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 [~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 (β=-0.07; CI=-0.13; -0.02), and socioeconomic outcomes, ie, educational attainment (β=-0.05; CI=-0.09; -0.01), income (β=-0.08; CI=-0.15; -0.02), and social deprivation (β=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),[1–8] as well lower intelligence and socioeconomic status (see also **Supplementary material eIntroduction**).[9–11] These findings are consistent with the Developmental Origins of Health and Disease Hypothesis (DOHaD),[12,13] 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.[14–20] 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.[21–23] Genetic variants are randomly allocated at conception and relatively independent of environmental confounding factors, therefore this design mimic 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).[21,22] 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.[24] 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.[25,26] 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[26] 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.[27] 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).[26] 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,[25] and maintaining statistical significance at $P < 1\times10^{-5}$. 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 $F > 10$.[28] 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,[29] autism spectrum disorder,[30] bipolar disorder,[31] major depressive disorders,[32] obsessive-compulsive disorder,[33] post-traumatic stress disorder (PTSD),[34] schizophrenia,[35] suicide attempt (i.e., hospital admission for a suicide attempt);[36] (2) cognitive outcome: intelligence (measured as the general factor of intelligence and primarily evaluating fluid domains of cognitive functioning);[37] (3) socioeconomic outcomes: educational attainment (measured as years of education),[38] household income (measured as total income before taxes using 5 income categories),[39] social deprivation (measured using the Townsend Social Deprivation Index)[39]. Details on phenotypes assessment can be found in the individual publications.

Data analysis

We conducted a two-sample Mendelian randomization analyses in R[40] using the TwoSampleMR,[41] MendelianRandomization,[42] 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 the 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),[22] 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,[43] 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),[44] 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)[45] 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 ($P < 1\times10^{-5}$) 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.

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 (β, -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; β, -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 (β, -0.05; CI, -0.09; -0.01; *P* = 0.011; *q* = .039), income (β, -0.08; CI, -0.15; -0.02; *P* = 0.013; *q* = .039), and social deprivation (β, 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 (β, -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: β, -0.09, CI, -0.17; -0.00; *P* = 0.041; MR-Egger: β, -0.11; CI, -0.25; 0.04; *P* = 0.139; MR-RAPS, β, -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 (**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.[28] 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,[26] 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,[25,26] failure to account for this confounding effect may create bias in the causal estimates.

Previous observational,[46,47] within-sibling[7] and twin[48] 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.[7,48] Both ADHD and autism spectrum disorder are neurodevelopmental disorders with childhood onset, and both had been associated with low birth weight.[7] 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 or a recent genetically informed (within sibling) study showing associations with both ADHD and autism, as well as with a common neurodevelopmental latent factor.[7] 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 [8] but not with a within-sibling Swedish study who failed to report an association of birth weight with suicide attempt in early adulthood.[49] 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.[50] As suicide risk is the result of both specific factors and factors shared with major psychiatric disorders comorbid with suicide,[51] 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,[52] but not with a within-sibling study.[7] 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 [7], are important, especially considering that available observational evidence was either contradictory (eg, for depression)[5,53] or suggested associations (eg, for schizophrenia).[1]

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.[9,10] 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,[11] 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.[54]

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,[55] 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.[55] 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 validly of their phenotypes. Second, due to data availability, this study is limited to individual 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.[26,49] 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.[23] 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)[56] are needed to corroborate our results.[57]

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

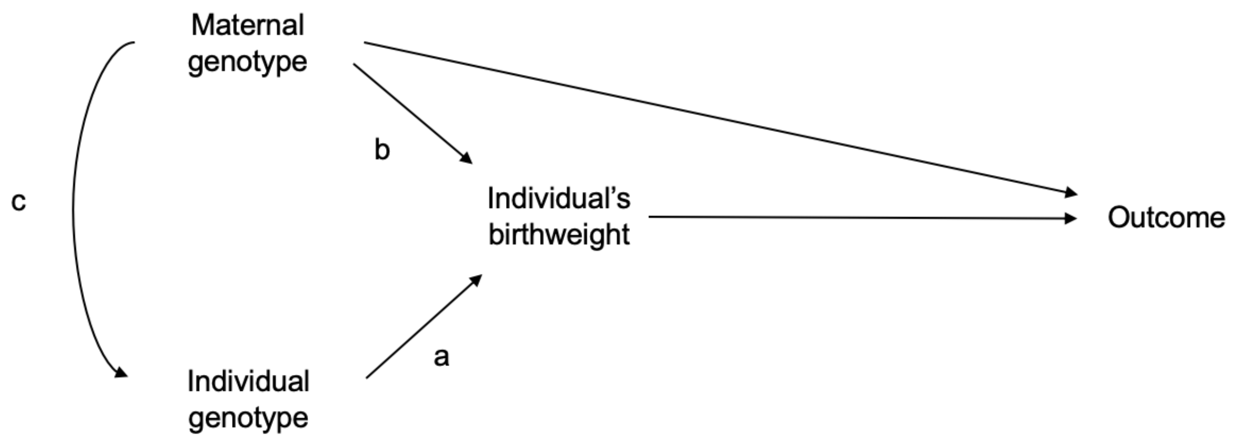
Phenotype	Source GWAS (Consortium)	Sample size			No. SNPs	Phenotype assessment
		N total	Cases	Controls		
Birth weight	EGG, UKB	264 498	-	-	48	Medical records, self-reports, midwife reports
ADHD	PGC, iPSYCH, EAGLE	53 293	19 099	34 194	42	Registry-based diagnoses, self-reports, diagnostic interviews
Autism 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).

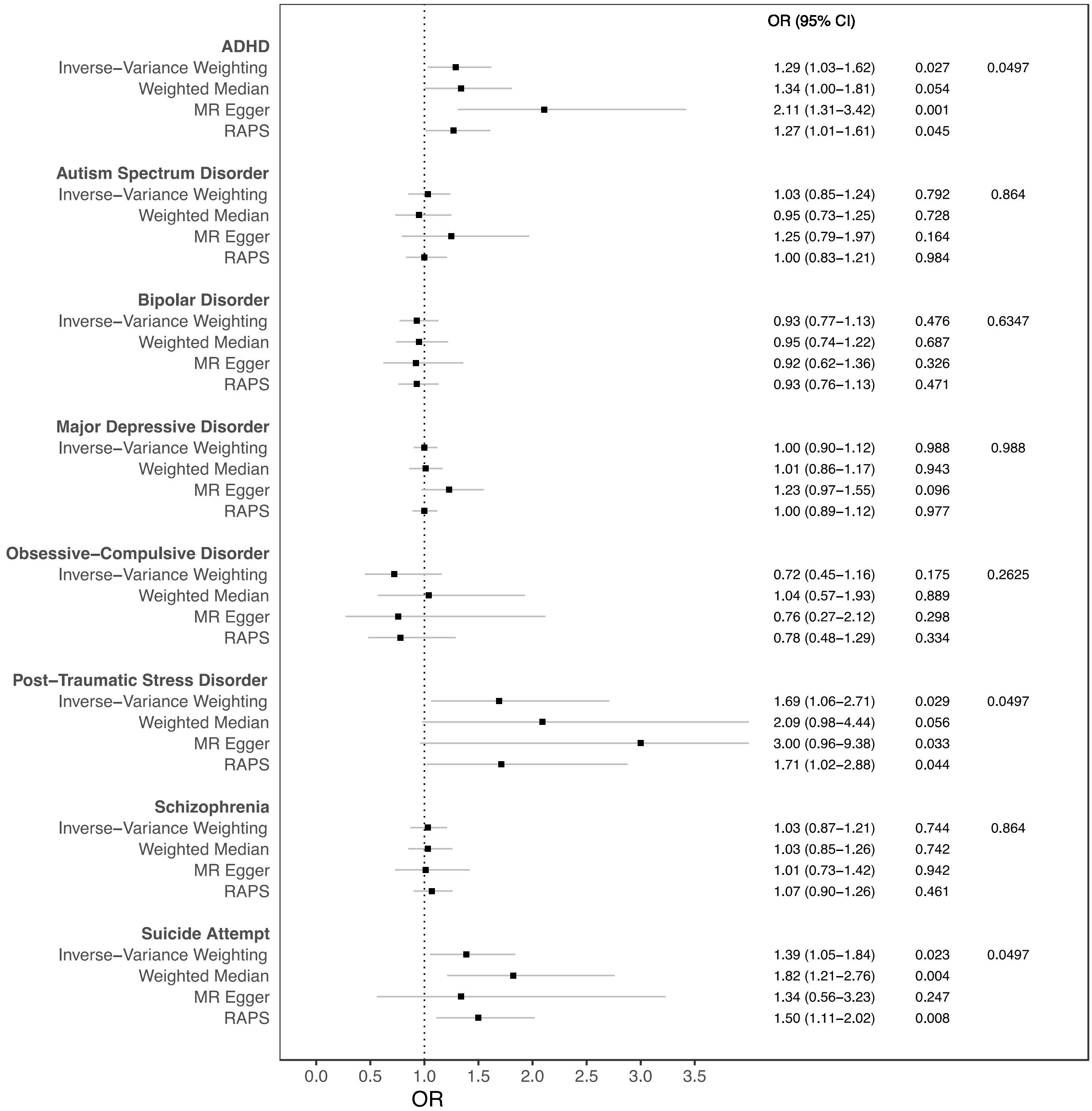
Figures

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



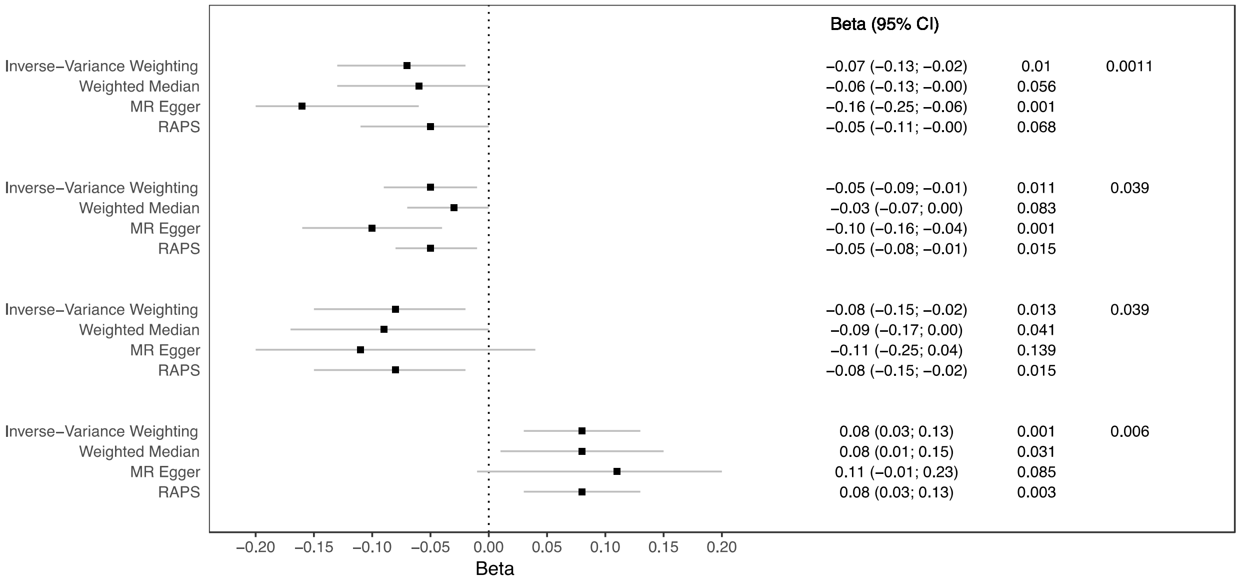
Using the Mendelian randomization design, it is possible to estimate the association between individual's birth weight and an outcome (*d* path in the figure) using individual genotype associated with birth weight as instrumental variable (*b* in the figure), instead of the observational assessment of 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~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).[26]

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