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Contribution of birth weight to mental health, cognitive and socioeconomic outcomes: two-sample Mendelian randomisation

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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 owing to confounding.

Aims

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

Method

We used 48 independent single-nucleotide polymorphisms as genetic instruments for birth weight (genome-wide association studies' total sample: $n = 264\,498$) and considered mental health (attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder, bipolar disorder, major depressive disorder, 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 s.d. unit decrease (~464 g) in birth weight, 1.29; 95% CI 1.03–1.62), PTSD (OR = 1.69; 95% CI 1.06–2.71) and suicide attempt (OR = 1.39; 95% CI 1.05–1.84), as well as for intelligence (β = −0.07; 95% CI −0.13 to −0.02) and socioeconomic outcomes, i.e. educational attainment (β = −0.05; 95% CI −0.09 to −0.01), income (β = −0.08; 95% CI −0.15 to −0.02) and social deprivation (β = 0.08; 95% 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 the hypothesis that birth weight could be an important element on the causal pathway to mental health, cognitive and socioeconomic outcomes.

Keywords

Psychiatric disorders; birth weight; Mendelian randomisation; socioeconomic outcomes; intelligence.

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 and suicide),[1–8] as well lower intelligence and socioeconomic status[9–11] (see also the Introduction in the supplementary material available at https://doi.org/10.1192/bjp.2021.15). These findings are consistent with the developmental origins of health and disease (DOHaD) hypothesis,[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 behaviours, 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, cognitive and socioeconomic problems is important for understanding their aetiology. Given that it is not possible to directly randomise birth weight to probe its causal role on later outcomes, the most robust evidence would come from quasi-experimental designs. Mendelian randomisation 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 are relatively independent of environmental confounding factors; therefore this design mimics that of a randomised trial in which treatment is randomly allocated and confounding factors do not depend on treatment allocation (Fig. 1; see supplementary material Methods for details on Mendelian randomisation assumptions).[21,22] A previous study that used Mendelian randomisation to investigate the role of birth weight in ADHD, major depressive disorder and schizophrenia found no evidence for a causal role of birth weight.[24] However, a major limitation of that study was the inability to account for the confounding effect of maternal genotype, which can lead to incorrect Mendelian randomisation estimates.[25,26] Maternal and individual (i.e. offspring) genotypes are correlated and any effect of intrauterine exposures or maternal behaviour influenced by the mother's genetic make up 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 single-nucleotide polymorphisms (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 randomisation study relies on summary statistics from the largest available GWASs to estimate the contribution of birth weight to mental health (including common psychiatric disorders and suicide attempt), cognitive (i.e. intelligence) and socioeconomic outcomes (including educational attainment, income and social deprivation).

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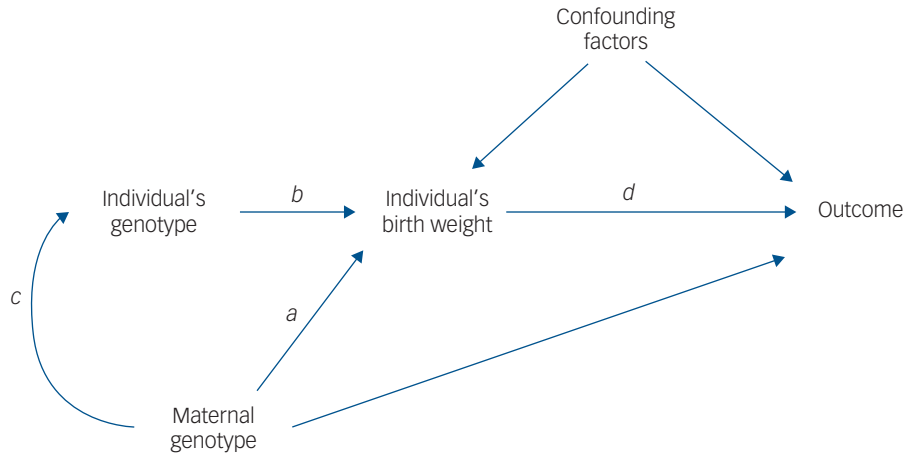

Fig. 1 Confounding effect of maternal genotype on the association between an individual's genotype and birth weight.

Using the Mendelian randomisation design, it is possible to estimate the association between an individual's birth weight and an outcome (path *d* in the figure) using the individual's genotype associated with birth weight as the instrumental variable (path *b*), 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 the individual's genotype (path *a*) and maternal genotype (path *b*) have influences on birth weight, the former directly, the latter through the intrauterine environment. Because of the correlation between the individual's genotype and their mother's genotype ($r \sim 0.5$; path *c*), the effect of the individual's phenotype on their birth weight may be confounded. To avoid this bias, we used estimates of the association between individuals' genetic variants adjusted for the correlated maternal effect as instruments (published in the most recent birth-weight GWAS).[26]

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 owing to specific linkage disequilibrium structures.[27] All the GWASs had been adjusted for population stratification using ancestry-informed principal components, as well as for other main covariates (e.g. age and gender; see details in cited publications). All phenotypes were primarily measured among adult individuals and summary statistics were available only for both genders combined. 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 Methods). Power analysis is presented in the online material (supplementary Methods).

Birth weight

In total, $n = 209$ independent genome-wide significant SNPs associated with birth weight were identified by the largest GWAS meta-analysis conducted by the Early Growth Genetics (EGG) consortium and including the UK Biobank sample ($n = 264\,498$).[26]

Table 1 Summary of genome-wide association studies used in the analyses

Phenotype	Source GWAS or consortium	Sample size, *n*			SNPs, *n*	Phenotype assessment
		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, medical records
Major depressive disorder	PGC	173 005	59 851	113 154	46	Register-based diagnoses, diagnostic interviews, questionnaires
Obsessive–compulsive disorder	IOCDF-GC, OCG-AS	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[a]

GWAS, genome-wide association study; SNP, single-nucleotide polymorphism; ADHD, attention-deficit hyperactivity disorder; EGG, Early Growth Genetics consortium; UKB, UK Biobank; PGC, Psychiatric Genomics Consortium; iPSYCH, Lundbeck Foundation Initiative for Integrative Psychiatric Research; EAGLE, Early Genetics and Lifecourse Epidemiology Consortium; IOCDF-GC, International Obsessive Compulsive Disorder Foundation Genetics Collaborative; OCG-AS, OCD Collaborative Genetics Association Studies; SSGAC, Social Science Genetic Association Consortium.
a. 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).

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Among these GWAS significant variants, we selected 48 SNPs identified as having an effect on birth weight after adjusting for the correlated maternal effect on birth weight,[25] 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 Methods), suggesting that all SNPs were strong instruments according to the suggested threshold of $F > 10$.[28] Birth weight (which had a mean of ~3407 g and standard deviation of ~464 g) was *z*-score transformed separately for males and females in the studies participating in the GWAS meta-analysis and adjusted for study-specific covariates, including gestational duration (where available).

Outcomes

We obtained the estimates of associations between the birth weight instrument SNPs and our outcomes from the GWAS summary statistics. Whenever possible, instrument SNPs that 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: (a) mental health outcomes (all binary variables): ADHD,[29] autism spectrum disorder,[30] bipolar disorder,[31] major depressive disorder,[32] obsessive–compulsive disorder,[33] post-traumatic stress disorder (PTSD),[34] schizophrenia[35] and suicide attempt (i.e. hospital admission for a suicide attempt);[36] (b) cognitive outcome: intelligence (measured as the general factor of intelligence (*g*) and primarily evaluating fluid domains of cognitive functioning);[37] (c) socioeconomic outcomes: educational attainment (measured as years of education),[38] household income (measured as total income before taxes using five income categories)[39] and social deprivation (measured using the Townsend Social Deprivation Index).[39] Details on phenotype assessment can be found in the individual publications.

Data analysis

We conducted a two-sample Mendelian randomisation analysis in R version 3.6 for Mac[40] using the TwoSampleMR,[41] MendelianRandomization[42] and MRPRESSO packages. In two-sample Mendelian randomisation, causal estimates can be obtained using summary statistics from different samples (i.e. GWASs), one for the instrument/SNP-exposure association, another for the instrument/SNP-outcome association. The two data-sets were harmonised and the positive strand alleles were 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 the 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-effects model. Heterogeneity across the meta-analysed estimates, which may be indicative of horizontal pleiotropy (i.e. the fact that the 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).

A range of analyses were used to test the sensitivity of the IVW estimation. First, Mendelian randomisation-Egger (MR-Egger) regression,[43] which relaxes the assumptions of Mendelian randomisation 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 the MR-Egger estimate and the 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). Second, we used the 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 the 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. Third, we used the robust adjusted profile score (RAPS),[44] which is an estimator that deals with weak instruments and is robust to pleiotropic effects.

We then performed four further analyses. First, MR-PRESSO (Mendelian Randomisation Pleiotropy Residual Sum and Outlier)[45] was used to detect and correct for outliers that 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, were 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 of 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 analysis 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 $P < 0.05$. Additionally, to account for the possibility of false-positive findings, we used the false discovery rate with a *q*-value <0.05.

Ethical approval

This study is based on publicly available summary statistics from studies that had 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 (95% CI 1.03–1.62; $P = 0.027$; $q < 0.05$) per 1 s.d. unit decrease in birth weight (Fig. 2). No evidence of horizontal pleiotropy was detected (MR-Egger intercept, $P = 0.653$; supplementary Table 4), but the *Q*-statistic indicated the presence of significant heterogeneity ($P = 0.002$). However, the association was consistent across the Mendelian randomisation methods used as sensitivity analyses (MR-RAPS OR = 1.27; 95% CI 1.01–1.61; $P = 0.045$; weighted median OR = 1.34; 95% CI 1.00–1.81; $P = 0.054$; MR-Egger OR = 2.11; 95% CI 1.31–3.34; $P = 0.001$) 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; 95% CI 1.06–2.71; $P = 0.029$; $q < 0.05$), with consistent estimates across sensitivity analysis methods (MR-RAPS OR = 1.71; 95% CI 1.02–2.88; $P = 0.044$; weighted median OR = 2.09; 95% CI 0.98–4.44; $P = 0.056$; MR-Egger OR = 3.00; 95% CI 0.96–9.38; $P = 0.050$) and no evidence for heterogeneity (*Q*-statistic, $P = 0.481$), unbalanced horizontal pleiotropy (MR-Egger intercept, $P = 0.957$) and outliers influencing

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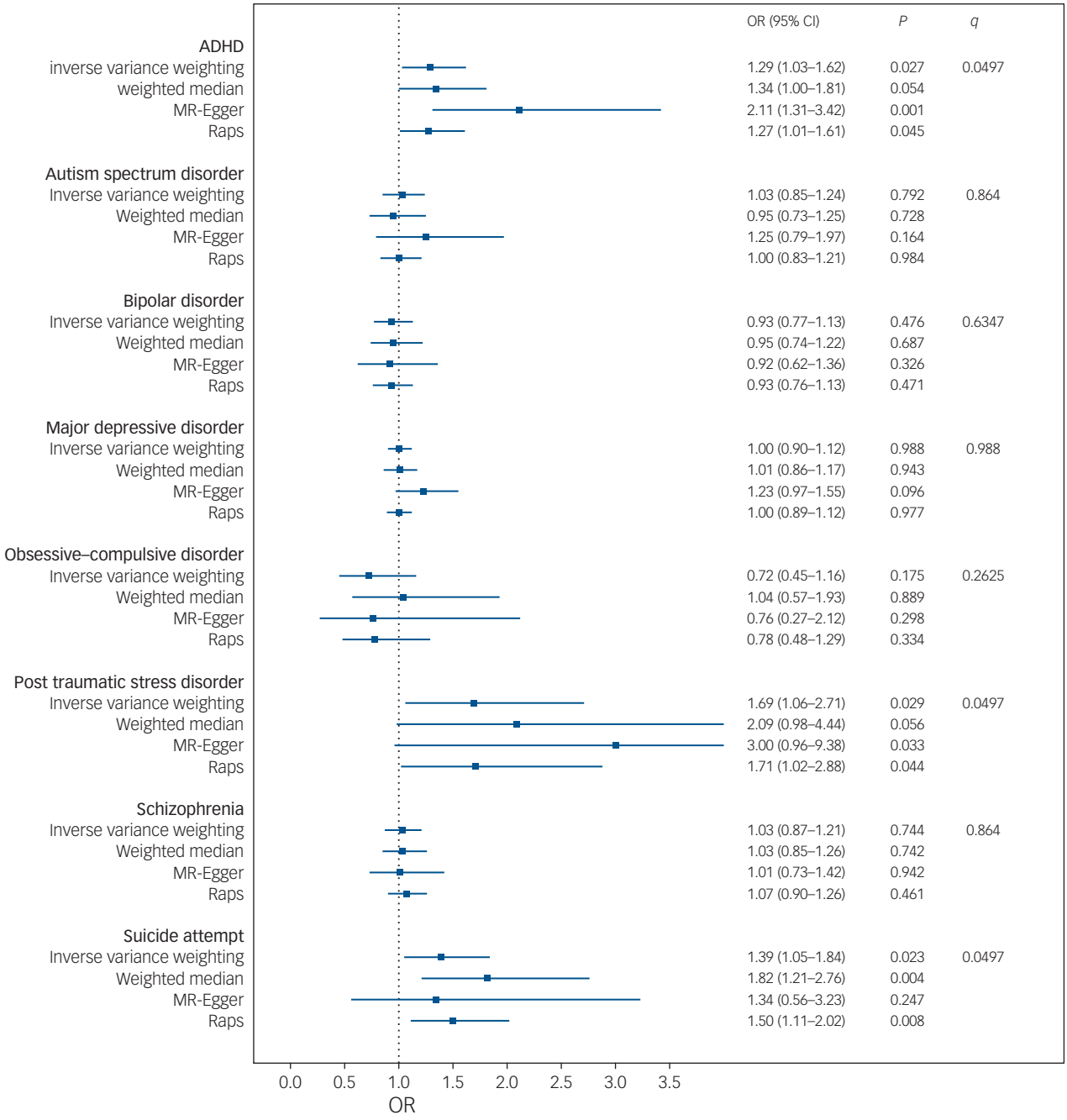

Fig. 2 Mendelian randomisation estimates for the association of birth weight with mental health. ADHD, attention-deficit hyperactivity disorder; MR-Egger, Mendelian randomisation-Egger regression; RAPS, robust adjusted profile score; *q*, *q*-value from the false discovery rate.

the results. We found no evidence supporting a contribution of birth weight to other psychiatric disorders, including autism spectrum disorder (OR = 1.03; 95% CI 0.85–1.24; $P = 0.792$), bipolar disorder (OR = 0.93; 95% CI 0.77–1.13; $P = 0.476$), major depressive disorder (OR = 1.00; 95% CI 0.90–1.12; $P = 0.988$), obsessive–compulsive disorder (OR = 0.72; 95% CI 0.45–1.16; $P = 0.175$) and schizophrenia (OR = 1.08; 95% CI 0.91–1.28; $P = 0.386$). 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; 95% CI 1.05–1.84; $P = 0.023$; $q < 0.05$). Consistent results were found in sensitivity analyses (MR-RAPS OR = 1.50; 95% CI 1.11–2.02; $P = 0.008$; weighted median OR = 1.82; 95% CI 1.21–2.76; $P = 0.004$; MR-Egger OR = 1.34; 95% CI 0.56–3.23; $P = 0.247$) and we did not find evidence for heterogeneity (*Q*-statistic, $P = 0.590$), unbalanced horizontal pleiotropy (MR-Egger intercept, $P = 0.172$) and outliers.

Contribution of birth weight to intelligence

We found evidence for a contribution of birth weight to intelligence ($\beta = -0.07$; 95% CI −0.13 to −0.02; $P = 0.010$; $q = 0.001$; Fig. 3) after exclusion of one outlier SNP (rs1482852; supplementary Results). This result remained after correction for an additional outlier SNP detected by the MR-PRESSO procedure (rs4144829; $\beta = -0.05$; 95% CI −0.11 to −0.01; $P = 0.036$). We did not find evidence for unbalanced horizontal pleiotropy (MR-Egger intercept,

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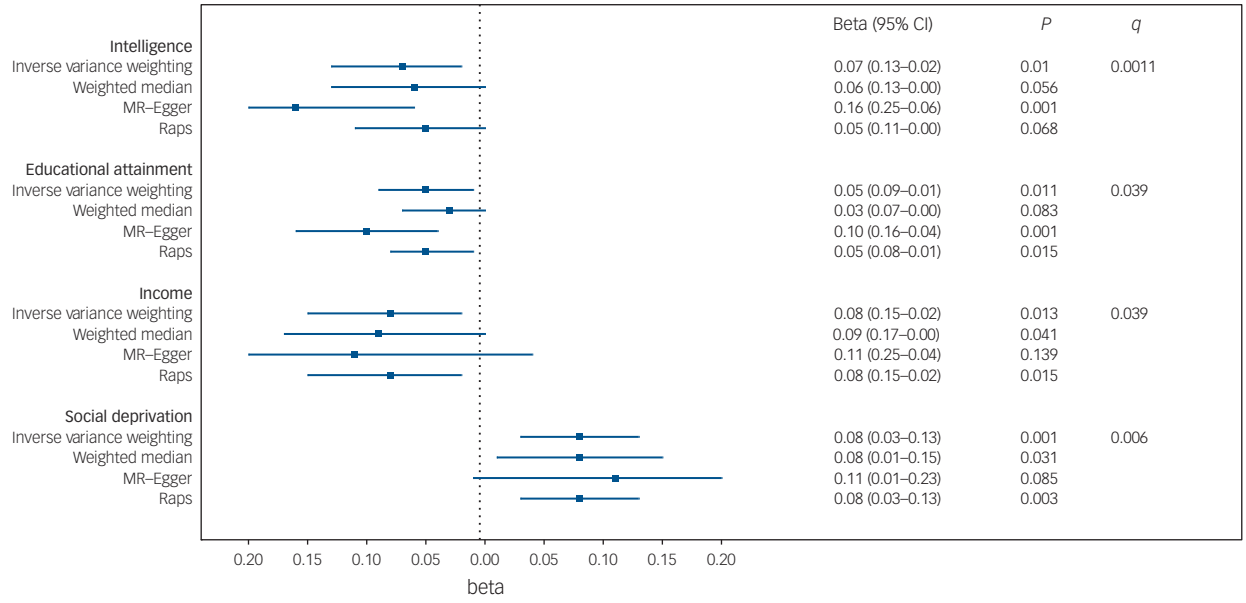

Fig. 3 Mendelian randomisation estimates for the association of birth weight with intelligence and socioeconomic outcomes. MR-Egger, Mendelian randomisation-Egger regression; RAPS, robust adjusted profile score; *q*, *q*-value from the false discovery rate.

$P = 0.123$), 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; 95% CI −0.09 to −0.01; $P = 0.011$; $q = 0.039$), income (β = −0.08; 95% CI −0.15 to −0.02; $P = 0.013$; $q = 0.039$) and social deprivation (β = 0.08; 95% CI 0.03–0.13; $P = 0.001$; $q = 0.006$) (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; 95% CI −0.08 to −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, 95% CI −0.17 to −0.00; $P = 0.041$; MR-Egger: β = −0.11; 95% CI −0.25 to 0.04; $P = 0.139$; MR-RAPS, β = −0.08; 95% CI −0.15 to −0.02; $P = 0.015$).

Additional sensitivity analyses

Searching the PhenoScanner database for each SNP instrument revealed associations between these SNPs and other anthropometric (e.g. height), metabolic (e.g. basal metabolism), hypertensive (e.g. blood pressure) and lipoprotein (e.g. high-density lipoproteins) 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 Results).

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, and 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 (i.e. educational attainment, income and social deprivation), but not to the other examined mental health outcomes.

This study relied on a robust two-sample Mendelian randomisation 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 aetiology 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 of 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 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,[49] which failed to find an association of birth weight with suicide attempt in early adulthood. Differences between the 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

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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 aetiology 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.

Our study could not support the contribution of birth weight to other psychiatric disorders, including depression, bipolar disorder, obsessive–compulsive disorder and schizophrenia. These findings, in line with those of other quasi-experimental studies,[7] are important, especially considering that available observational evidence was either contradictory (e.g. for depression)[5,53] or suggested associations (e.g. 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. the *P*-factor), but rather specific contributions to ADHD, PTSD and suicide attempt risk. However, future Mendelian randomisation investigations designed to specifically address this hypothesis may be informative to clarify the potential contribution of birth weight to 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 with normal birth-weight children but 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 the hypothesis 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]

Implications

Future studies should attempt to clarify the putative causal mechanisms explaining the associations that we found. It has been suggested that restricted fetal growth has a negative impact on 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 the brain's 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 on 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 well-being among low birth-weight children.

Limitations

First, the phenotypes considered in this study rely on the definitions and samples used in the original GWASs, 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 GWASs seem to corroborate the validly of their phenotypes. Second, owing to data availability, this study is limited to individuals of European ancestry. Third, because a large proportion of individuals included in the birth-weight GWASs had a 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 outcomes. Additionally, our analyses assume a linear relation between birth weight and outcomes.[26,49] Fourth, we could not explore potential gender differences in the association between birth weight and mental health, as gender-specific GWAS summary statistics were not available. Fifth, although we conducted a large array of sensitivity analyses showing the 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 adults and they may differ during other developmental periods. Seventh, although our analyses took into account the correlated role of maternal genotype, residual confounding dynastic effects 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 GWASs (currently not largely available but necessary to go beyond the assumptions of between-family Mendelian randomisation designs)[56] are needed to corroborate our results.[57]

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Supplementary material

Supplementary material is available online at https://doi.org/10.1192/bjp.2021.15.

Data availability

This study is based on publicly available summary statistics.

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Author contributions

M.O. designed the study, performed data analyses, interpreted the data and drafted the manuscript. J.-B.P. contributed to the study design, data analysis, data interpretation and writing of the final manuscript. All authors contributed to data interpretation and writing of the manuscript.

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Declaration of interest

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EXTRA CONTENT ONLINE

psychiatry in literature

The lady of the house

Stephen Wilson

In his *American Notes* (1842), Charles Dickens describes a visit to the State Hospital for the Insane in Boston which, he says, was an institution admirably conducted on enlightened principles of conciliation and kindness:

> '"Evince a desire to show some confidence, and repose some trust, even in mad people," said the resident physician, as we walked along the galleries, his patients flocking round us unrestrained.'

Dickens notes with approval the beneficial influence of the physician's wife, seated calmly with another lady and a couple of children, in one of the wards where patients worked, read and played at skittles. He notices an elderly female sitting by the chimneypiece and leaning her head against it with a great assumption of dignity and refinement of manner. A head which he says was so strewn with scraps of gauze and cotton and bits of paper, and had so many queer odds and ends stuck all about it, that it looked like a bird's nest. The lady was radiant with imaginary jewels and wore a rich pair of undoubted gold spectacles. Dickens uses the physician's introduction of this person as an example of his manner of gaining and retaining the confidence of his patients:

> '"This," he said aloud, taking me by the hand, and advancing to the fantastic figure with great politeness – not raising her suspicions by the slightest look or whisper, or any kind of aside to me: "This lady is the hostess of this mansion, Sir. It belongs to her. Nobody else has anything whatever to do with it. It is a large establishment, as you see, and requires a great number of attendants. She lives, you observe, in the very first style. She is kind enough to receive my visits, and to permit my wife and family to reside here; for which it is hardly necessary to say, we are much indebted to her. She is exceedingly courteous, you perceive," on this hint she bowed condescendingly, "and will permit me to have the pleasure of introducing you: a gentleman from England, ma'am: newly arrived from England, after a very tempestuous passage: Mr. Dickens, – the lady of the house!"'

Every patient in this asylum, Dickens says, sits down to dinner every day with a knife and fork, and in the midst of them sits the gentleman whose manner of dealing with his charges I have just described.

By contrast, reports of the Physician Superintendent of Littlemore Hospital, Oxford, some 80 years later: 'I regret that I had to summarily dismiss Male Nurse Frank Johnson. He overstayed his leave and entered the Hospital through a ward window on Dec 27'. 'I regret that I have to report that on April 17th I summarily dismissed Night Nurse O'Hara for leaving knives about in the kitchen of the admission ward'. History's arrow is not straight forward.

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