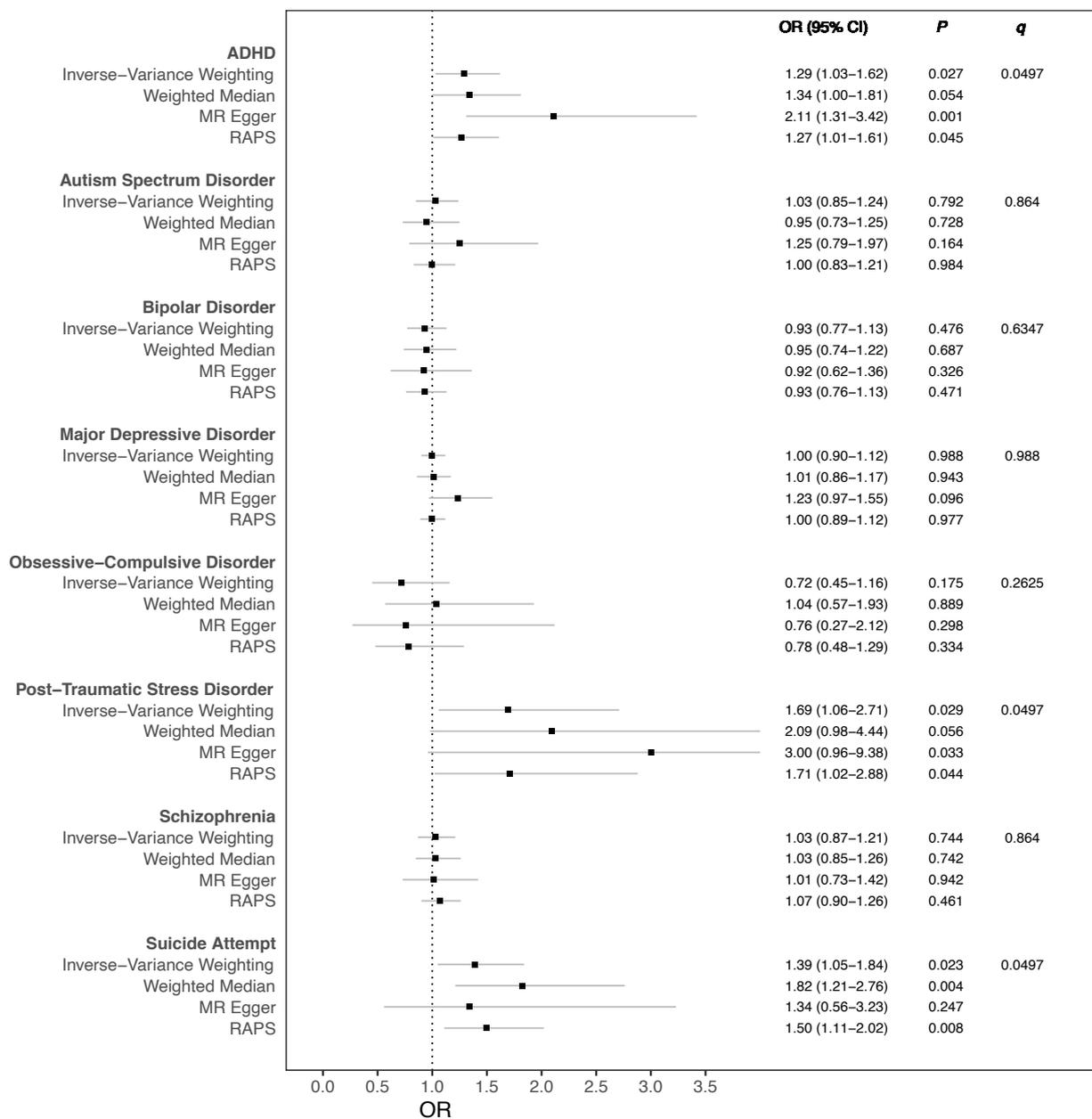
## Figures

**Fig 1. Confounding effect of maternal genotype on the association between individual's genotype and birth weight**



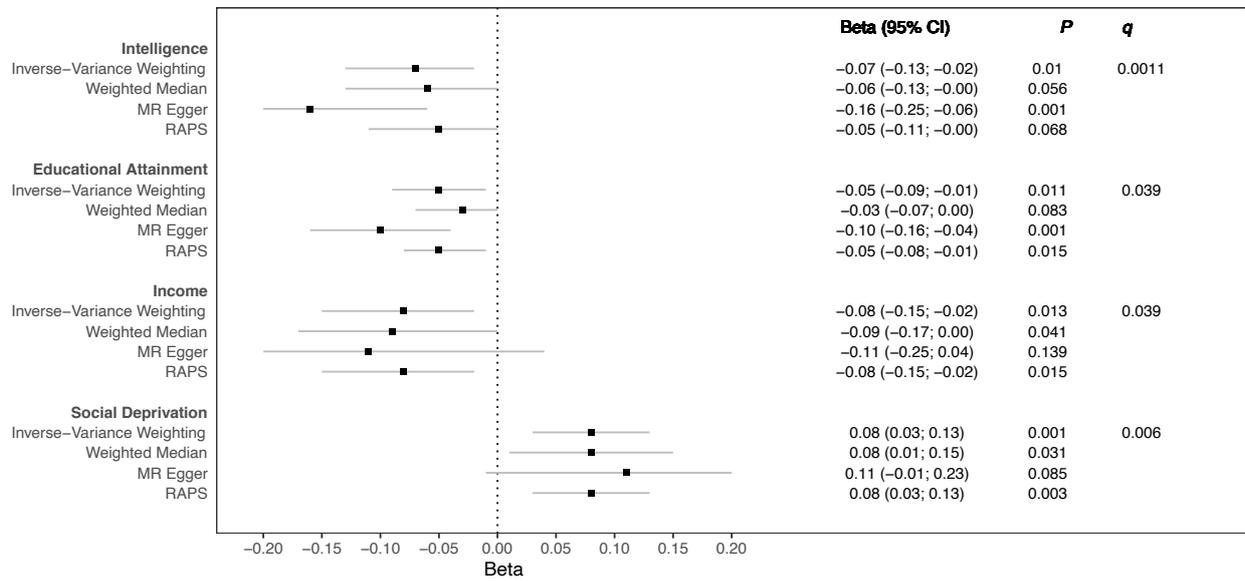
Using the Mendelian randomization design, it is possible to estimate the association between individual's birth weight and an outcome (*d* path in the figure) using individual genotype associated with birth weight as instrumental variable (*b* in the figure), instead of the observational assessment of birth weight. The association estimated in this way is not confounded by factors (such as maternal substance use) that may confound the association between birth weight and outcome in observational studies. However, this design alone does not take into account the confounding effect of maternal genotype. Indeed, both individual's genotype (*a* path in the figure) and maternal genotype (*b* path in the figure) have influences on birth weight, the former directly, the latter through the intrauterine environment. Because of the correlation between individual's genotype and his/her mother's genotype ( $r \sim 0.5$ ; *c* path in the Figure), the effect of the individual's phenotype on his/her own birth weight may be confounded. To avoid this bias, we used estimates of the association between individual's genetic variants adjusted for the correlated maternal effect as instruments (published in the most recent birth weight GWAS).<sup>26</sup>

**Fig 2. Mendelian randomization estimates for the association of birth weight with mental health**



ADHD, Attention-Deficit/Hyperactivity Disorder; RAPS, Robust Adjusted Profile Score; *P*, *p*-value; *q*, *q*-value from False Discovery Rate

**Fig 3. Mendelian randomization estimates for the association of birth weight with intelligence and socioeconomic outcomes**



RAPS, Robust Adjusted Profile Score; *P*, *p*-value; *q*, *q*-value from False Discovery Rate

## Supplemental material

### Examining the contribution of birth weight to mental health, cognitive, and socioeconomic outcomes: A two sample Mendelian randomization

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## eIntroduction

### **Evidence before this study: additional detailed information from a systematic search**

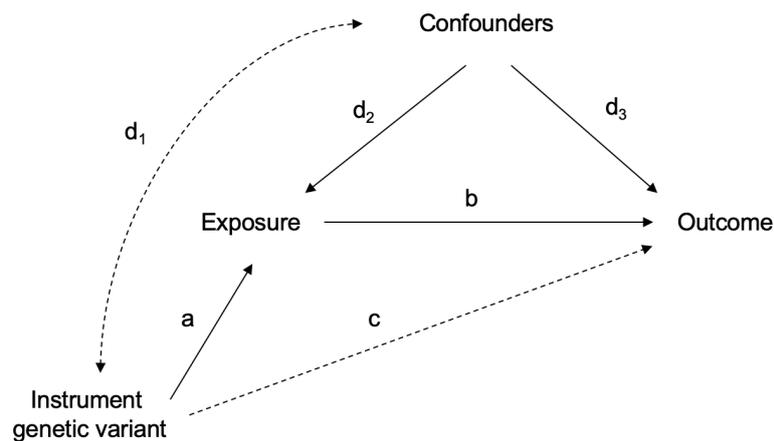
We systematically searched Medline without date limitations up to April 30, 2019 (updated on July 16, 2019), using the following keywords: (“Mental Health”[Mesh] OR “Substance-Related Disorders”[Mesh] OR “Smoking”[Mesh] OR suicid\* OR “suicide attempt” OR “social class”[Mesh] OR “Social Welfare”[Mesh] OR Education[Mesh] OR “Cognitive Dysfunction”[Mesh] OR “Intelligence”[Mesh]) AND (“birth weight” OR “birthweight” OR “fetal growth” OR “low birth weight” OR “low birthweight”). One researcher searched among the 7635 retrieved articles (filters were: English, Humans, Journal article) for pertinent articles reporting on the association between birth weight and later mental health, cognitive, and socioeconomic outcomes. Additionally, manual search on key journals was performed. Most of the available evidence came from studies using classic epidemiological designs (eg, cohort study, registers), including meta-analysis of observational studies. Overall, studies suggested associations of low birth weight with higher risk of psychiatric disorders such as depression, schizophrenia, suicidal behavior, ADHD, intelligence, socioeconomic status (eg, <sup>1-11</sup>). However, a number of studies failed to find associations, and the overall evidence resulted contradictory. For example, of two meta-analyses on the association between birth weight and depression, only one found evidence of increased risk of adult depression for low birth weight children <sup>6,12</sup>. Only few studies (mainly from northern European countries and the United Kingdom) relied on quasi-experimental designs to investigate the association between birth weight and various mental health problems (eg, <sup>4,13,14</sup>). These studies found that most of these associations were no longer significant using robust designs such as twin or sibling comparison. For example, a Swedish study found that while nine outcomes were significantly associated with birth weight in the population at large, only three (depression, ADHD and autism spectrum disorders) remained associated when a within-sibling design was used <sup>4</sup>. The association between birth weight and ADHD was the most consistently reported across studies using classic observational <sup>15,16</sup>, sibling <sup>4</sup>, and twin designs <sup>13</sup>. Only one previous study used a Mendelian randomization design <sup>17</sup>. This study investigated the association of birth weight with ADHD, major depressive disorder, and schizophrenia, reporting no evidence for a contribution of birth weight to these outcomes. However, this study did not take into account the confounding effect of maternal genotype when used individual’s SNPs as instruments for birth weight. We found no study using Mendelian randomization to investigate the association between birth weight and cognitive or socioeconomic outcomes.

## eMethods

### Mendelian randomization: method and assumptions

A schematic representation of the Mendelian randomization (MR) model is presented in **eFigure 1**. In two-sample MR, association between the instrument genetic variant(s) and the exposure comes from a GWAS, and the association between these same genetic variant(s) and the Outcome come from a different GWAS. The unconfounded association of the Exposure with the Outcome ( $b$  in the figure) is estimated as  $c/a$ .

eFigure 1. Mendelian randomization model



The same assumption as other instrumental variable approaches held for Mendelian randomization analyses. These are the following:

**Relevance.** The instrument used must be robustly associated with the exposure. In our study, we selected 48 SNPs as instruments of birth weight. These were selected from an initial pool of 209 SNPs showing genome wide statistical significance ( $P < 6.6 \times 10^{-9}$ ) in the birth weight GWAS, and still maintained statistical significance ( $P < 1 \times 10^{-6}$ ) once adjusted for the correlated maternal effect. The validity of the instrument can be quantified using the  $F$  statistic, with  $F > 10$  indicating strong instruments. The  $F$  statistics for our instrument ranged from 19 to 182 (median, 28; mean, 36), suggesting that all SNPs were strong instruments.

**Exchangeability.** Instruments must be independent from confounding of the exposure-outcome association ( $d_1$  non-significant). This assumption is not empirically testable in two-sample MR. However, we conducted a search in the phenoScanner database to verify whether, in the literature, the SNPs instruments have been associated with traits likely to be considered confounders of the exposure-outcome association.

**Exclusion restriction criterion.** There is no association between the instrument and the outcome conditional on the exposure. Differently said, the only pathway of association of the instrument to the outcome must be the through the

exposure. This assumption may be violated by the pleiotropic effects of the SNPs used as instruments (or those in linkage disequilibrium with them). Pleiotropy refers to the effect of a SNP on multiple traits/genes, and can be distinguished in horizontal and vertical pleiotropy. Horizontal pleiotropy refers to the association of the instrument SNPs with traits/genes that can potentially open alternative pathways through which the instruments may be associated with the outcome, and that are not in the causal pathway between the instruments and the outcome. Horizontal pleiotropy, if unbalanced, violates the exclusion restriction criterion. Vertical pleiotropy refers to the association of the instrument SNPs with traits/genes that can be in the causal pathway between the instruments and the outcome. For example, when studying the association between birth weight and ADHD, vertical pleiotropy would be represented by the association between the instrument SNPs and intelligence, which in turn is associated with ADHD. Vertical pleiotropy does not violate the exclusion restriction criterion. To evaluate the possible violation of this assumption, we used 3 strategies. First, we evaluate the presence of unbalanced horizontal pleiotropy by testing the significance of the intercept of the MR-Egger regression, and evaluating the presence of heterogeneity using the  $Q$  statistic. Second, we used a range of sensitivity analyses in addition to our primary MR analyses; all these methods differ in the assumptions regarding horizontal pleiotropy. Third, we conducted a search in the PhenoScanner database to find the traits that have been associated with each SNP instrument (and the SNPs in linkage disequilibrium,  $r^2 \geq .80$ ) in the literature.

## F statistic

The  $r^2$  and F statistic for each SNP are reported in the table below:

**eTable 1.** F statistic and  $r^2$  for each SNP

SNP	$r^2$	F
rs1012167	0.00058	36.00
rs10181515	0.00130	26.45
rs10265057	0.00078	31.36
rs10935733	0.00044	27.56
rs11042596	0.00073	45.56
rs11055030	0.00048	19.36
rs11096402	0.00048	30.25
rs112139215	0.00314	49.00
rs1129156	0.00048	19.36
rs116807401	0.00774	30.25
rs11698914	0.00084	33.64
rs11711420	0.00048	19.36
rs12401656	0.00084	23.36
rs13266210	0.00090	36.00
rs134594	0.00048	30.25
rs138715366	0.05523	114.10
rs1480470	0.00078	49.00
rs1482852	0.00292	182.25
rs1547669	0.00032	20.25
rs222857	0.00068	42.25
rs2282978	0.00044	27.56
rs2551347	0.00084	33.64
rs28457693	0.00160	32.65
rs28505901	0.00058	23.04
rs3933326	0.00053	33.06
rs41311445	0.00116	23.59
rs41355649	0.00176	27.56
rs4144829	0.00102	40.96
rs4444073	0.00053	33.06
rs4511593	0.00036	22.56
rs4953353	0.00036	22.56
rs56188432	0.06250	26.03
rs6575803	0.00116	23.59
rs6930558	0.00048	19.36
rs7076938	0.00084	33.64
rs72681869	0.01166	26.45
rs73143584	0.00096	19.61
rs732563	0.00036	22.56
rs7402983	0.00073	45.56
rs753381	0.00032	20.25
rs754868	0.00036	22.56
rs7772579	0.00073	29.16
rs7819593	0.00053	21.16
rs7968682	0.00137	85.56
rs80278614	0.00270	33.38
rs8106042	0.00053	21.16
rs8756	0.00137	85.56
rs9909342	0.00036	22.56
<b>Sum</b>	0.17579	1744.05

## **Fetal and maternal effects on birth weight**

Associations between individual's genetic variants and birth weight may result from (i) the direct effect of the individual's own genotype on their birth weight, (ii) the effect of the maternal genotype on the individual's birth weight, i.e. the maternal genotype (or behavior depending on maternal genotype) influencing the intrauterine environment, in turn influencing birth weight, (iii) the combination of both (same gene having both fetal and maternal effect, either in the same direction or in opposite directions). Such multiple sources of variation in birth weight must be taken into account to study the genetic association between birth weight and later outcomes. Indeed, the correlation ( $r \sim 0.5$ ) between an individual's genotype and his/her mother's genotype may introduce confounding effects due to the indirect effect of maternal genotype on the intrauterine environment. To estimate the unbiased effect of the individual's genotype on his/her own birth weight, a structural equation model has been proposed and implemented in a large GWAS. This model allows one to statistically adjust the influence of genetic variants on the individual genotype for the maternal effect on birth weight taking into account the correlation between the 2 genotypes. Details on the model can be found elsewhere<sup>18,19</sup>. In this study, we selected as instruments the SNPs having a fetal effect only, and the beta value for the association was adjusted for the correlated maternal effect.

## Power analysis

Formulas are available to estimate the power of one-sample Mendelian randomization analysis. However, to our knowledge, there is no formula allowing one to estimate the power in a two-sample Mendelian randomization analysis. We therefore estimated our statistical power considering the sample size of the SNP-outcome GWAS, because the hypothesis testing refers to a difference in the outcome according to the level of the exposure (birth weight). The results of the power calculation are presented in **eTable 2**. For categorical outcomes, we reported the power given by our sample size to detect 20%, 30%, and 40% difference (ie, OR 1.20/0.80, 1.30/0.70, and 1.40/0.60, respectively) in the risk of the outcome per 1 SD-unit increase in the exposure. For continuous outcomes, we reported the power given by our sample size to detect 20%, 30%, and 40% of a SD in the outcome per 1 SD-unit increase in the exposure. Analyses were performed using the web application: <https://sb452.shinyapps.io/power/>.

These analyses suggested for all outcomes adequate power (ie,  $\geq 90\%$ ) to detect associations as small as 20% change in the outcome for 1-SD unit change in the birth weight.

**eTable 2. Power analysis**

Trait	N	Cases/controls ratio	Power (%) to detect the following OR		
			1.2	1.3	1.4
ADHD	53293	0.56	100	100	100
Autism Spectrum Disorder	46350	0.66	100	100	100
Bipolar Disorder	46582	0.65	99.9	100	100
Major Depression Disorder	173005	0.53	100	100	100
Obsessive-Compulsive Disorder	9725	0.38	92.6	99.8	100
Post-Traumatic Stress Disorder	9537	0.34	90.8	99.7	95.7
Schizophrenia	105318	0.63	100	100	100
Suicide attempt	50264	0.14	100	100	100
Intelligence	264498	-	100	100	100
Educational attainment	264498	-	100	100	100
Income	96900	-	100	100	100
Social deprivation	112005	-	100	100	100

ADHD, Attention-Deficit/Hyperactivity Disorder

## Details on samples overlap

In two-sample Mendelian randomization, bias may emerge from the overlap between the instrument-exposure and instrument-outcome datasets. Overlap for outcomes such as ADHD, Educational attainment, Intelligence, Income, and Social deprivation is present. The bias on the MR estimate due to the overlap has been quantified as explained by Burgess, Davies, and Thompson<sup>20</sup> and using the web application: <https://sb452.shinyapps.io/overlap/>. We estimated the bias under 2 hypothetical situations (i) with a bias of the observational estimate of 0.4 per standard deviation change in the risk factor, and (ii) with a bias of the observational estimate of 0.8 per standard deviation change in the risk factor. Additionally, as precisely calculating the proportion of overlap is not possible with summary statistics, we calculate the bias for all ranges of overlap up until complete (100%) overlap. We calculate the bias for the smallest sample among our outcomes. The analyses suggest virtually no bias, with no inflation of type I error, even in the case of total overlap between samples (**eTable 3**).

**eTable 3. Potential bias due to samples overlap**

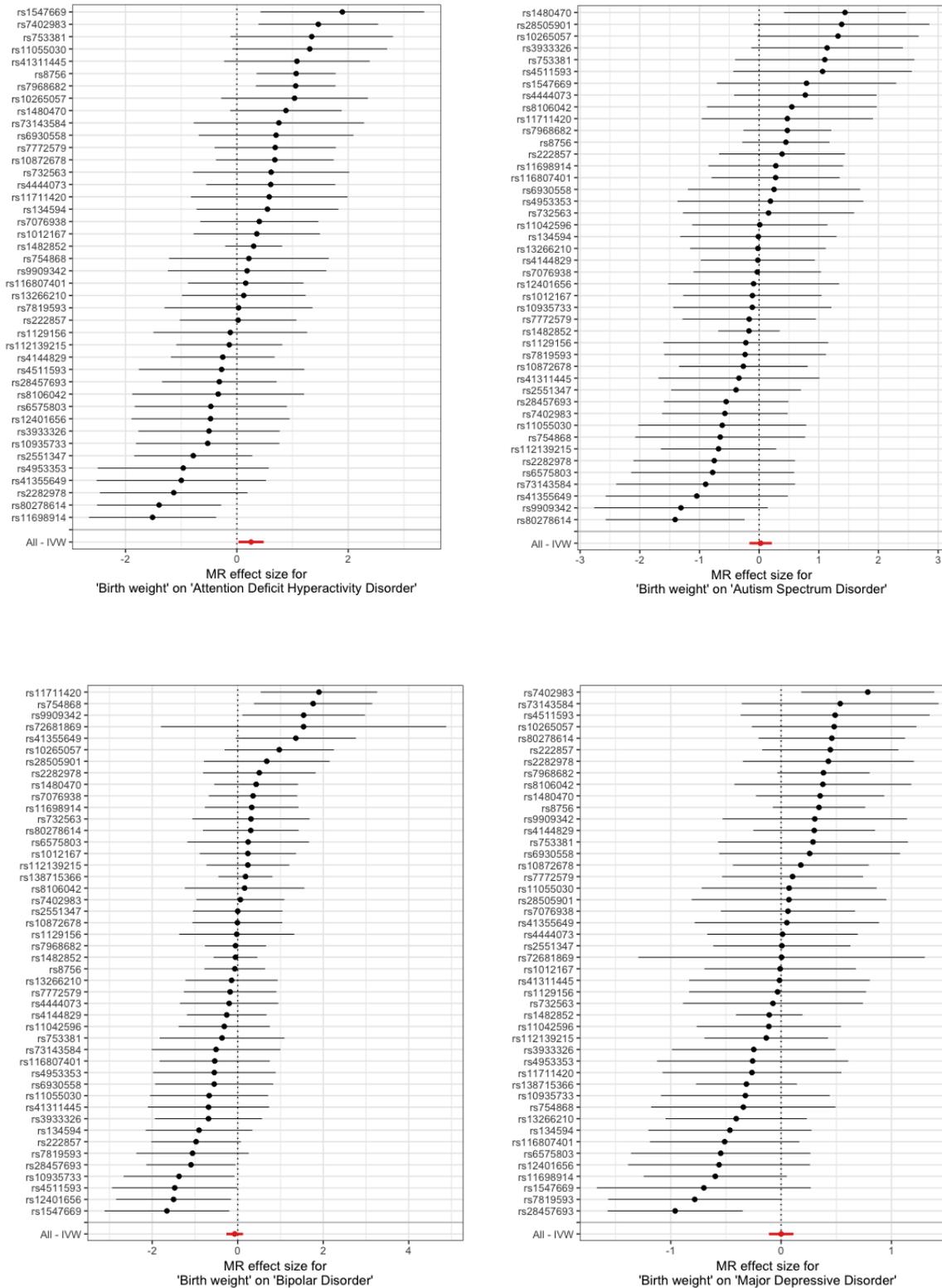
Smallest N among the analyzed outcome	Overlap proportion	Bias of the observational estimate, 0.4		Bias of the observational estimate, 0.8	
		Bias MR estimate	Type I Error	Bias MR estimate	Type I Error
Binary outcome, N=9537	0	0.000	0.05	0.000	0.05
	0.1	0.000	0.05	0.000	0.05
	0.2	0.000	0.05	0.000	0.05
	0.3	0.000	0.05	0.000	0.05
	0.4	0.000	0.05	0.000	0.05
	0.5	0.000	0.05	0.000	0.05
	0.6	0.000	0.05	0.000	0.05
	0.7	0.000	0.05	0.000	0.05
	0.8	0.000	0.05	0.000	0.05
	0.9	0.000	0.05	0.000	0.05
1	0.000	0.05	0.000	0.05	
Continuous outcome, N=96900	0	0.000	0.05	0.000	0.05
	0.1	0.000	0.05	0.000	0.05
	0.2	0.000	0.05	0.000	0.05
	0.3	0.000	0.05	0.000	0.05
	0.4	0.000	0.05	0.000	0.05
	0.5	0.000	0.05	0.000	0.05
	0.6	0.000	0.05	0.000	0.05
	0.7	0.000	0.05	0.000	0.05
	0.8	0.000	0.05	0.000	0.05
	0.9	0.000	0.05	0.000	0.05
1	0.000	0.05	0.000	0.05	

# eResults

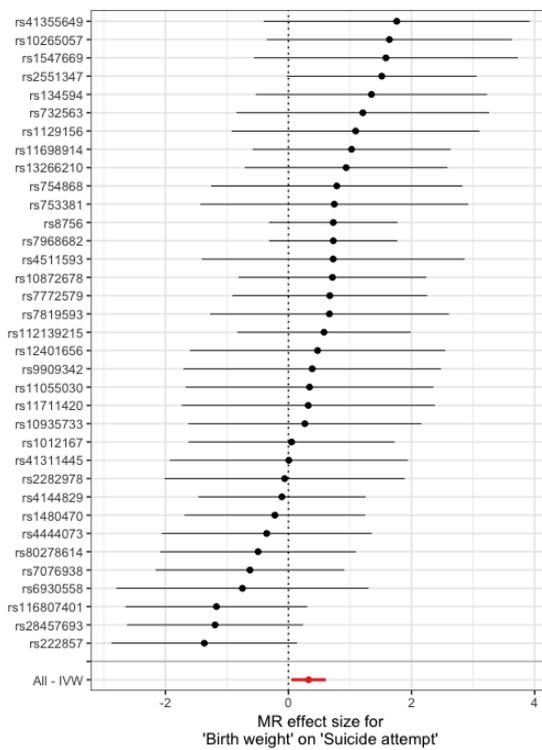
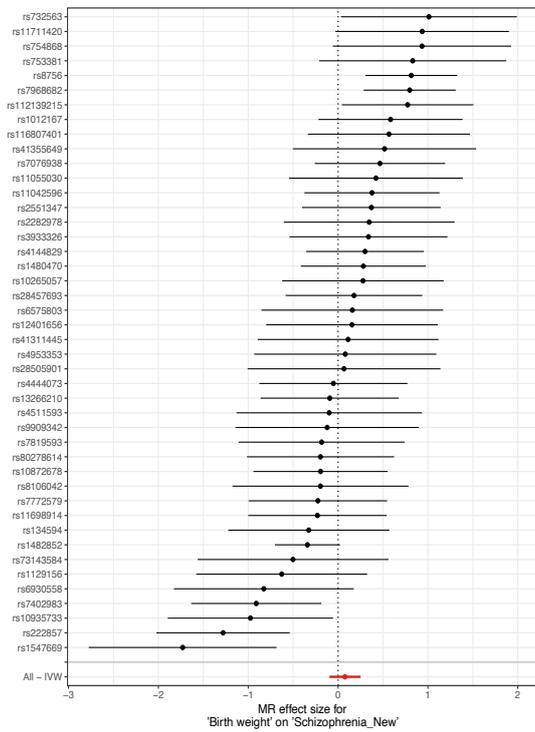
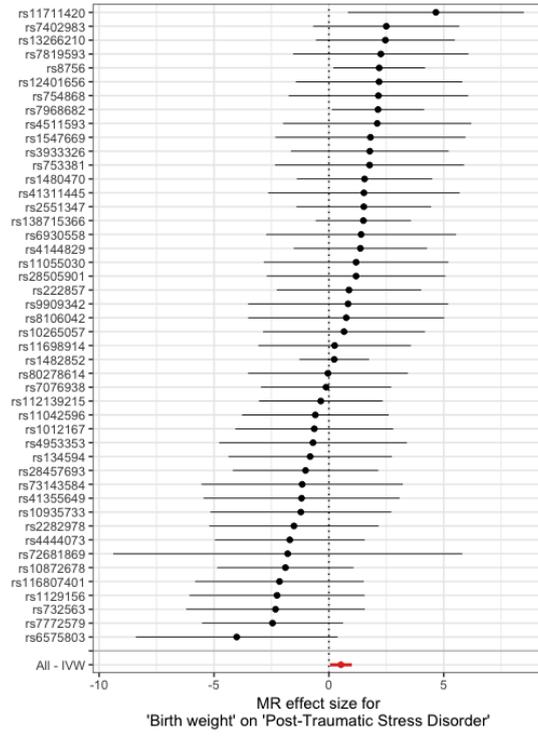
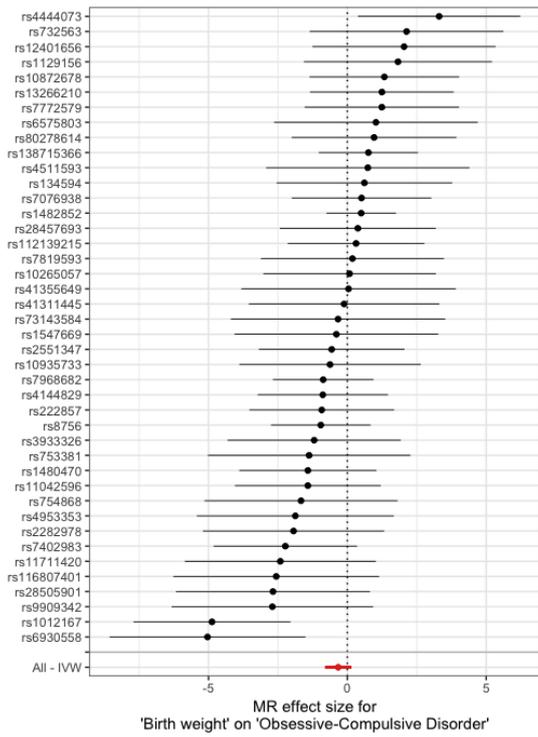
## Single SNP effects

The forest plots in the figure show, for each outcome, the Wald estimate for each single SNPs, as well as the pooled Inverse-Variance Weighted (IVW) effect (in red).

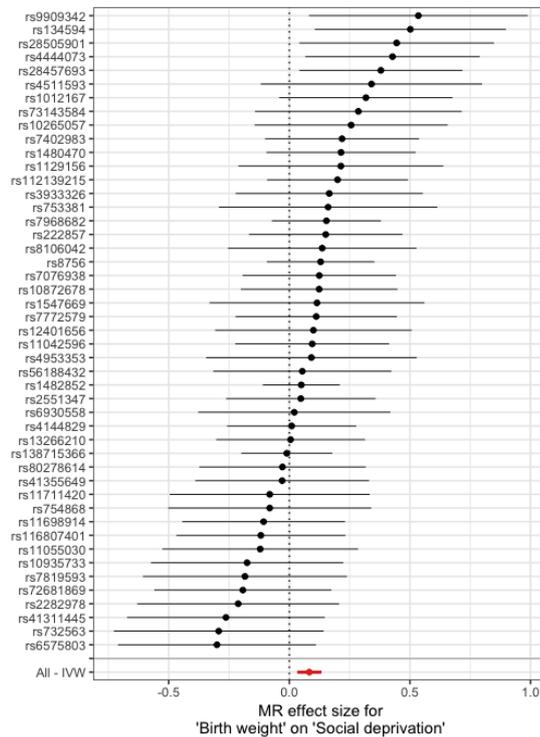
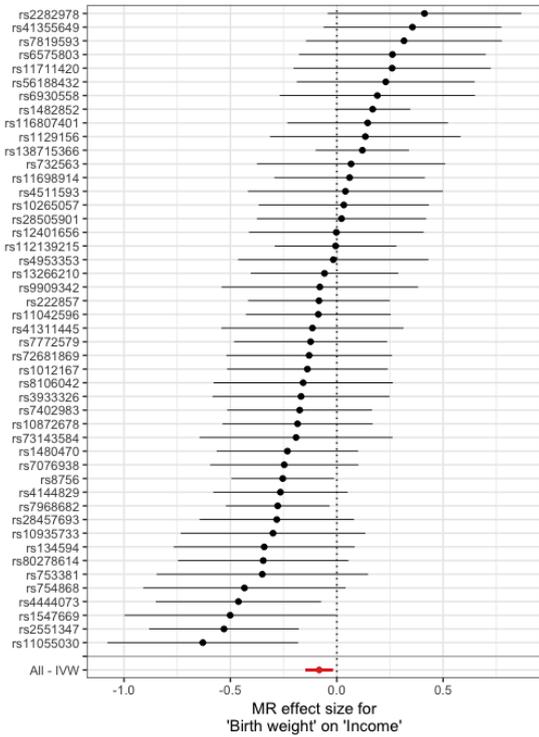
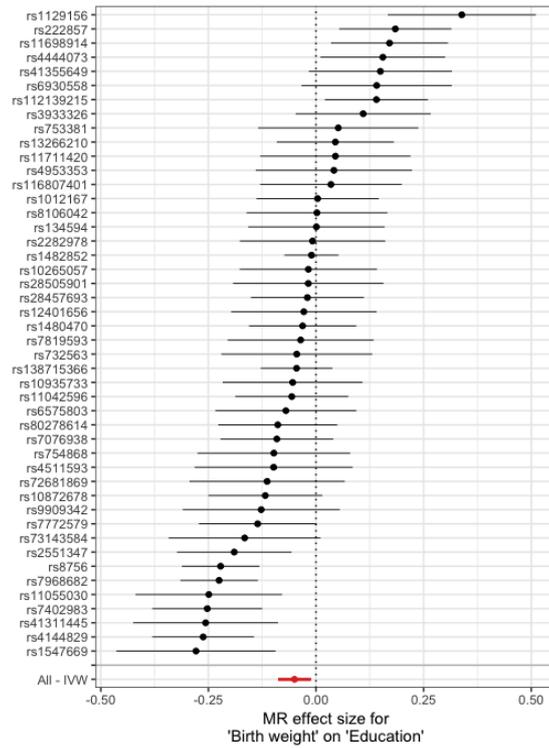
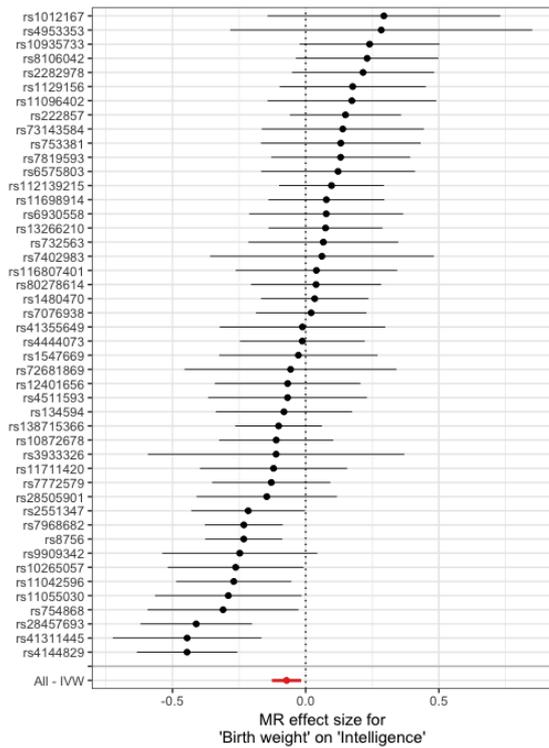
eFigure 2. Forest plot reporting Single SNP effects



(eFigure 2 continued)



(eFigure 2 continued)



## Results of the tests for pleiotropy

The table reports the results for the heterogeneity test (Q statistics) and the test of the MR-Egger intercept (unbalanced horizontal pleiotropy test).

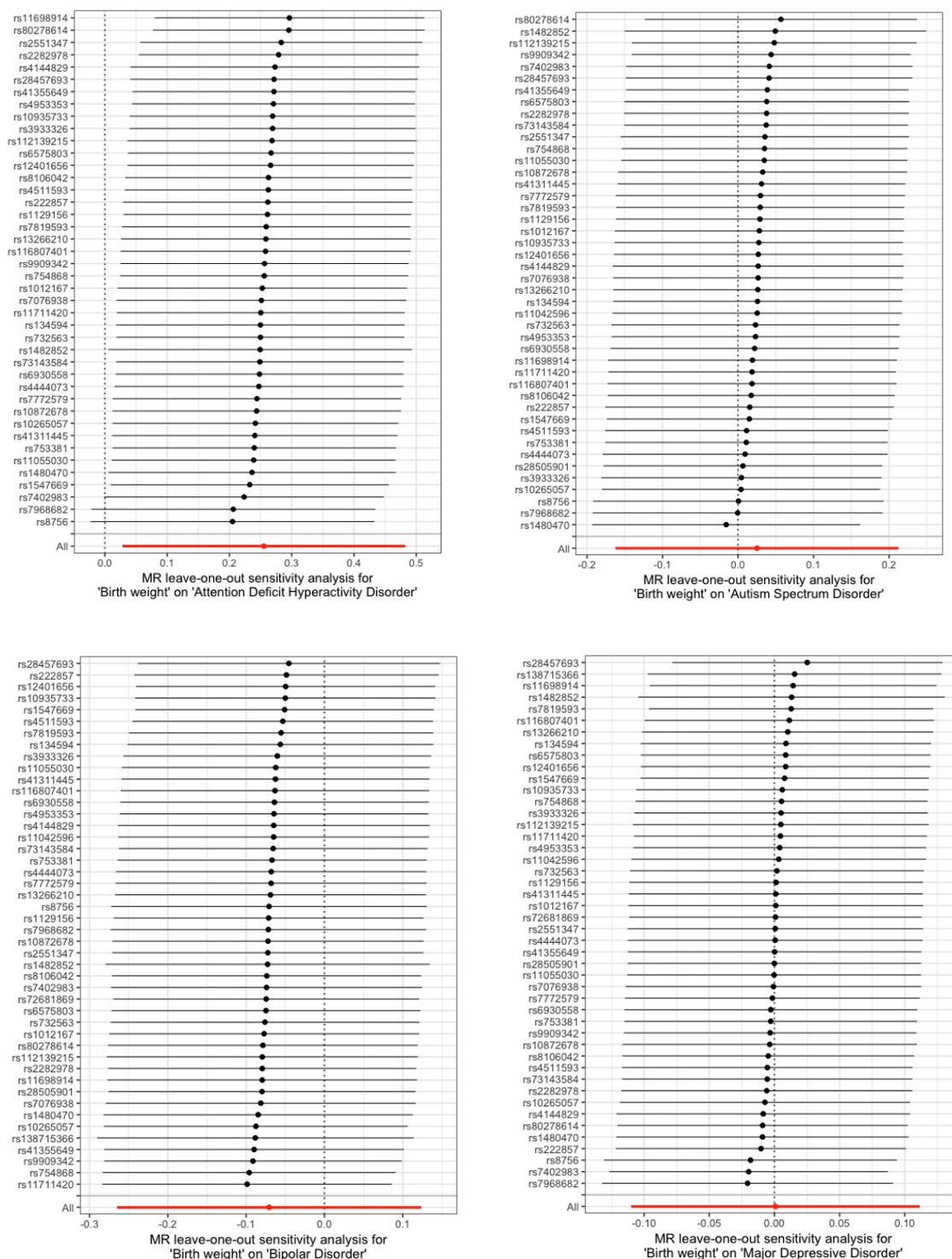
eTable 4. Results of the tests for pleiotropy

Outcome	Q statistic		MR-Egger intercept		
	Q value (DF)	P	MR-Egger intercept	SE	P
Attention-Deficit/Hyperactivity Disorder	71.49 (41)	0.002	0.00	0.01	0.653
Autism Spectrum Disorder	51.42 (43)	0.177	-0.01	0.01	0.157
Bipolar Disorder	64.77 (45)	0.028	0.01	0.01	0.404
Major Depressive Disorder	59.36 (45)	0.074	0.00	0.00	0.433
Obsessive-Compulsive Disorder	52.25 (41)	0.112	0.03	0.02	0.078
Post-Traumatic Stress Disorder	44.78 (45)	0.481	0.00	0.02	0.957
Schizophrenia	90.42 (43)	<0.001	0.00	0.01	0.373
Suicide attempt	31.51 (34)	0.590	-0.02	0.01	0.172
Intelligence	104.79 (45)	<0.001	0.00	0.00	0.123
Educational attainment	161.93 (45)	<0.001	0.00	0.00	0.741
Income	70.75 (46)	0.011	0.01	0.00	0.024
Social deprivation	49.09 (46)	0.350	0.00	0.00	0.148

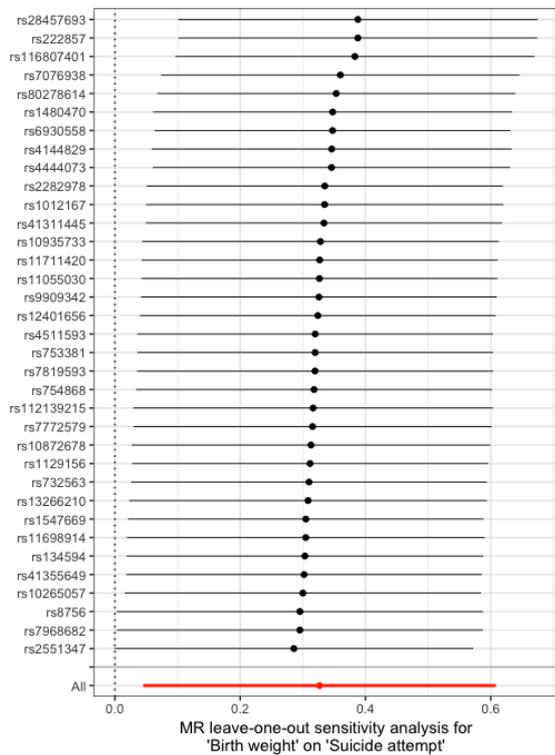
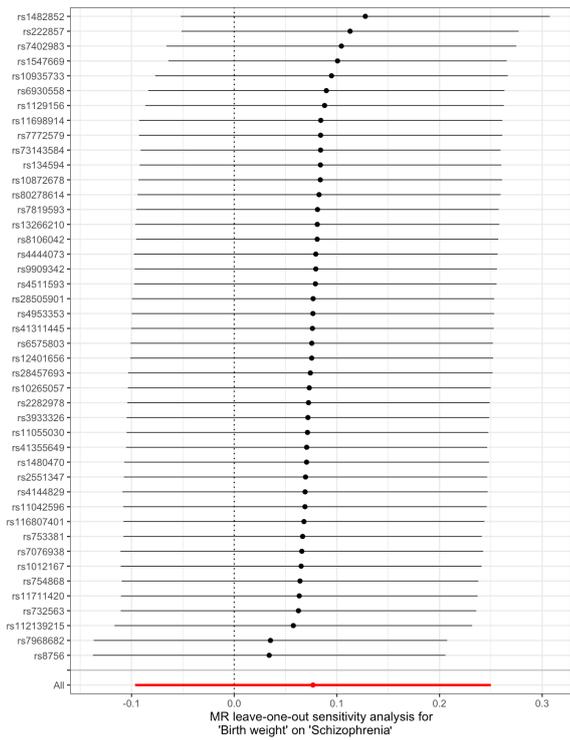
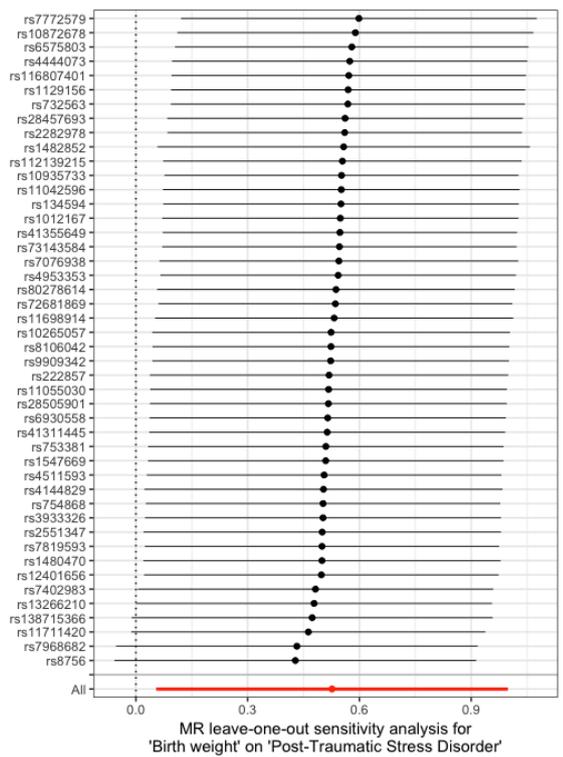
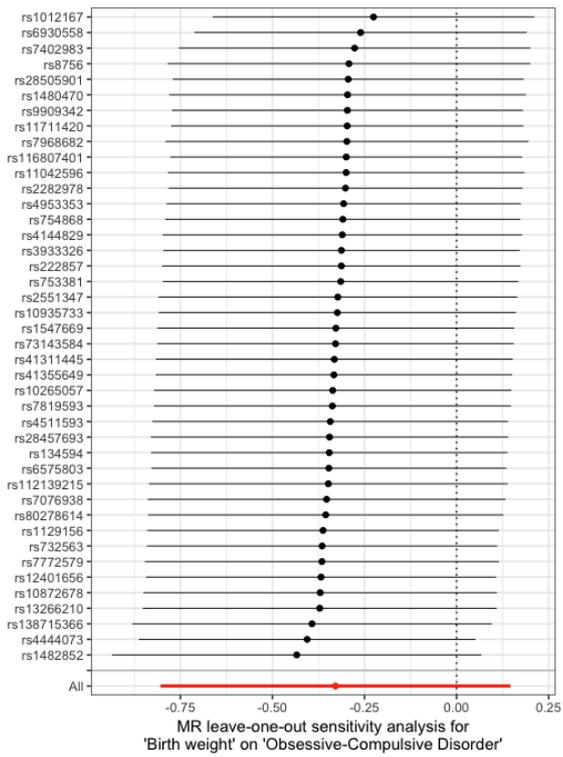
## Leave-one-out analysis

The forest plots in **eFigure 3** show, for each outcome, the Inverse-Variance Weighted (IVW) estimate calculated excluding one SNP instrument at the time, as well as the IVW instrument obtained considering all available SNP instruments (in red).

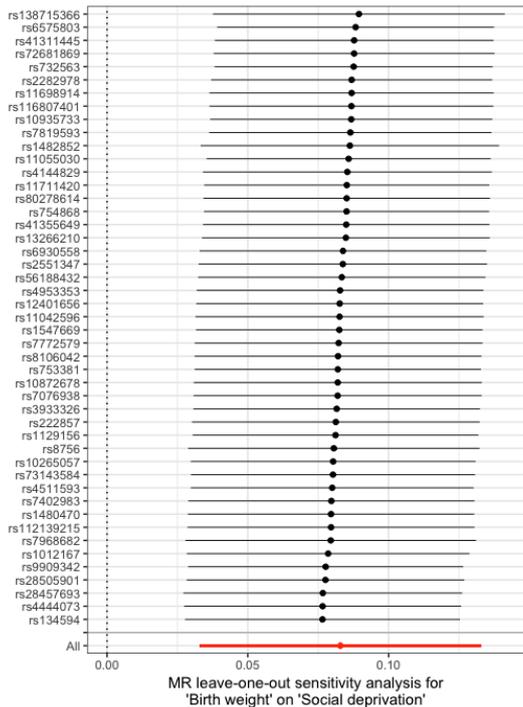
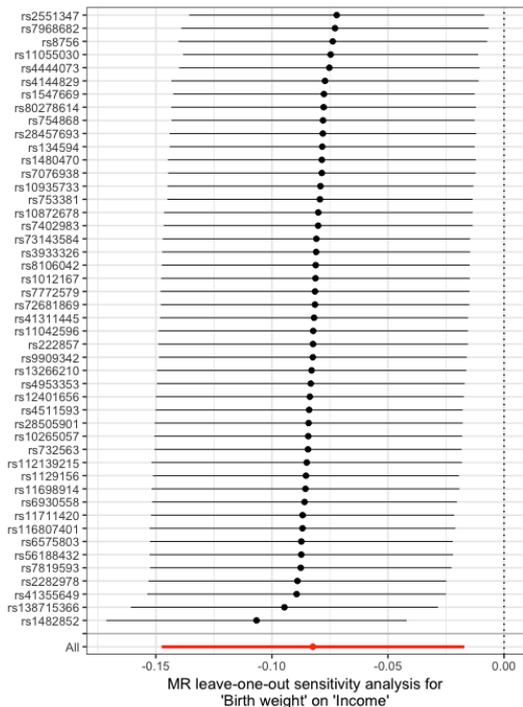
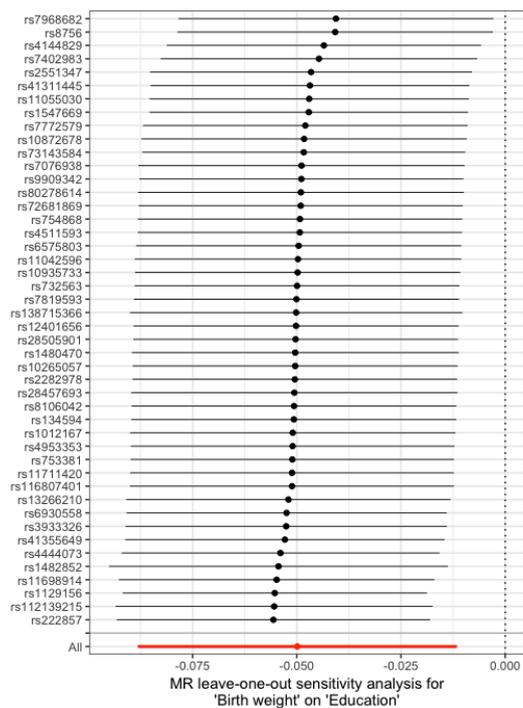
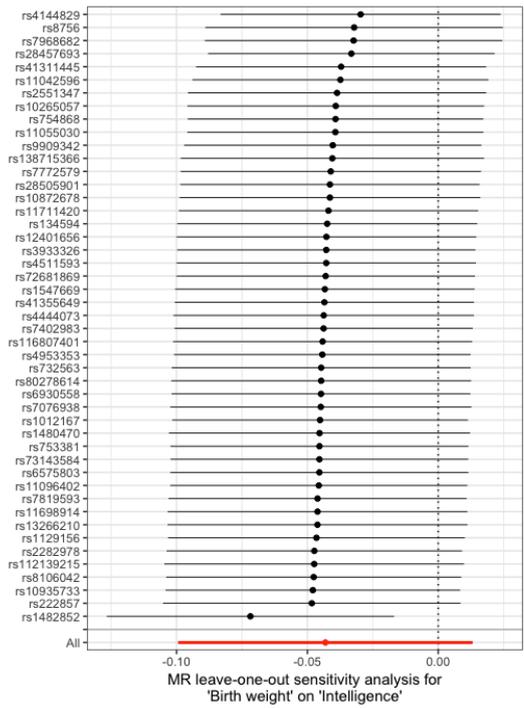
**eFigure 3. Forest plots for the leave-one-out analysis**



(eFigure 3 continued)



(eFigure 3 continued)



## PhenoScanner Search

The PhenoScanner database was searched to identify the known association between the SNP instruments (and those in linkage disequilibrium with  $r^2 \geq 0.80$ ) and traits explored in the literature. The aim was to identify potential source of horizontal pleiotropy or potential associations with traits that can confound the exposure-outcome association. Findings (ie, the traits associated with the SNPs of interest according to the phenoScanner search) are visualized in **eFigure 4** using a word cloud in which the dimension of each word (ie, trait) is proportional to the number of SNPs associated with that trait.

**eTable 4. Results of the PhenoScanner Search**

SNP	CHR	Function	Gene	Associated traits
rs1012167	20	intergenic	LINC01728	Cholesterol, lipoproteins, body fat
rs10181515	2	intergenic	NEU2	Impedance, body fat
rs10265057	7	intergenic	TNS3	
rs10935733	3	intron	RP11-680B3.2	
rs11042596	11	intergenic	IGF2	Height, length menstrual cycle
rs11055030	12	upstream	APOLD1	Height, lymphocyte count, metabolism, body fat, hypertension
rs11096402	X	intron	PLAC1	
rs112139215	7	intron	MLXIPL	
rs1129156	19	synonym	MAP3K10	pulse rate
rs116807401	4	missense	PABPC4L	Height, body mass
rs11698914	20	intron	COMMD7	Height, monocyte count, basophil count
rs11711420	3	upstream	KLHL24	Weight, body fat
rs12401656	1	upstream	RNU6-880P	
rs13266210	8	int	ANK	Diabetes, Reticulocyte
rs134594	22	upstream	KREMEN1	Bone density, Reticulocyte, arm impedance
rs138715366	7	intron	YKT6	Subdural hemorrhage/hematoma
rs1480470	12	intergenic	RP11-366L20.4	Body fat, pulse rate
rs1482852	3	upstream	LINC02029	Height, body fat, waist circumference, high-density lipoprotein, age at menarche, hemoglobin
rs1547669	6	-	-	Height, rheumatoid arthritis, Plateletcrit, platelet count, alcohol intake past 10 years
rs222857	-	-	-	
rs2282978	7	intron	CDK6	Height, body fat, monocyte count, blood pressure, bone density, rheumatoid arthritis
rs2551347	2	intron	KLHL29	Height, body fat, lymphocyte count, impedance, white cell count
rs28457693	9	intron	PTCH1	Height, body fat, impedance, forced expiratory volume
rs28505901	9	intron	GPSM1	Height, diabetes
rs3933326	9	intron	PHF19	
rs41311445	22	3_prime_UTR	SNU13	Body fat mass, height, impedance arm
rs41355649	19	downstream	CEBPA	Impedance, lymphocyte count
rs4144829	4	intron	LCORL	Body fat mass, height, basal metabolic rate, weight
rs4444073	11	downstream	ADM	Impedance, body fat, metabolism, height
rs4511593	17	intron	TNFSF12-TNFSF13	Impedance, blood pressure, body fat, testosterone
rs4953353	2	intron	EPAS1	
rs56188432	2	missense	ACVR1C	Neoplasm, emphysema, intracranial hemorrhage, body size, cholangitis, somnolence/stupor/coma
rs6575803	14	intron	MEG3	Body fat
rs6930558	6	-	-	
rs7076938	10	intergenic	ADRB1	Vascular/hearth problems, hypertension, high-density lipoprotein, height
rs72681869	14	missense	SOS2	Blood pressure, hip circumference, body fat, hemoglobin
rs73143584	20	intron	ZBTB46	Blood pressure, vascular problems, coronary artery disease
rs732563	8	upstream	CTC-756D1.1	Height, body fat, hip circumference
rs7402983	15	intron	IGF1R	Height, body fat, hip circumference, hip circumference, water mass, impedance
rs753381	20	missense	PLCG1	Cholesterol, lipoproteins, hematocrit
rs754868	2	intergenic	AC016735.1	Blood pressure
rs7772579	6	intron	ESR1	Bone density, HDL cholesterol
rs7819593	8	intron	ZFPM2	
rs7968682	12	intergenic	HMGA2	Height, body fat, forced expiratory volume, blood pressure
rs80278614	11	intergenic	TBX15	Height
rs8106042	19	intron	INSR	Height
rs8756	12	3_prime_UTR	HMGA2	Height, body fat, forced expiratory volume
rs9909342	7	intergenic	RP11-173M1.4	

SNP, Single Nucleotide Polymorphism; CHR, Chromosome



## Steiger filtering

The table below presents results of the Steiger filtering sensitivity analysis.<sup>21</sup> This analysis verifies whether the variance in the exposure explained by the instrument SNPs is larger than the variance in the outcome explained by the instrument SNPs. As shown in the table below, this analysis suggested that the direction of the tested associations is correct (i.e., the instrument SNPs explains a larger proportion of the variance of the exposure –birth weight– than the outcomes), and the sensitivity analyses after filtering are consistent with the main analyses. Of note, MR analyses while excluding potentially problematic SNPs reduce power. For this reason, despite our hypothesized direction of causation is correct and despite results are largely consistent with the main analyses, the CI for PTSD is large and includes 1. This may likely be due to reduced power after the exclusion of potentially problematic SNPs (the PTSD GWAS has relative low sample size). It is also worth noting that Steiger filtering relies on an approximation and may be numerically unstable because  $R^2$  should be estimated directly from independent replication samples (which is not the case here).

Outcome	SNP $R^2$ exposure <sup>a</sup>	SNP $R^2$ outcome <sup>b</sup>	Correct causal direction <sup>c</sup>	OR/Beta (CI) after Steiger filtering <sup>d</sup>	OR/Beta (CI) main analysis <sup>e</sup>
ADHD	0.0054	0.0012	True	1.26 (1.01-1.58)	1.29 (1.03-1.62)
PTSD	0.0062	0.0052	True	1.26 (0.69-2.31)	1.69 (1.06-2.71)
Suicide attempt	0.0042	0.0011	True	1.39 (1.05-1.84)	1.39 (1.05-1.84)
Intelligence	0.0056	0.0007	True	-0.07 (-0.13; -0.02)	-0.07 (-0.13; -0.02)
Education attainment	0.0047	0.0001	True	-0.04 (-0.07; -0.01)	-0.05 (-0.09; -0.01)
Income	0.0063	0.0008	True	-0.08 (-0.15; -0.01)	-0.08 (-0.15; -0.02)
Social deprivation	0.0063	0.0005	True	0.08 (0.03; 0.13)	0.08 (0.03; 0.13)

<sup>a</sup> Proportion of variance in the exposure (birth weight) explained by the instrument SNPs. Should be greater than SNP  $R^2$  outcome

<sup>b</sup> Proportion of variance in the outcome explained by the instrument SNPs. Should be smaller than SNP  $R^2$  exposure;

<sup>c</sup> Is the hypothesized causal direction correct (based on SNP  $R^2$  exposure > SNP  $R^2$  outcome criterion)?

<sup>d</sup> Association if problematic SNPs are filtered out

<sup>e</sup> Main association

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