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Evaluating causal influence of maternal educational attainment on offspring birthweight via observational study and Mendelian randomization analyses

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ABSTRACT

Background: Although extensive discussions on the influence of maternal educational attainment on offspring birthweight, the conclusion remains controversial, and it is challenging to comprehensively assess the causal association between them.

Methods: To estimate effect of maternal educational attainment on the birthweight of first child, we first conducted an individual-level analysis with UK Biobank participants of white ancestry ($n = 208{,}162$). We then implemented Mendelian randomization (MR) methods including inverse variance weighted (IVW) MR and multivariable MR to assess the causal relation between maternal education and maternal-specific birthweight. Finally, using the UK Biobank parent-offspring trio data ($n = 618$), we performed a polygenic score based MR to simultaneously adjust for confounding effects of fetal-specific birthweight and paternal educational attainment. We also conducted simulations for power evaluation and sensitivity analyses for horizontal pleiotropy of instruments.

Results: We observed that birthweight of first child was positively influenced by maternal education, with 7 years of maternal education as the reference, adjusted effect = 44.8 (95%CIs 38.0–51.6, $P = 6.15 \times 10^{-38}$), 54.9 (95% CIs 47.6–62.2, $P = 4.21 \times 10^{-128}$), and 89.4 (95%CIs 82.1–96.7, $P = 4.28 \times 10^{-34}$) for 10, 15 and 20 years of maternal educational attainment, respectively. A causal relation between maternal education and offspring birthweight was revealed by IVW MR (estimated effect = 0.074 for one standard deviation increase in maternal education years, 95%CIs 0.054–0.093, $P = 2.56 \times 10^{-13}$) and by complementary MR methods. This connection was not substantially affected by paternal education or horizontal pleiotropy. Further, we found a positive but insignificant causal association (adjusted effect = 24.0, 95%CIs −150.1–198.1, $P = 0.787$) between maternal education and offspring birthweight after simultaneously controlling for fetal genome and paternal education; this null causality was largely due to limited power of small sample sizes of parent-offspring trios.

Conclusion: This study offers supportive evidence for a causal association between maternal education and offspring birthweight, highlighting the significance of enhancing maternal education to prevent low birthweight.

1. Introduction

Birthweight is an indicator of cumulative fetal growth, which is directly related to health outcomes in later life and can indirectly reflect living conditions of the population (Dai, et al., 2022; Khera et al., 2016). Birthweight is affected by many factors including fetal and maternal

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genetics (Warrington et al., 2019), maternal health and nutrition (Buck, et al., 2019), and placental function (Zhang, et al., 2022). Low birthweight generally indicates intrauterine growth restriction (Gil-Kulik, et al., 2022), while high birthweight is sometimes related to maternal conditions like gestational diabetes (Araya, Padilla, Garmendia, Atalah, & Uauy, 2014) or excessive weight gain during pregnancy (Pereda, Bove, & Pineyro, 2020). In both developing and developed countries, it is frequently observed that newborns with low birthweight are more likely to experience short-term adverse birth outcomes (e.g., stillbirth and neonatal death (Hediger, et al., 1999; Spittle et al., 2014; Spittle, Orton, Anderson, Boyd, & Doyle, 2015)) as well as long-term adverse health events (e.g., cancers (O'Neill, et al., 2015), stroke (Wang, et al., 2020), type II diabetes (T2D) (Harder, Rodekamp, Schellong, Dudenhausen, & Plagemann, 2007), and coronary heart disease (Wang, et al., 2014; Zeng & Zhou, 2019a, 2019b)). In addition, the relationship between offspring birthweight and maternal age was U-shaped. Specifically, young mothers, especially those who are underage (≤16 years), are associated with intrauterine growth restriction, low birthweight, preterm birth, child mortality, delayed child development, and maternal anemia during pregnancy (Gibbs, Wendt, Peters, & Hogue, 2012; Workicho et al., 2020); meanwhile, advanced maternal age (>35 years) is also associated with an increased risk of adverse pregnancy outcomes, such as low birthweight and preterm birth (Aradhya, et al., 2023). Consequently, understanding which maternal factors causally affect offspring birthweight is imperative to elucidate the mechanisms underlying these associations and to potentially pave the way for intervening abnormal birthweight.

Among numerous possible determinants influencing offspring birthweight (e.g., gestation length, maternal smoking, maternal drinking, maternal nutrition, prenatal health care, maternal stress, and genetic factors) (Brito Nunes, et al., 2023; Decina et al., 2023; Hwang, Lawlor, Freathy, Evans, & Warrington, 2019; Moen et al., 2020; Yajnik et al., 2014), parental educational attainment, as an important measure of socioeconomic status, has been shown to significantly associate with offspring health outcomes (Balaj, et al., 2021; Johnson et al., 2022; Kong et al., 2018; Lu et al., 2023; Noghanibehambari, Salari, & Tavassoli, 2022). Particularly, maternal educational attainment is closely related to the birthweight of offspring by modifying intrauterine environments (e.g., maternal nutrition and maternal health) and taking health care behaviors (Godah, et al., 2021; Silvestrin et al., 2013). Educational attainment plays a vital role in influencing the intrauterine environment in a variety of ways, including, but not limited to, the following: education empowers pregnant women to adopt a healthy lifestyle, including proper nutrition and diet (Biasini, Rosi, Menozzi, & Scazzina, 2021), and education promotes the mental health of pregnant women and equips them with effective stress management skills (Thygesen, et al., 2021). Additionally, education informs pregnant women of the importance of avoiding the use of harmful substances in order to safeguard the health and safety of the mother and the fetus (Bigsby, et al., 1999).

Although there have been extensive discourses surrounding the impact of maternal educational attainment on birthweight (Godah, et al., 2021; Silvestrin et al., 2013), the conclusion is still controversial and a comprehensive assessment of the causal association between them is challenging (Fig. 1). First, previous studies have tended to overlook paternal educational attainment, which is correlated with maternal educational attainment as implied by educational assortative mating (Domingue, Fletcher, Conley, & Boardman, 2014; Noghanibehambari et al., 2022) and is also relevant to offspring outcomes including birthweight (Alio, Salihu, Kornosky, Richman, & Marty, 2010; Balaj et al., 2021; Guarnizo-Herreño, Torres, & Buitrago, 2021; Shapiro et al., 2017). As a result, it is difficult to distinguish the independently maternal role from the parental impacts. Second, prior findings were primarily generated from traditional observational studies, which presented much great vulnerability to pre-existing maternal, familial, social and environmental confounders such as maternal health condition, maternal behaviors and lifestyles, household income and geographical area of residence (Decina, et al., 2023). Third, methodological limitations of observational research (e.g., recall bias and residual confounding) can lead to a deep concern when interpreting those relations as causality.

To efficiently overcome possible confounding effects, we here performed a Mendelian randomization (MR) study to investigate the causal association of maternal educational attainment with offspring birthweight. Compared to traditional epidemiological methods, MR employs single nucleotide polymorphisms (SNP) as instrumental variables for the exposure (e.g., maternal educational attainment) to examine its causal effect on the outcome (e.g., birthweight of offspring) (Angrist, Imbens, & Rubin, 1996; Davey Smith & Hemani, 2014; Greenland, 2000; Sheehan, Didelez, Burton, & Tobin, 2008). Because the two alleles of a SNP are segregated during gamete formation and conception randomly under Mendel's law and such segregation is uncorrelated with confounders, the results of MR are less susceptible to confounding factors (Davey Smith & Ebrahim, 2003). Further, due to the wide availability of summary statistics from large-scale genome-wide association studies (GWAS) (Abdellaoui, Yengo, Verweij, & Visscher, 2023; Loos, 2020; Pasaniuc & Price, 2016), MR avoids the need to record and control for all potential confounding factors present in one single study, and has become a cost-effective causal inference approach in observational studies (Brion, Shakhbazov, & Visscher, 2013; Evans, Moen, Hwang, Lawlor, & Warrington, 2019; Moen, Hemani, Warrington, & Evans,

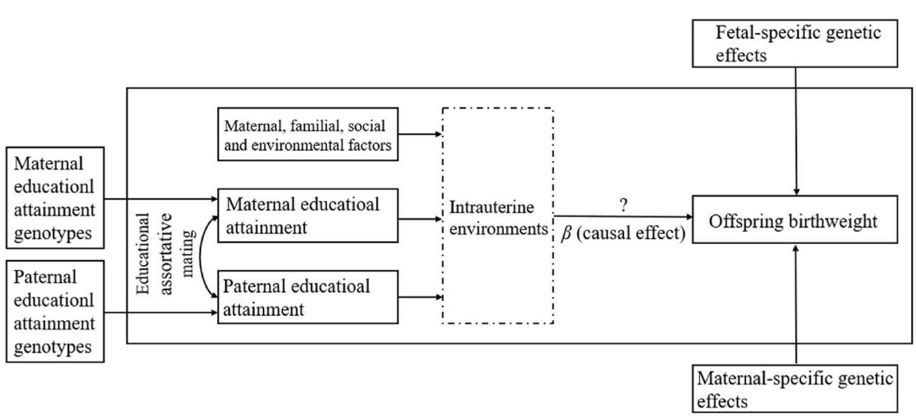

Fig. 1. A diagram demonstrating how various factors affect the birthweight of offspring. Environmentally, offspring birthweight is directly affected by in utero exposures which are in turn influenced not only by the parental educational attainment but also by other maternal, social and environmental factors. Genetically, offspring birthweight is influenced by both fetal and maternal genotypes, which cannot be directly adjusted for in the traditional observational study. Our aim is to examine whether there presents a causal relation between maternal educational attainment and offspring birthweight.

2019; Warrington, Freathy, Neale, & Evans, 2018; Yu, Yuan, et al., 2020; Zeng, Wang, Zheng, & Zhou, 2019; Zeng & Zhou, 2019a, 2019b).

To fill the knowledge gap mentioned above, in the present study we aimed to examine the causal relation between maternal education and offspring birthweight, as well as to ascertain whether maternal education functioned as an independent protective factor against low birthweight. To this goal, we first conducted an individual-level analysis to estimate the effect of maternal educational attainment on the birthweight of first child in the UK Biobank cohort (Sudlow, et al., 2015). Then, we implemented several two-sample MR approaches including inverse-variance weighted MR and multivariable MR to assess the causal relation between them using summary statistics of educational attainment from (Okbay, et al., 2022) and summary statistics of offspring birthweight from (Warrington et al., 2019). Finally, we performed a polygenic score (PGS)-based MR analysis to simultaneously adjust for the confounding effects of fetal-specific birthweight and paternal educational attainment. Meanwhile, we performed simulations for power evaluation and a range of sensitivity analyses for horizontal pleiotropy of instruments to strengthen the reliability of our results.

2. Methods

2.1. Individual-level analysis in the UK Biobank cohort

2.1.1. Offspring birthweight

The individual-level data of maternal educational attainment and offspring birthweight were obtained from the UK Biobank cohort (Sudlow, et al., 2015). The birthweight of first child was obtained by asking the question: “What was the birthweight of your first child in pounds?” The answers were reported solely by the mothers. We analyzed the association between maternal educational attainment and offspring birthweight, consistently converting the birthweight from pounds to grams during our analyses.

2.1.2. Maternal educational attainment

Maternal educational attainment was measured by the question: “Which of the following credentials do you possess?” We transformed the answered credential into educational attainment according to International Standard Classification of Education (ISCED) categories (Hill, et al., 2018; Lee et al., 2018). The first three response categories were: (i) no qualifications = 7 years of education; (ii) CSEs (Certificate of Secondary Education) or equivalent, or O levels/GCSEs (Ordinary level exams/General Certificate of Secondary Education) or equivalent = 10 years of education; (iii) college or university degree = 20 years of education.

As it has already demonstrated that the participants with NVQ (National Vocational Qualification), or HND (Higher National Diploma), or HNC (Higher National Certificate) equivalent qualifications previously coded as having 19 years of education would inflate the average education years in the UK Biobank data (Okbay, et al., 2022), we thus combined A (Advanced level general certificate of education) or AS (Advanced Subsidiary level general certificate of education) levels or equivalent, other professional qualifications, and NVQ or HNC or equivalent into the fourth category with 15 years of education (an intermediate point between 10 and 20 years of education). We excluded participants who had missing (and unknown) values in offspring birthweight and maternal educational attainment, resulting in a final sample of 208,162 individuals of white ancestry.

2.1.3. Calculate the effect of maternal educational attainment on offspring birthweight

We first performed a multiple linear regression to estimate the effect of maternal educational attainment ($\boldsymbol{X}$) on the birthweight of first child ($\boldsymbol{Y}$) in the individual-level UK Biobank data

$$\boldsymbol{Y} = \beta_0 + \boldsymbol{X} \times \beta + \mathbf{Z} \times \boldsymbol{w} + \boldsymbol{e} \tag{1}$$

where β is the effect of interest, $\mathbf{Z}$ is the design matrix of covariates with $\boldsymbol{w}$ the effect vector, β_0 is the intercept, and $\boldsymbol{e}$ is the residual vector.

We included maternal age at first live birth as one covariate in the main analysis. As a sensitivity analysis assessing the robustness of our results against the confounding influences of other mother’s conditions, we attempted to incorporate additional covariates such as Townsend deprivation index (TDI), body mass index (BMI), income, and physical activity (Table 1). However, we had to utilize measurements obtained at the time of completing the questionnaire as proxy measures for these mothers’ covariates, as the UK Biobank cohort did not collect accurate maternal covariates at the time of delivery.

Since increasing or advanced maternal age is widely recognized as a risk factor of preterm delivery and intrauterine growth restriction (Fall et al., 2015; Hart, 2016), we thus implemented a sub-group analysis in terms of the maternal age at first live birth to evaluate whether the effects of maternal educational attainment on offspring birthweight were heterogeneous. Specifically, based on the maternal age at first live birth (non-advanced maternal age ≤35 years and advanced maternal age >35 years) (Smithson, Greene, & Esakoff, 2022), we carried out the same linear regression in each maternal age group.

Summary-level analysis with summary statistics data via two-sample MR methods.

2.2. Summary statistics of educational attainment

We obtained the summary statistics of educational attainment of European individuals (n = ~3 millions) from (Okbay, et al., 2022), where educational attainment was constructed by mapping each major educational qualification identified from the cohort’s survey measure to an ISCED category and imputing a years-of-education equivalent for each ISCED category (Lee, et al., 2018), consistent with our treatments described before. More importantly, although both male and female individuals were analyzed, this GWAS offered convincing evidence that the genetic effects of attainment education were almost identical between males and females (Okbay, et al., 2022), with the estimated genetic correlation as high as 0.98 (se = 0.03) (Okbay, et al., 2016).

The above finding is also supported by well-known educational assortative mating (e.g., the contingency coefficient of education between couples in the UK Biobank parent-offspring trio data (see the Section of Parent-offspring trios) is 0.225, $P = 1.34 \times 10^{-4}$) (Domingue, et al., 2014), which can result in a high genetic similarity between couples. Since all the interaction terms were null ($P < 0.05/1,465$, ranging from

Table 1
Descriptive statistics and participant characteristics for the used UK Biobank cohort data.

Variables	n or mean (±sd)
Birthweight of first child (g)	3184.8 ± 542.6
Low birthweight (<2,500g)	16,657
Normal birthweight (2500~3,999g)	173,094
High birthweight (≥4000g)	18,411
Age at first live birth (years)	25.4 ± 4.6
TDI	−1.6 ± 2.9
BMI (kg/m^2)	27.1 ± 5.1
Income	52,843
<£18,000	
£18,000~£30,999	54,445
£31,000~£51,999	52,389
£52,000~£100,000	38,256
>£100,000	10,229
Years of education (years)	
7	41,367
10	61,904
15	46,189
20	58,702
Physical activity (low/moderate/high)	38,563/88,832/80,767

Note: BMI: body mass index; TDI: Townsend deprivation index; n: the sample size of diverse variables; sd: standard deviation.

2.6×10^{-4} to 0.99), we concluded that there did not exist any SNP-sex interaction effects on educational attainment for significant SNPs (Fig. S1), which also indicated the absence of sex difference in genetic influences (Supplementary Note). Hence, it is reasonable to utilize this mixed-sex summary statistics dataset as a proxy for maternal-only educational attainment; actually, analogous treatments were widely employed in previous work when investigating maternal exposures on offspring outcome events (Brito Nunes, et al., 2023; Decina et al., 2023; Hwang et al., 2019; Moen et al., 2020).

2.3. Summary statistics of birthweight

We yielded the summary statistics of birthweight from (Warrington et al., 2019a, 2019b). Based on 297,356 European individuals with their own birthweight and 210,248 European individuals with offspring birthweight, the maternal-specific SNP effect on birthweight after considering offspring genotypes and the fetal-specific SNP effect on birthweight after explaining mother genotypes were generated. For convenience, we next referred to birthweight influenced by genotypes after adjusting for the offspring's effect as maternal-specific birthweight and birthweight affected by genotypes after adjusting for the mother's effect as fetal-specific birthweight (Jin, et al., 2023). More detailed description of the summary statistics can be found in the Supplementary Note.

2.4. Estimate causal effect of maternal educational attainment on offspring birthweight via MR methods

We obtained 3952 independent significant SNPs ($r^2 < 0.1$ and $P < 5 \times 10^{-8}$) from (Okbay, et al., 2022) to serve as the instrumental variables of maternal educational attainment. Among these SNP instruments, these were 3919 SNPs that were common to the summary statistics of offspring birthweight (Warrington et al., 2019).

To estimate the causal influence of maternal educational attainment on offspring birthweight, we primarily implemented the two-sample inverse variance weighted (IVW) MR method (Burgess, Butterworth, & Thompson, 2013; Lawlor, 2016). Denote the effect of the jth SNP instrument as $\widehat{\alpha}_j^X$ for maternal educational attainment, and the maternal-specific effect and variance of the same instrument as $\widehat{\alpha}_j^Y$ and $\mathrm{var}(\widehat{\alpha}_j^Y)$ for birthweight. Then, with the K selected instruments, the IVW effect estimate was calculated as

$$\widehat{\beta} = \frac{\sum_{j=1}^{K} \mathrm{var}\left(\widehat{\alpha}_j^Y\right)^{-1} \widehat{\alpha}_j^Y \widehat{\alpha}_j^X}{\sum_{j=1}^{K} \mathrm{var}\left(\widehat{\alpha}_j^Y\right)^{-1} \left(\widehat{\alpha}_j^X\right)^2} \tag{2}$$

Along with IVW, we additionally performed three complementary methods: (i) the maximum likelihood method (Burgess, et al., 2013); (ii) the weighted median-based method (Bowden, Davey Smith, Haycock, & Burgess, 2016); (iii) the MR-Egger regression to evaluate the directional pleiotropy of instruments (Bowden, Davey Smith, & Burgess, 2015).

We also conducted the multivariable MR (MVMR) method (Burgess & Thompson, 2015; Rees, Wood, & Burgess, 2017; Sanderson, Davey Smith, Windmeijer, & Bowden, 2019) to determine the causal relation between maternal educational attainment and offspring birthweight while adjusting for the influence of paternal educational attainment

$$\widehat{\boldsymbol{\alpha}}^Y = \widehat{\boldsymbol{\alpha}}^{XM} \times \beta_+ \widehat{\boldsymbol{\alpha}}^F \times b + \boldsymbol{e}, \boldsymbol{e} \sim N\left(0, \sigma^2 \times \mathrm{var}\left(\widehat{\boldsymbol{\alpha}}^Y\right)\right) \tag{3}$$

where $\widehat{\boldsymbol{\alpha}}^{XM}$ is the marginal effect vector of SNP instruments of maternal educational attainment with the effect β as our interest, and $\widehat{\boldsymbol{\alpha}}^F$ is the marginal effect vector of these instruments for paternal educational attainment with the confounding effect b, $\boldsymbol{e}$ is the residual vector with σ^2 the variance.

To carry out the MVMR analysis, we required both paternal and maternal summary statistics of educational attainment (i.e., $\widehat{\boldsymbol{\alpha}}^{XM}$ and $\widehat{\boldsymbol{\alpha}}^F$). To this aim, we conducted the single-marker analysis for each SNP instrument in the UK Biobank cohort with only male ($n = 137{,}683$) or female ($n = 169{,}346$) participants of white ancestry. More detailed information regarding genotyping, imputation, and quality control in the UK Biobank study can be found elsewhere (Bycroft, et al., 2018) and was also described in the Supplementary Note.

2.5. PGS-based MR analysis in the UK Biobank parent-offspring trio data

2.5.1. Parent-offspring trios

Besides the two-sample MR and MVMR analyses described above, we further conducted a polygenic score (PGS)-based MR study with parent-offspring trio data available from the UK Biobank cohort. Technical details regarding how to determine parent-offspring trios could be found in our previous work (Jin, et al., 2023). After excluding participants with missing values in offspring birthweight, we retained 618 parent-offspring trios of white ancestry.

2.5.2. Polygenic score based MR analysis

We sought to examine the association between maternal educational attainment and offspring birthweight while controlling for the confounding effects of fetal-specific birthweight and paternal educational attainment. To this aim, we first calculated the PGS of maternal educational attainment (Kullo, et al., 2022): $\mathrm{PGS}^{\mathrm{M}}_{\mathrm{education}} = \sum_{j=1}^{m} g_j \widehat{\alpha}_j$, here m was the number of available SNP instruments, $\widehat{\alpha}_j$ was the marginal effect obtained from (Okbay, et al., 2022), and g_j was the maternal genotype of the SNP instrument (coded as 0, 1, or 2 indicating the number of effect alleles) in parent-offspring trios. We next employed 64 fetal-only birthweight-associated SNPs (Warrington et al., 2019) to produce a PGS for fetal-specific birthweight of offspring: $\mathrm{PGS}_{\mathrm{FB}} = \sum_{j=1}^{64} g_j^{FB} \widehat{\alpha}_j^{FB}$, here g_j^{FB} denoted the offspring genotype, and $\widehat{\alpha}_j^{FB}$ was the fetal-specific effect on birthweight. We also generated a PGS for paternal educational attainment: $\mathrm{PGS}^{\mathrm{F}}_{\mathrm{education}} = \sum_{j=1}^{m} g_j \widehat{\alpha}_j^F$, here $\widehat{\alpha}_j^F$ denoted the paternal effect of instrument estimated from the UK Biobank cohort as described before, and g_j was the paternal genotype of the instrument.

Using these PGSs, we performed the following linear regression

$$\boldsymbol{Y} = \beta_0 + \mathrm{PGS}^{\mathrm{M}}_{\mathrm{education}} \times \beta + \mathrm{PGS}^{\mathrm{F}}_{\mathrm{education}} \times b^F + \mathrm{PGS}_{\mathrm{FB}} \times b^{FB} + \boldsymbol{e} \tag{5}$$

where $\boldsymbol{Y}$ is the offspring birthweight in parent-offspring trios and was derived from the question: "participants were asked to enter their own birthweight", β is the effect of maternal educational attainment on offspring birthweight, b^F is the effect of paternal educational attainment, and b^{FB} is the effect of offspring fetal-specific birthweight.

2.6. Evaluate the influence of horizontal pleiotropy

To assess the influence of potential horizontal pleiotropy (Bowden, et al., 2015; Qi & Chatterjee, 2019), we excluded SNP instruments that were highly correlated ($P < 5 \times 10^{-8}$) with smoking, alcohol consumption, BMI, T2D, glucose, and hypertension (Table S1), leaving a final total of 3686 SNPs as instrumental variables for maternal educational attainment. We employed these remaining SNP instruments to conduct the similar MR analyses demonstrated above.

2.7. Statistical software and significance

The overall flow chart of our statistical analyses is illustrated in Fig. 2. In the individual-level study, the imputation of missing values of covariates was implemented with the R mice (version 4.1.1) package (van Buuren & Groothuis-Oudshoorn, 2011). In the summary-level study, the MR analyses were conducted with the R MendelianRandomization (version 0.3.0) package (Yavorska & Burgess, 2017). All other analyses were also performed under the R software computing environment. The P value was two-sided and the significance level was set to

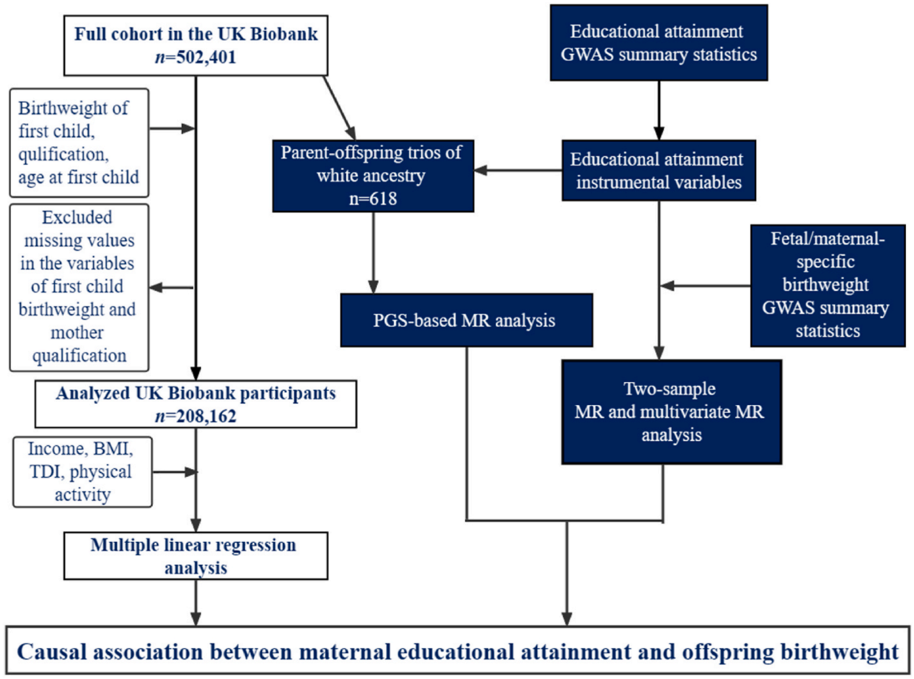

Fig. 2. Statistical flow chart to evaluate the causal association between maternal educational attainment and offspring birthweight using observational studies as well as various MR analyses.

0.05.

3. Results

3.1. Estimated effect of educational attainment on offspring birthweight

3.1.1. Estimated effect in the full UK Biobank cohort

The average (standard deviation (sd)) birthweight of first child is 3184.8 (542.6) across all analyzed UK Biobank participants; approximately 28.2% of mothers had 20-year educational attainment, whereas 19.9% of mothers did not have any qualifications. Summary information for all considered covariates is displayed in Table 1. We first analyzed maternal educational attainment as a continuous variable. With maternal age at first live birth as an adjusted covariate, we observed that maternal educational attainment was positively related to the birthweight of first child ($\widehat{\beta} = 5.8$, 95%CIs 5.3–6.3, $P = 2.76 \times 10^{-114}$). When incorporating additional covariates (e.g., BMI, TDI, income, and physical activity), we found a slight decrease in the estimated effect ($\widehat{\beta} = 4.8$, 95%CIs 4.3–5.4, $P = 2.24 \times 10^{-71}$).

We also constructed four dummy variables for maternal educational attainment. With 7 years of maternal educational attainment (i.e., no qualifications) as the reference, we discovered a significantly positive connection between various maternal qualifications and the birthweight of first child after controlling for available covariates (e.g., maternal age at first live birth), with $\widehat{\beta} = 44.8$ (95%CIs 38.0–51.6, $P = 6.15 \times 10^{-38}$), 54.9 (95%CIs 47.6–62.2, $P = 4.21 \times 10^{-128}$), and 89.4 (95%CIs 82.1–96.7, $P = 4.28 \times 10^{-34}$) for 10, 15 and 20 years of maternal educational attainment (Fig. 3A), respectively.

After adjusting for more covariates (e.g., BMI, TDI, income, and physical activity), we identified slightly reduced effects (Fig. 3B), with $\widehat{\beta} = 34.1$ (95%CIs 27.1–41.0, $P = 5.47 \times 10^{-22}$), 41.9 (95%CIs 34.4–49.3, $P = 5.14 \times 10^{-28}$), and 74.2 (95%CIs 66.5–81.9, $P = 9.71 \times 10^{-79}$) for 10, 15, and 20 years of maternal educational attainment, respectively.

Further, compared to the mothers without any qualifications (i.e., 7 years of maternal educational attainment), the birthweight of first child was higher for those with qualifications (i.e., >7 years of maternal educational attainment) ($\widehat{\beta} = 60.2$, 95%CIs 54.1–66.2, $P = 1.50 \times$

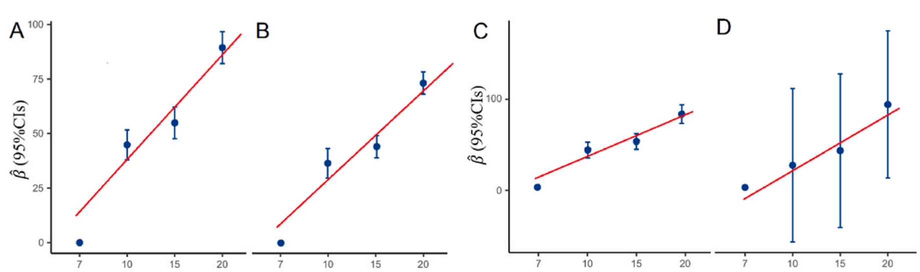

Fig. 3. Estimated effect of maternal educational attainment (with 7 years of educational attainment as the reference) on the birthweight of first child in the full UK Biobank cohort. (A) Effect of maternal educational attainment on the birthweight of first child adjusting for only maternal age at first live birth in the full UK Biobank cohort; (B) Effect of maternal educational attainment on the birthweight of first child adjusting for more adult covariates (e.g., BMI, TDI, income, and physical activity) in the full UK Biobank cohort; (C) Effect of maternal educational attainment on the birthweight of first child while adjusting for several adult covariates (e.g., BMI, TDI, income, and physical activity) in the non-advanced maternal age group; (D) Effect of maternal educational attainment on the birthweight of first child while adjusting for several adult covariates (e.g., BMI, TDI, income, and physical activity) in the advanced maternal age group. The red trend line in each panel is determined by the least squares method. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

10^{-84}).

3.1.2. Estimated effect in the two groups of maternal age at first live birth in the UK Biobank cohort

We here conducted a stratified analysis by age at first live birth with maternal educational attainment as a continuous variable. We found that maternal educational attainment was positively relevant to offspring birthweight ($\widehat{\beta} = 4.8$, 95%CIs 4.2–5.3, $P = 2.40 \times 10^{-67}$) in the non-advanced maternal age group (n = 203,145). In the advanced maternal age group ($n = 5017$), we saw an increased effect compared to that in the non-advanced maternal age group ($\widehat{\beta} = 7.0$, 95%CIs 3.2–10.8, $P = 2.89 \times 10^{-4}$). However, the effect difference between the two groups was non-significant ($P = 0.870$) in terms of an approximate normal test (Altman & Bland, 2003).

When maternal educational attainment was analyzed as a categorical variable, there existed a significantly positive effect of 10, 15, or 20 years of maternal educational attainment on the birthweight of first child among participants with non-advanced maternal age (Table 2); for instance, $\widehat{\beta} = 83.2$ (95%CIs 75.6–90.7, $P = 2.00 \times 10^{-102}$) for 20 years of maternal educational attainment (Fig. 3C). However, except for participants with 20 years of educational attainment in the advanced maternal age group ($P = 0.027$), the estimated effects for other levels of educational attainment were non-significant (Fig. 3D), which was likely a direct consequence of small sample sizes as only 5017 participants were analyzed.

Causal effects of maternal educational attainment on offspring birthweight estimated via the two-sample MR.

3.1.3. Estimated causal effect via two-sample MR

These chosen SNP instruments explained approximately 7.0% of the phenotypic variation in educational attainment. The minimum F-statistic was more than 10 (ranging from 29.71 to 635.69), implying the absence of weak instrumental bias. Through the random-effects IVW method ($P_{\text{heterogeneity}} = 8.57 \times 10^{-27}$ in terms of the Cochran's Q test), we detected a statistically significant association between maternal educational attainment and maternal-specific offspring birthweight ($\widehat{\beta} = 0.074$ for 1sd increase in maternal education years, 95%CIs 0.054–0.093, $P = 2.56 \times 10^{-13}$) (Fig. 4). Other complementary MR methods (e.g., MR-Egger, maximum likelihood method, and weighted median method) also produced very similar causal estimates (Table 3), offering supportive evidence for such a causal connection between maternal educational attainment and offspring birthweight. Furthermore, the intercept of MR-Egger regression did not significantly deviate from zero (intercept = 5.39×10^{-5} and $P = 0.850$), indicating the minimal impact of horizontal pleiotropy.

3.1.4. Estimated causal effect via multivariable MR

With parental summary statistics of educational attainment estimated from the UK Biobank cohort and summary statistics of maternal-specific birthweight, we performed MVMR to control for the confounding impact of paternal educational attainment. It was shown that maternal educational attainment remained positively associated with offspring birthweight ($\widehat{\beta} = 0.037$, 95%CIs 0.013–0.061, $P = 2.26 \times 10^{-3}$).

Causal effects of maternal educational attainment on offspring birthweight estimated via the PGS-based MR.

We leveraged parent-offspring trios from the UK Biobank cohort to simultaneously adjust for the confounding effects of fetal-specific birthweight and paternal educational attainment. We identified a positive but insignificant effect of maternal educational attainment on offspring birthweight ($\widehat{\beta} = 24.0$, 95%CIs −150.1–198.1, $P = 0.787$).

The non-significant association discovered above was possibly due to limited sample sizes in parent-offspring trios. We conducted simulations to validate this conjecture (Supplementary Note), and found that there was only a power of 5.8% under the setting of current effect estimate and sample size. We would need approximately 65,000 parent-offspring trios to achieve an expected power of 80.0% if the causal effect was set to 24 (Fig. S2), and we had an expected power of 15.3% when $\beta = 80$ and 618 trios.

Table 2
Subgroup analysis of the maternal age at first live birth that was categorized into advanced age (>35 years) and non-advanced age (≤35 years).

Educational attainment (years)	maternal age at first live birth (≤35) (n = 203,145)		maternal age at first live birth (>35) (n = 5017)	
	β (95%CIs)	P	β (95%CIs)	P
10	37.6 (30.7–44.6)	1.48×10^{-26}	24.3 (−59.8–108.4)	0.571
15	46.9 (39.4–54.3)	7.02×10^{-35}	40.3 (−43.9–124.5)	0.348
20	83.2 (75.6–90.7)	2.00×10^{-102}	91.0 (10.4–171.5)	0.027

Note: These estimate results were obtained with 7 years of maternal educational attainment as the reference.

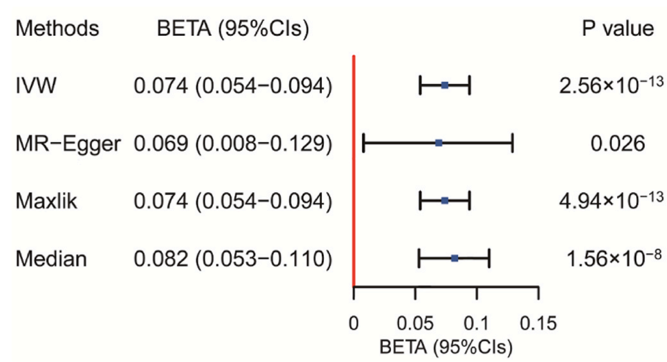

Fig. 4. Forest plot showing estimated causal effects of maternal educational attainment on offspring birthweight using various two-sample MR methods.

Table 3
Causal effect estimates of maternal educational attainment on offspring birthweight using various two-sample MR methods.

Methods	Estimated causal effect	SE	P
IVW	0.074	0.010	2.56×10^{-13}
MR Egger	0.069	0.031	0.026
Maxlik	0.074	0.010	4.94×10^{-13}
Median	0.082	0.014	1.56×10^{-8}

Note: SNP: single-nucleotide polymorphism; SE: standard error. IVW: random-effects IVW method; MR Egger: MR-Egger regression; Maxlik: maximum likelihood method; Median: weighted median method.

4. Results of sensitivity analysis for horizontal pleiotropy

Finally, after the removal of SNP instruments with potential horizontal pleiotropy, we employed the remaining genetic instrumental variables to investigate the causal relationship between maternal educational attainment and maternal-specific birthweight. We still observed significantly positive associations between maternal educational attainment and offspring birthweight in terms of various two-sample MR methods (Table S2). For example, we discovered a significant association between maternal educational attainment and maternal-specific birthweight ($\widehat{\beta} = 0.069$, 95%CIs 0.048–0.089, $P = 4.83 \times 10^{-11}$) according to the random-effects IVW MR method. The results of other complementary MR approaches were given in the Supplementary Note.

In the PGS-based MR analyses for parent-offspring trio data in the UK Biobank cohort, we also observed a positive association between maternal educational attainment and offspring birthweight, although the effect was not statistically significant again largely due to limited power (Supplementary Note). Finally, we highlighted that our MR analyses were conducted under the guidelines of STROBE-MR (Skrivankova, et al., 2021), with the checklist provided in Table S3.

5. Discussion

5.1. Summary of our results

In the present study, we have revealed a significant association between maternal educational attainment and the birthweight of offspring. Such an association was consistently observed in both individual-level observational studies and summary-level causal inference analyses. Specifically, in the individual-level analyses, we found that the birthweight of first child for mothers with a higher educational attainment trended to be heavier. In the summary-level analyses, we discovered that maternal educational attainment had a causal influence on offspring birthweight in terms of distinct two-sample MR studies. We further conducted a PGS-based MR analysis in parent-offspring trios and also observed a positive causal association between maternal educational attainment and offspring birthweight although this relation was insignificant due to limited power. Overall, our study implied that higher maternal educational attainment was an independent protective factor against low birthweight.

Indeed, it has shown that mothers with higher educational attainment generally have better resources and more health investments for prenatal care, nutrition, prenatal consultations, and living/working conditions, all of which could potentially affect birthweight (Noghani-behambari, et al., 2022; Silvestrin, Hirakata, da Silva, & Goldani, 2020). In addition, maternal education can also directly and indirectly affect offspring outcomes including birthweight through choosing more promising partner, suitable timing of fertility and number of offspring, improving marriage prospects, and stopping unhealthy behaviors (e.g., smoking and drinking) before and during pregnancy (Guarnizo-Herreño, et al., 2021), which ultimately reduce the possibility of low birthweight.

5.2. Comparison to previous studies

As mentioned before, exploring the causal relation between maternal educational attainment and the birthweight of offspring is exceptionally challenging. Several prior studies were based on traditional epidemiological designs (Godah, et al., 2021; Guarnizo-Herreño, et al., 2021; Shapiro et al., 2017); however, they are vulnerable to confounding factors such as social and environmental influences, selective mating, as well as fetal genotypes, all of which are difficult to adjust for through a conventional manner.

In contrast, our study employed MR methods to examine the causal association between maternal education and offspring birthweight; methodologically, MR approaches are robust against confounders and thus can provide a more credible assessment of causality (Angrist, et al., 1996; Brion et al., 2013; Davey Smith & Hemani, 2014; Evans et al., 2019; Greenland, 2000; Moen et al., 2019; Sheehan et al., 2008; Warrington et al., 2018; Yu, Yuan, et al., 2020; Zeng et al., 2019; Zeng & Zhou, 2019a, 2019b). Compared to existing studies, one of our greatest advantages is that we can explain the confounding effects of fetal-specific birthweight and paternal educational attainment by leveraging novel MR methods in two-sample analyses and parent-offspring trios.

A recent two-sample MR study also explored the causal influence of maternal educational attainment on offspring birthweight and indicated the existence of causal association (Liu, et al., 2022); however, this work did not sufficiently take into account the effect of fetal genome. Since birthweight is affected by both maternal and fetal genotypes, previous MR studies have demonstrated that resolving the genetic effect of birthweight into fetal-specific and maternal-specific components holds the key when elucidating the association between maternal exposures and offspring birthweight (Brito Nunes, et al., 2023; Decina et al., 2023; Hwang et al., 2019; Jin et al., 2023; Moen et al., 2020; Yu, Yuan, et al., 2020). Note that, our objective is to examine whether maternal educational attainment would exert an immediate causal influence on offspring birthweight, which requires the utilization of maternal-specific birthweight when implementing MR analyses.

5.3. Limitations of our work

There are some limitations of this study. First, there may be an inaccurate classification of qualifications and years of education. Specifically, even though there is a clear classification (based on ISCED category definitions), it has been found that NVQ or HNC or equivalent qualifications coded as having 19 years of education would exaggerate their average years of education in the UK Biobank (Hill, et al., 2018; Lee et al., 2018; Okbay et al., 2022). We are not sure whether this will be the case for other classifications.

Second, previous research has demonstrated a positive correlation between education level and physical activity (Donnelly, et al., 2016), indicating that individuals with higher levels of education would also engage in high levels of physical activity. It is worth noting that high levels of physical activity are typically associated with a normal BMI (Koolhaas, et al., 2017), and maternal BMI has been shown to have a positive impact on fetal development and birthweight (Goldstein, et al., 2017). However, because of data unavailability from the UK Biobank cohort, we did not have those important covariates (e.g., maternal BMI and physical activity) at the time of the maternal first birth. Additionally, in the maternal age stratification analysis, we found that mothers with 20 years of education in the advanced maternal age group had a significant effect on the birthweight of the first child ($P = 0.027$). The possible reason for this finding is that mothers with higher educational attainment may have a higher level of psychological maturity (Suzuki, et al., 2015), which may enable them to provide a better emotional environment during pregnancy. In this case, the educational attainment may be only an indirect indicator, while psychological maturity is likely a more important factor. Therefore, our study cannot completely eliminate the effect of potential confounders, which possibly biased the true relation between maternal educational attainment and offspring birthweight in the individual-level analyses.

Third, 2qin our PGS-based MR analysis, we had very limited power due to the scarcity of parent-offspring trios; thus, it is necessary to validate our findings further with larger sample sizes of parent-offspring trios.

5.4. Public health implications of our findings

Low birthweight is a significant public health issue in both developing and developed countries, and is the primary risk factor for early neonatal mortality and morbidity (Assefa, Berhane, & Worku, 2012; Dai et al., 2022; de Chrisman et al., 2016; Khera et al., 2016; Rezen). Regions with the highest prevalence of low birthweight, such as sub-Saharan Africa and southern Asia, contribute to almost three-quarters of global live births with low birthweight (Blencowe, et al., 2019). One factor contributing to this phenomenon is the potential insufficient maternal educational attainment (Mahumud, Sultana, & Sarker, 2017). Previous studies have shown that lower levels of educational attainment among both mothers and fathers are significant risk factors for infant mortality, regardless of wealth or income status, or the sex of the child (Balaj, et al., 2021). Therefore, our findings suggest that increasing maternal educational attainment can improve economic conditions, health knowledge and awareness, hygiene practices and living environments, as well as social status and autonomy, thus contributing to lowering the risk of low birthweight as well as improving health and long-term outcomes of offspring.

Indeed, increasing the access to quality education not only has substantial returns for current generations and next generations, but also is beneficial for previous generations (e.g., more longevity) (Lu, et al., 2023); it is also one of the most cost-effective ways to alleviate socio-economic and health inequalities around the world especially in low and middle-income countries (Godah, et al., 2021; Graetz et al., 2020; Guarnizo-Herreño, et al., 2021; Ye et al., 2023).

6. Conclusion

This study provides supportive evidence for a significantly causal association of maternal educational attainment on offspring birthweight via both observational studies and various Mendelian randomization analyses. The findings reveal that higher maternal educational attainment is an independent protective factor against low birthweight and possess the potential to encourage improving educational attainment among non-pregnant female adults.

Ethics approval

The UK Biobank had approval from the North West Multi-Centre Research Ethics Committee (MREC) as a Research Tissue Bank (RTB) approval. All participants provided written informed consent before enrolment in the study, which was conducted in accordance with the Declaration of Helsinki. This approval means that other researchers do not require separate ethical clearance and can operate under the RTB approval.

7. Consent for publication

Not applicable.

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CRediT authorship contribution statement

Yiyang Zhu: Data curation, Formal analysis, Writing – original draft. **Hao Zhang:** Data curation. **Jike Qi:** Methodology. **Yuxin Liu:** Data curation. **Yu Yan:** Methodology. **Ting Wang:** Supervision, Funding acquisition. **Ping Zeng:** Data curation, Funding acquisition, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no competing interests.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ssmph.2023.101587.

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