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Association between age at first birth and postpartum depression: A two-sample mendelian randomization analysis

Zhaoxing Ou [a,1], Ziqing Gao [a,1], Qi Wang [a], Yuhong Lin [a,**], Dalin Ye [a,*]

[a] Department of ultrasound, The Fifth Affiliated Hospital of Sun Yat-sen University, Zhuhai, China

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ABSTRACT

Background: Previous observational research has documented an association between age at first childbirth (AFB) and postpartum depression (PPD). However, the causal relationship remains unclear. This study aimed to assess the causal effects of AFB on PPD using a two-sample Mendelian randomization (MR) analysis.

Methods: Three sets of instrumental variables were obtained from the United Kingdom Biobank (UK Biobank), Neale Lab consortium and a meta-analysis of genome-wide association studies (GWAS). Single-nucleotide polymorphisms (SNPs) associated with the PPD phenotype were obtained from the Finngen consortium, which included 13,657 cases and 236,178 controls. Inverse variance weighted (IVW), weighted median, weighted mode, and MR-Egger methods to evaluate causal effects. Heterogeneity was assessed using Cochran's Q test and funnel plots. Horizontal pleiotropy and sensitivity were assessed using the MR-Egger intercept test and "leave-one-out" analysis, respectively. Further meta-analysis was performed to validate the robustness of this relationship. Additionally, the potential mediating effects of risk factors associated with PPD were analyzed.

Results: Strong causal effects between AFB and PPD was found in both IVW and weighted median methods, which was further supported by meta-analysis (IVW, odds ratio [OR] 0.59 [95% confidence interval (CI) 0.36–0.96, p = 0.03]; weighted median, OR 0.59 [95% CI 0.37–0.95, p = 0.03]). The power of the MR supports the robustness of the findings. Heterogeneity or horizontal pleiotropy was not observed. Major depressive disorders, family income levels, and marital stress were identified as potential mediating factors in the causal relationships.

Conclusion: Results of MR analysis supported the causal effect of increased AFB in reducing the risk for PPD.

1. Introduction

Postpartum depression (PPD) is a common complication of childbirth and a curable mental disorder that occurs after delivery [1]. In developed countries, the prevalence of PPD ranges from 5% to 30%, while in low- and middle-income countries, it ranges from 6.5% to 12.9%, although sometimes even higher [2]. PDD increases the risk for impaired emotional, social, and cognitive development in

* Corresponding author. The Fifth Affiliated Hospital of Sun Yat-sen University, No. 52, Meihua East Road, Zhuhai 519000, China.
** Corresponding author. The Fifth Affiliated Hospital of Sun Yat-sen University, No. 52, Meihua East Road, Zhuhai 519000, China.
E-mail addresses: linyh97@mail.sysu.edu.cn (Y. Lin), dalinye2019@163.com (D. Ye).
[1] Zhaoxing Ou and Ziqing Gao contributed equally to this work and share first authorship.

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infants; in extremely rare cases, it can also increase the risk for infanticide or suicide among mothers [3].

Postponement of childbearing has become a social trend. According to the World Health Organization, the age at first birth (AFB) among women is now >25 years globally, and has even reached 30 years in many countries [4]. Interestingly, some studies have reported a potential correlation between AFB and PDD [5–7]. In an observational study, Mirowsky et al. found a stable negative correlation between AFB and PPD [5]. AFB may be a crucial influential factor associated with the risk for PDD [5], and the stability of marital status, family income, and mental health condition may be potential factors contributing to this association [5,8]. In addition, some studies have linked AFB to an increased risk for cardiovascular and gynecological diseases among women and schizophrenia in offspring [9–12]. Conversely, recent studies have suggested a curvilinear relationship between maternal age and depression [6,7]. Understanding the correlation between AFB and PPD may assist physicians and healthcare professionals in implementing appropriate preventive and intervention measures, including aiding fertility decision-making, enhancing psychological health education, and emphasizing individualized care based on AFB. However, due to the impact of confounding factors, the association between AFB and PPD has not yet been systematically studied. Moreover, a causal relationship between AFB and PPD remains unclear.

Mendelian randomization (MR) is a powerful methodology that uses genetic variation as an instrumental variable to establish causal relationships between risk factors and diseases. This helps overcome the inherent biases present in observational studies, providing robust and representative results [13]. Two-sample MR analysis uses summary statistics from genome-wide association studies (GWAS), enabling researchers to conduct MR studies without directly analyzing individual-level data. This approach enhances the efficiency and facilitates large-scale investigations.

The present study aimed to explore the causal relationship between AFB and PPD using a two-sample MR analysis.

2. Method

2.1. Research hypothesis

A two-sample MR analysis was performed using publicly available GWAS datasets. The data used in this study are publicly available; as such, separate ethical approval was not required for this study. A flow-diagram illustrating workflow of this study is presented in Fig. 1. Additionally, the GWAS data used in this study fulfilled three assumptions: the instrumental variable was strongly correlated with the exposure (linkage disequilibrium [LD] $r^2 < 0.001$, F-statistics >10, $P < 5 \times 10^{-8}$); the instrumental variable was unrelated to the outcome (P for outcome $\geq 5 \times 10^{-8}$); and the instrumental variable was not correlated with any confounding factors.

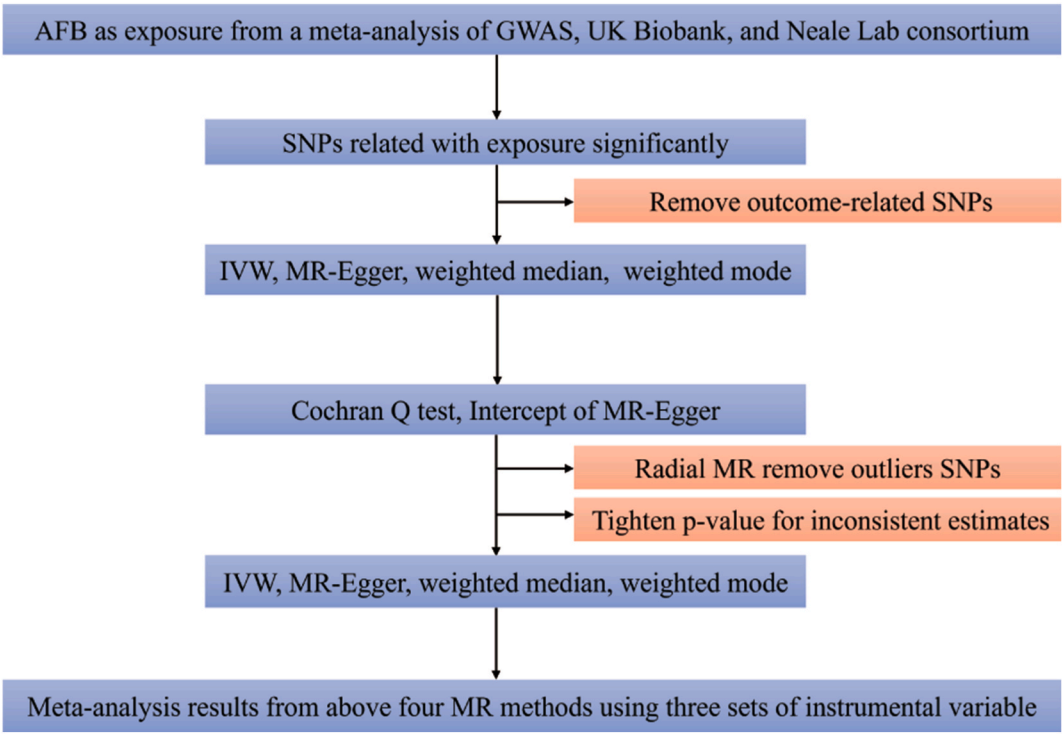

Fig. 1. The study workflow of two-sample MR analysis
MR, Mendelian randomization; **GWAS**, genome-wide association studies; **AFB**, age at first childbirth; **IVW**, inverse variance weighted; **SNPs**, single-nucleotide polymorphisms.

2.2. GWAS data for AFB

A set of genetic instruments was obtained from a recent meta-analysis of 36 cohorts [14]. The GWAS data included individuals of European ancestry, with a sample size of 418,758 females who had given birth, and 371 genetic variants associated with externalizing behavior were identified after strict quality control. AFB was measured continuously in individuals who had previously given birth [14]. Detailed information regarding quality control filters is available in the original publication [14].

GWAS data were screened using several criteria. First, single-nucleotide polymorphisms (SNPs) significantly associated with AFB were identified. Second, palindromic SNPs were excluded through harmonization with GWAS data related to PPD. Third, SNPs that were strongly correlated with the PPD were removed. Fourth, PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk) was used to remove SNPs related to confounding factors, such as major depressive disorder, low family income, marital stress, social anxiety, or phobia. Finally, SNPs with F-statistics <10 were excluded. The F-statistic was a measure used to assess the statistical strength of the SNPs in the MR studies, and was calculated using equation $F=(R^2 \times (N\text{-}1\text{-}K))/((1\text{-}R^2) \times K)$, in where R^2 represents the proportion of exposure variance explained by genetic variation, N represents sample size, and K represents the number of SNPs considered in the analysis. The F-statistic helps to assess instrument validity and provides insights into the reliability of the instrumental variable in estimating causal effects.

To ensure robustness of the results, two sets of genetic instrumental variables related to AFB were selected from the UK Biobank (sample size: 170,498) and Neale Lab (sample size: 123,846) databases based on the same criteria.

2.3. GWAS data for PPD

PPD-related GWAS data used in this study were obtained from the Finngen public database (F8). This study included 13,657 patients with PPD and 236,178 control cases of European ancestry. PPD is defined as depression occurring within a short period after delivery (within 4 weeks, or at 3, 6, or 12 months) [8,15].

2.4. GWAS data for risk factors related to PPD

To investigate the potential mediating effects of risk factors on the relationship between AFB and PPD, a two-sample MR analysis was performed with AFB as the exposure factor and the risk factors as the outcome. Potential risk factors include major depressive disorder, family income level, marital stress, social anxiety, and phobia. GWAS data for these phenotypes were obtained from the Psychiatric Genomic Consortium (PGC), UK Biobank, and Neale Lab consortium. Detailed information regarding the GWAS datasets used in this study is summarized in Table 1.

2.5. Statistical analysis

The causal effects of AFB on PPD were evaluated using four MR methods: inverse variance-weighted (IVW), weighted median, weighted mode, and MR-Egger. These methodologies, which make distinct assumptions based on varying levels of horizontal pleiotropy, have facilitated comprehensive evaluation of the causal relationship between AFB and PPD. IVW assumes no horizontal pleiotropy among the SNPs and provides a summary causal estimate by combining the Wald ratios for each SNP. However, MR-Egger and weighted median consider the presence of horizontal pleiotropy and can provide more reliable estimates in broader situations but with wider confidence intervals. The weighted mode exhibits less bias than the MR-Egger but may cause overfitting. IVW was applied as the main outcome measure, other methods were used for supplementary analysis. If there was inconsistency in estimates across these methods in the present study, a stricter instrument p-value threshold was set.

Outliers were removed using radial MR, after which IVW, weighted median, weighted mode, and MR-Egger methods were re-evaluated. Meta-analysis was performed for the results obtained from different exposure sources using four MR methods. The power of MR estimation was calculated using an online source (https://shiny.cnsgenomics.com/mRnd/).

Cochran's Q test and funnel plots were used to detect heterogeneity. Heterogeneity was considered present if the p-value from Cochran's Q test was <0.05. Funnel plots were used to visually assess potential heterogeneity. The MR-Egger intercept test and "leave-

Table 1
Data source of the GWAS included in the two-sample MR analysis.

Consortium	Traits	Sample size	Ancestry	Web source
A meta-analysis of 36 cohorts	AFB	542,901	European	https://www.nature.com/articles/s41562-021-01135-3
UK Biobank	AFB	170,498	European	https://gwas.mrcieu.ac.uk/datasets/ukb-b-12405/
Neale Lab	AFB	123,846	European	http://www.nealelab.is/uk-biobank
Finngen	PPD	249,835	European	https://r8.finngen.fi/pheno/O15_POSTPART_DEPR
PGC	Major depression	500,199	European	https://www.nature.com/articles/s41593-018-0326-7
UK Biobank	Household income	397,751	European	https://gwas.mrcieu.ac.uk/datasets/ukb-b-7408/
UK Biobank	Marital stress	459,742	European	https://gwas.mrcieu.ac.uk/datasets/ukb-b-14624/
Neale Lab	Social anxiety or social phobia	117,716	European	http://www.nealelab.is/uk-biobank

GWAS, genome-wide association studies; **MR**, mendelian randomization; **AFB**, age at first childbirth; **PPD**, postpartum depression; **UK Biobank**, United Kingdom Biobank; **PGC**, Psychiatric Genomic Consortium.

one-out" (LOO) analysis were utilized to assess horizontal pleiotropy and stability of the results. Horizontal pleiotropy was considered present if the p-value from the MR-Egger intercept test was <0.05. LOO analysis involved sequentially removing exposure-related SNPs in the IVW analysis to determine whether any SNPs influenced causal estimation.

Statistical analysis was performed using R-Studio version 4.2.1. The MR analysis was performed using the "TwoSampleMR version 0.5.6" and "Radial MR" packages.

3. Results

3.1. MR analysis and sensitivity

MR results for the various datasets related to AFB are summarized in Table 2. Supplemental tables 1–3 list the details of SNPs in the three sets of instrumental variables. Using 55 SNPs from GWAS datasets, a statistically significant potential negative correlation was found between AFB and PPD (odds ratio [OR] 0.85 [95% confidence interval (CI) 0.80–0.91]; $p = 1.61 \times 10^{-6}$). Additionally, the weighted median method produced similar results (OR 0.84 [95% CI 0.77–0.93]; $p = 3.93 \times 10^{-4}$). MR-Egger and weighted mode indicated a causal relationship between AFB and PPD, but this association was not statistically significant (OR 0.77 [95% CI 0.55–1.07], p = 0.13; OR 0.86 [95% CI 0.69–1.07], p = 0.19, respectively). Consistent findings were observed using a set of 19 SNPs from the Neale Lab consortium and 29 SNPs from the UK Biobank as instrumental variables (OR 0.49 [95% CI 0.32–0.74], $p = 9.14 \times 10^{-4}$; OR 0.42 [95% CI 0.31–0.56], $p = 4.41 \times 10^{-9}$, respectively). The power values for the MR results suggested that the results were highly reliable (power value, 0.82 for SNPs from Neale Lab; power value, 0.99 for SNPs from UK Biobank).

Sensitivity assessment of the MR results is summarized in Table 2. All p-values for Cochran's Q test and MR-Egger intercept tests were >0.05, indicating no heterogeneity or horizontal pleiotropy. Similarly, the funnel plots were symmetrical, indicating no heterogeneity (Supplemental figs. 1–3). Furthermore, LOO analysis revealed no SNPs driving the results, indicating the high stability of the results (Supplemental figs. 4–6).

3.2. Meta analysis

Further meta-analysis was performed on the results of the four MR methods (Fig. 2A–D). Meta-analysis of IVW (Fig. 2A) revealed a negative correlation between AFB and PPD (OR 0.59 [95% CI 0.36–0.96]; p = 0.03). The meta-analysis using the weighted median method (Fig. 2C) supported this relationship (OR 0.59 [95% CI 0.37–0.95]; p = 0.03). Although the meta-analysis of MR-Egger (Fig. 2B) and weighted mode (Fig. 2D) suggested a potential causal relationship between AFB and PPD (OR 0.39 [95% CI 0.12–1.25], p = 0.11; OR 0.86 [95% CI 0.69–1.07], p = 0.19), it was not statistically significant.

3.3. Risk factor analysis

Table 3 presents the results of the MR method used to investigate the potential mediation between AFB and increased risk for PPD. Risk factor analysis revealed that depression, low family income, and marital status may mediate the causal relationship between AFB and PPD. Sensitivity analysis of these risk factors revealed no heterogeneity or horizontal pleiotropy.

Table 2
Results of the two-sample MR analysis.

	A meta-analysis of 36 cohorts	Neale Lab	UK Biobank
SNPs	55	18	27
IVW			
OR 95%CI	0.85 (0.79, 0.90)	0.51 (0.36, 0.73)	0.44 (0.34, 0.57)
p-value	1.61×10^{-6}	1.52×10^{-4}	4.21×10^{-9}
Weighted median			
OR 95%CI	0.84 (0.77, 0.93)	0.51 (0.33, 0.78)	0.44 (0.30, 0.63)
p-value	3.93×10^{-4}	1.91×10^{-3}	1.60×10^{-6}
MR-Egger			
OR 95%CI	0.77 (0.55, 1.07)	0.30 (0.04, 2.22)	0.15 (0.04, 0.60)
p-value	0.13	0.26	1.41×10^{-2}
Weighted mode			
OR (95%CI)	0.86 (0.69, 1.07)	0.51 (0.23, 1.14)	0.30 (0.13, 0.67)
p-value	0.19	0.12	7.78×10^{-3}
Pleiotropy			
MR-Egger intercept	7.53×10^{-3}	0.01	0.03
p-value	0.54	0.6	0.13
Heterogeneity			
Q value	41.18	17.38	23.76
p-value	0.55	0.18	0.42
Power	0.34	0.82	0.99

MR, mendelian randomization; **UK Biobank**, United Kingdom Biobank; **SNPs**, single-nucleotide polymorphisms; **IVW,** inverse variance weighted.

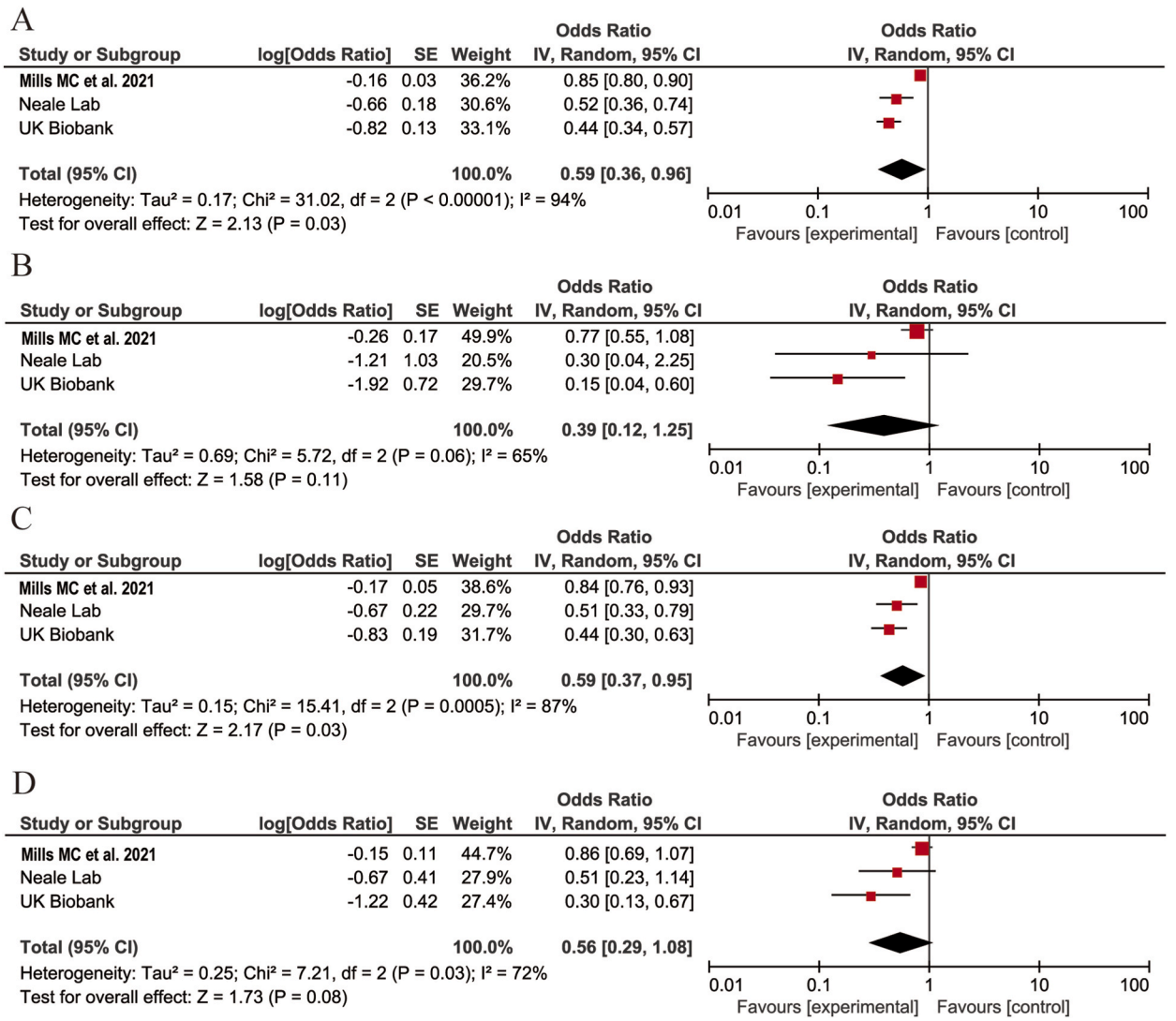

Fig. 2. Meta-analysis of the causal association between AFB and PPD. (A) Meta-analysis of IVW revealed a causal relationship between AFB and PPD. (B) Meta-analysis of MR-Egger showed a lack of statistically significant causal relationship between AFB and PPD. (C) Meta-analysis of weighted median supported a causal relationship between AFB and PPD. (D) Meta-analysis for weighted mode suggested a lack of statistically significant causal relationship between AFB and PPD.
AFB, age at first childbirth; **PPD**, postpartum depression; **IVW**, inverse variance weighted.

Table 3
Risk factor analysis.

Outcome	IVW		Heterogeneity		Pleiotropy	
	Causal effect (95% CI)	p-value	Q value	p-value	MR-Egger intercept	p-value
Major depression	0.87 (0.85–0.90)	2.46×10^{-27}	39.98	0.34	2.30×10^{-3}	0.58
Household income	1.11 (1.10–1.13)	7.05×10^{-40}	58.20	0.06	1.63×10^{-3}	0.52
Divorced or widowed	0.995 (0.994–0.997)	4.87×10^{-7}	55.31	0.31	1.08×10^{-4}	0.72
Social anxiety or phobia	0.999 (0.997–1.001)	0.95	61.49	0.26	-1.30×10^{-4}	0.68

IVW, inverse variance weighted.

4. Discussion

PPD is the most common complication of childbirth and can have negative effects on maternal health, with suicide accounting for 20% of postpartum deaths [1,16,17]. In addition, maternal depression can have adverse effects on infant behavior, emotional and

cognitive development. The relationship between AFB and PPD remains controversial, although research has reported correlations between AFB and endometrial and pancreatic cancers and cardiovascular disease [9,10,18,19]. In this study, we used three sets of SNPs from different datasets as genetic instruments to perform MR analysis of the potential causal relationship between AFB and PPD. To ensure the robustness of the results, we performed a meta-analysis as an additional analysis of the results of the different MR methods. Additionally, we conducted a preliminary analysis of potential risk factors mediating the causal relationship between AFB and PPD. Our results not only provide more hope for the prevention of PPD but also offer more possible clues for further exploration of the mechanism of PPD.

We found that AFB exhibited a negative linear correlation with PPD. An observational study reported that AFB was negatively correlated with depressive symptoms after adjusting for confounding factors [5]. Conversely, Carlson et al. found a non-linear relationship between AFB and PPD in women, with AFB being negatively related to depression risk in women <31 years of age and positively related to depression risk in those >32 years of age [6]. Ni et al. found a negative correlation between AFB and the risk for schizophrenia in women <26 years of age, although this relationship was reversed in those >26 years of age [7]. In addition, Tabet et al. found that low-income adolescent girls were more likely to experience mental disorders [20]. However, these studies did not strictly classify the PPD. PPD is classified as a subtype of severe depressive disorder and defined as the onset of depressive symptoms within 4 weeks–12 months after delivery [8,15]. Furthermore, these studies could not exclude the impact of confounding factors on the results. MR analysis establishes a causal relationship between exposure and outcome by using genetic variants as instrumental variables, which can overcome the inherent bias in observational studies and has a high degree of reliability and representativeness [13]. Recently, MR analysis revealed a potential causal relationship between AFB and cardiovascular disease, with increased AFB associated with a lower risk for cardiovascular disease [9,10]. Based on the MR analysis, we found that increased AFB may be associated with a reduced risk for PPD and obtained robust and sensitive results. Our results have strong statistical power, supporting the robustness of our findings. In addition, we enhanced the reliability of the results by performing a meta-analysis that integrated the outcomes of the different MR methods. Our results confirmed the negative linear correlation reported in previous observational studies [5,7], which demonstrated a higher level of reliability and effectiveness.

Further risk factor analysis revealed that major depressive disorders, family income levels, and marital stress may mediate the causal relationship between AFB and PPD. Untreated antenatal depression or anxiety, lack of financial support, marital stress, and domestic violence are important risk factors for PPD [16,21]. Genetic factors have also been documented to be linked with PPD [22]. Evidence from twin and family studies has supported a role for that genetics factors in PPD [23,24]. Specific candidate genes and potential pathways associated with PPD have been identified through GWAS, highlighting the involvement of estrogen signaling and the hypothalamic-pituitary-adrenal axis [25,26]. Genes commonly associated with major depressive disorders, including serotonin transporter protein, tryptophan hydroxylase 2, brain-derived neurotrophic factor, monoamine oxidase, and catechol-*O*-methyltransferase, have been the primary focus of candidate gene studies. In addition, a GWAS involving over >1200 women identified genetic variations in chromosomes 1q21.3–q32.1, and 9p24.3–p22.3, as well as multiple estrogen binding sites containing hemicentin-1 [25]. However, these genetic factors have not been reproduced in subsequent studies, potentially owing to the heterogeneity among patient populations. Our results imply that psychological conditions and social environmental factors may contribute to the causal relationship between AFB and PPD, which helps to reveal the role of AFB in the pathogenesis of PPD. Younger mothers would confront significant changes in educational, familial, and professional roles, which impose a considerable strain on mental well-being. Mental stress may also increase the risk for developing PPD. Insufficient social support from family and friends may exacerbate PPD in younger mothers.

In addition, hormones may contribute to the underlying mechanisms of the relationship between AFB and PPD [16,17,27,28]. Studies have indicated that a decline in allopregnanolone levels following delivery may be associated with the onset of PPD [29,30]. A rapid decline in allopregnanolone levels can potentially trigger PPD by affecting gamma-aminobutyric acid receptor activity [28]. Younger mothers may experience a more pronounced reduction in allopregnanolone, thereby, increasing the risk for PPD. However, it is important to note that the exact mechanisms of PPD remains incompletely understood. Further studies are required to elucidate the mechanisms of the relationship between AFB and PPD.

The present study had some major limitations. First, it is important to note that the current study was conducted exclusively on individuals of European descent. As such, further research is required to investigate the causal relationship between AFB and PPD in other ethnic groups. Second, we did not obtain personalized data for the MR analysis, which may have led to biased interpretations of the nonlinear relationships observed in observational studies. Single genetic variations may not fully reflect the complexity of specific biological indicators. However, our findings are robust and reliable because they were obtained through a meta-analysis of MR results from three GWAS datasets.

5. Conclusion

The causal relationship between AFB and PPD was confirmed using MR analysis. Moreover, major depressive disorders, family income levels, and marital stress were identified as potential factors mediating this association. Therefore, AFB may be an important risk factor that may provide more clues for PPD prevention and treatment.

Ethics statement

The data of this study were obtained from public databases, having obtained informed consent from all participating studies in accordance with the protocols approved by their institute's ethics committee. No separate ethical approval is required for this study.

Data availability statement

The datasets analyzed during the current study are available in the FinnGen (https://r8.finngen.fi/), Neale Lab (http://www.nealelab.is/uk-biobank) and the UK Biobank repository (https://gwas.mrcieu.ac.uk/datasets/).

CRediT authorship contribution statement

Zhaoxing Ou: Investigation, Writing – original draft. **Ziqing Gao:** Data curation, Software, Writing – review & editing. **Qi Wang:** Software, Writing – review & editing. **Yuhong Lin:** Supervision, Writing – review & editing. **Dalin Ye:** Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20500.

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