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Original Research

Association Between Household Income-Related Education and Postpartum Depression: A Two-Step Mendelian Randomization Study

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Abstract

Background: Previous research has demonstrated the associations between educational attainment, economic status, and postpartum depression (PPD). However, the associations between educational attainment, household income, and PPD based on Mendelian randomization (MR) have yet to be fully elucidated. Moreover, whether household income serves as a mediator in the association between education and PPD remains unclear. **Methods**: Using single-nucleotide polymorphisms (SNPs) extracted from genome-wide association studies (GWAS) as instrumental variables (IVs), we assessed the associations between education, household income, and PPD using MR analysis methods, such as inverse-variance weighting (IVW). The mediating effect was evaluated by examining (1) the association between education and household income and (2) the role of household income in the education—PPD relationship. Sensitivity analyses, including MR-Egger intercept analysis, leave-one-out analysis, Cochran's Q test, and MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO), were performed to assess robustness. **Results**: The MR analysis indicated that higher education (odds ratio (OR) = 0.877, 95% confidence interval (CI): 0.828–0.930; p = 1.050 $\times$ 10^{-5}) and greater household income (OR = 0.443, 95% CI: 0.204–0.962; p = 0.040) were both associated with a reduced risk of PPD. Furthermore, we identified a significant association between education and household income (OR = 1.095, 95% CI: 1.085–1.105; p = 2.805 $\times$ 10^{-87}). The mediation analysis demonstrated that household income partially mediated the relationship between education and PPD, with an indirect effect of –0.074 (95% CI: –0.146 to –0.004), accounting for 56.67% of the total effect. **Conclusions**: These findings suggest that household income significantly mediates the association between education and PPD. Moreover, higher education and increased household income can serve as important protective factors against PPD, underscoring the necessity for socioeconomic interventions aimed at reducing the risk of PPD.

Keywords: association; genetic evidence; education; household income; postpartum depression

1. Introduction

Postpartum depression (PPD), classified as a depressive disorder with peripartum onset, is a psychiatric condition affecting women after childbirth that is typically identified through standardized screening scales [1]. Most cases manifest within six weeks postpartum, and although the majority of patients experience spontaneous remission, approximately 20% may develop persistent symptoms lasting years [2]. The incidence of PPD is influenced by multiple socioeconomic and cultural factors, resulting in significant cross-national prevalence variations ranging from 0.5% to 60.0% [3]. In China, reported prevalence rates range from 6.7% to 56.7% [4]. PPD typically presents with core symptoms including depressed mood, profound sadness, persistent fatigue, anxiety, and appetite loss, frequently accompanied by diminished mother-infant bonding. In severe cases, suicidal ideation or infanticidal tendencies may occur. Substantial evidence confirms that PPD contributes to delayed cognitive and behavioral development in infants, compromising offspring development while imposing significant burdens on families and society [5–7]. Therefore, early identification of risk factors combined with timely psychological interventions and pharmacological management is essential for enhancing maternal quality of life, promoting neonatal development, and maintaining familial and societal well-being [8,9].

PPD is a complex multifactorial disorder with an unclear etiology. Cumulative evidence from numerous studies has identified key correlates of PPD, including a history of psychiatric disorders, antenatal depressive symptoms [10], neonatal or obstetric complications [11], and inadequate social support [12]. A study has shown that income is associated with the incidence of PPD [13]. Additionally, research indicates that lower household income is linked to heightened financial strain following childbirth, thereby increasing the risk of depression [14]. In turn, education has been recognized as a critical determinant of household income. However, the interplay among these three factors—education, household income, and PPD—lacks robust empirical validation.

To further investigate and clarify the association between educational attainment and PPD, as well as the mediating role of household income in this association, we employed Mendelian randomization (MR) analysis based on genome-wide association study (GWAS) data. This approach enables the assessment of potential associations between specific phenotypic traits and disease outcomes. By minimizing confounding biases and reverse association, while also offering significant efficiency in terms of time and cost, MR has proven to be clinically valuable. Consequently, it has emerged as a widely adopted tool in research on disease mechanisms and clinical decision-making [15].

2. Materials and Methods

2.1 Study Design

In this study, we conducted a two-step, two-sample MR analysis that included three specific analyses: the relationship between education and PPD, education and household income, and household income and PPD (Fig. 1). This approach aimed to assess the associations among educational level, household income, and PPD. Details regarding the GWAS datasets can be found in the "**Availability of Data and Materials**" section. The educational-level dataset comprised 461,457 individuals of European origin. In terms of household income data, 397,751 participants were involved. The PPD-related dataset covered 67,205 individuals, with 7604 diagnosed with PPD and 59,601 acting as controls.

2.2 Instrumental Variables (IVs) Selection

First, a selection threshold of $p < 5 \times 10^{-8}$. was established for single-nucleotide polymorphisms (SNPs). To validate the selected instrumental variables (IVs), we conducted the linkage disequilibrium (LD) analysis on the screened SNPs, with the window size parameter set to 10,000 kb and the R^2 threshold set to less than 0.001. Additionally, by leveraging the PhenoScanner tool (https://www.phenoscanner.medschl.cam.ac.uk), we identified genome-wide features significantly associated ($p < 5 \times 10^{-8}$) with these SNPs [16]. This step aimed to exclude SNPs linked with confounding factors related to education, household income, and PPD, thereby enhancing the reliability of subsequent analyses.

Second, to ensure the validity of the MR results, three key assumptions needed to be verified throughout the entire process [17]:

(i) IVs should have a direct association with the exposure factor;

(ii) IVs should not directly influence the outcome factor;

(iii) IVs should not be affected by the potential confounders that influence both the exposure and the outcome. To implement this step, we performed two key actions: first, we searched the PhenoScanner database (https://www.phenoscanner.medschl.cam.ac.uk) to identify features associated with confounding factors; second, we applied the MR-Egger intercept method and the MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) method to analyze and remove IVs with horizontal pleiotropy.

Third, we evaluated the strength of each instrumental variable. Weakly correlated IVs were excluded by calculating the F-statistic using the formula: $F = R^2(N – 2)/(1 – R^2)$. In this formula, R^2 represents the proportion of variance in the exposure factor explained by each IV, and N denotes the sample size of the GWAS for the exposure factor. An F-statistic exceeding 10 indicates that the IVs are sufficiently robust, ensuring adequate validity for subsequent MR analyses and eliminating bias caused by weak instruments [18].

In summary, we implemented stringent screening of IVs to ensure the robustness and reliability of the MR analysis. The screening process included: applying a strict significance threshold ($p < 5 \times 10^{-8}$), removing SNPs in LD, using the PhenoScanner database to eliminate SNPs associated with confounding factors, examining and excluding SNPs showing significant horizontal pleiotropy, and filtering out SNPs with low F-statistics.

2.3 Statistical Analyses

In the present study, the inverse variance weighting (IVW) method was primarily used to infer potential associations. Additionally, four complementary approaches—MR-Egger, weighted median, simple mode, and weighted mode—were utilized alongside the IVW method to validate these associations [19]. A two-sided *p*-value of less than 0.05 was considered statistically significant. Cochrane's Q statistic (Q) was applied. Furthermore, a leave-one-out analysis was performed to identify individual SNPs that significantly influenced the results. Directed pleiotropy was evaluated by examining the deviation of the MR-Egger intercept, with a *p*-value of less than 0.05 indicating the presence of horizontal pleiotropy [20,21]. The MR-PRESSO method was further applied to detect SNPs with horizontal pleiotropy [22]. Both the MR-Egger intercept and MR-PRESSO methods can also verify whether all IVs satisfy the third assumption of MR. Finally, the coefficient product method was adopted: the indirect effect was calculated by multiplying the effect of education on household income by the effect of household income on PPD. All statistical analyses were conducted using the TwoSampleMR and MR-PRESSO packages in R software version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1 IVs Selection

A total of 101 SNPs were included as IVs when education was the exposure factor and PPD was the outcome factor. There were 147 SNPs included as IVs when education was the exposure factor and household income was the outcome. Additionally, 15 SNPs were included as IVs

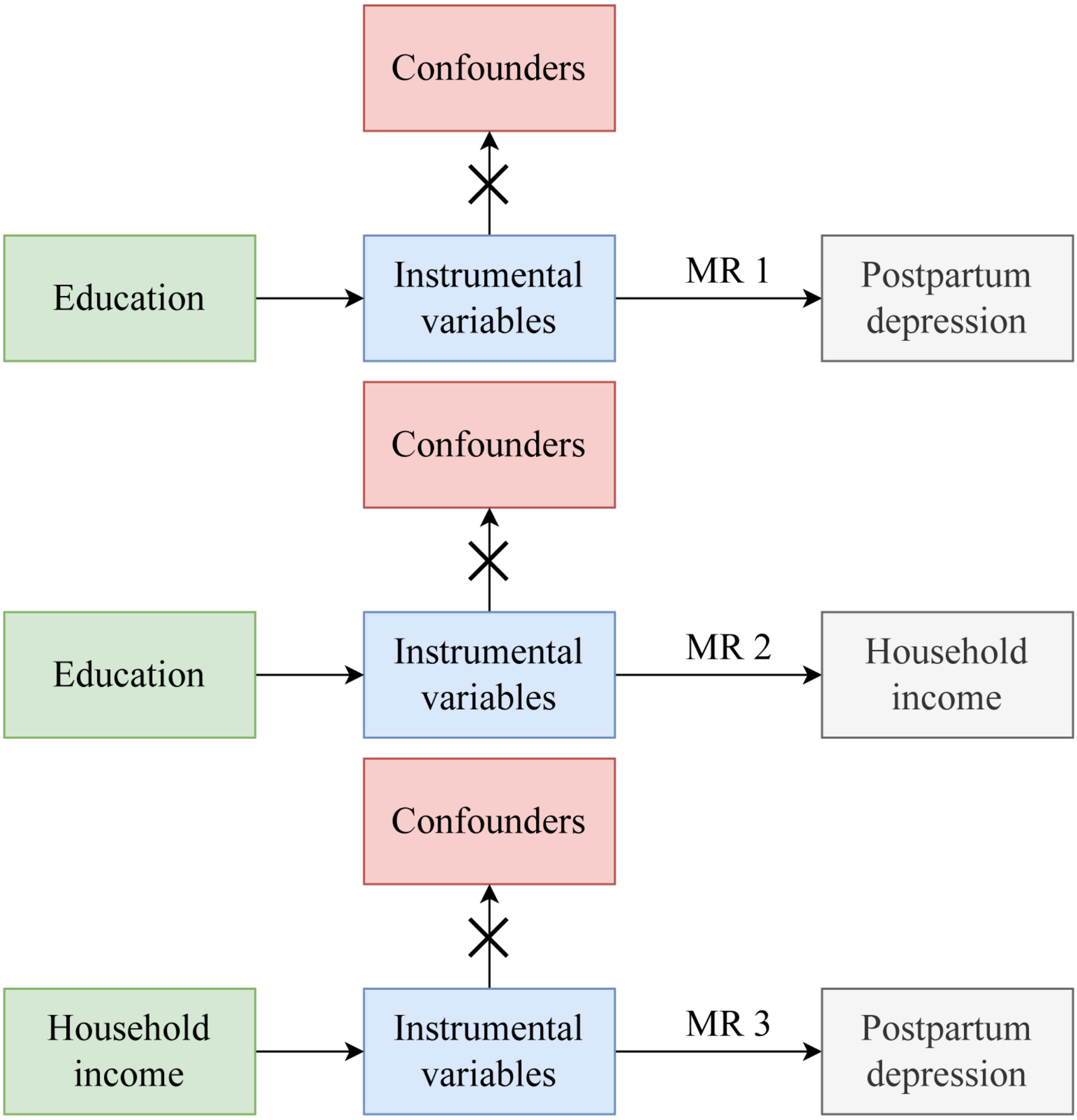

Fig. 1. Flowchart of research design for two-step Mendelian Randomization analysis. MR, Mendelian randomization.

when household income was the exposure factor and PPD was the outcome factor. The F-statistics for all SNPs were greater than 10.

3.2 MR Analysis

IVW analysis showed a negative association between education and PPD (OR = 0.877, 95% CI: 0.828–0.930, p = 1.050×10^{-5}); a positive association between education and household income (OR = 1.095, 95% CI: 1.085–1.105, $p = 2.805 \times 10^{-87}$); and a negative association between household income and PPD (OR = 0.443, 95% CI: 0.204–0.962, $p = 0.040$). The remaining four methods showed that the results of the IVW method are stable and reliable (Table 1). The results of the coefficient product method showed a mediating effect coefficient of –0.074 (95% CI: –0.146 to –0.004), which accounted for 56.67% of the total effect.

3.3 Sensitivity Analysis

Cochrane's Q statistics demonstrated that no heterogeneity was present in the IVs incorporated in both the IVW and MR-Egger methods for the associations between education and PPD, as well as household income and PPD (both $p > 0.05$). However, the heterogeneity of IVs was more salient in MR analyses where education was the exposure factor and household income was the outcome factor ($p < 0.05$, Table 2). Leave-one-out analyses showed that results were susceptible to a single IV when household income was the exposure factor and PPD was the outcome factor, whereas the other two MR analyses did not see an IV that significantly affected the results of the analyses (Fig. 2). MR-Egger intercept analysis (Fig. 3, Table 3) indicated that there was potential horizontal pleiotropy in the MR analysis between household income and PPD. However, the results of the MR-PRESSO analysis (Table 3) demonstrated that

Table 1. Results of MR analyses conducted to estimate potential associations between exposure and outcome.

Exposure/Outcome factor	Methods	IVs	β	OR	95% CI		p-value
					Lower	Upper	
Education/PPD	MR-Egger	101	–0.167	0.847	0.668	1.072	0.171
	Weighted median	101	–0.129	0.879	0.805	0.959	0.004
	IVW	101	–0.131	0.877	0.828	0.930	1.050×10^{-5}
	Simple mode	101	–0.124	0.883	0.709	1.101	0.272
	Weighted mode	101	–0.128	0.880	0.707	1.096	0.256
Household income/PPD	MR-Egger	15	–4.681	0.009	0.001	0.134	0.004
	Weighted median	15	–0.967	0.380	0.149	0.972	0.043
	IVW	15	–0.814	0.443	0.204	0.962	0.040
	Simple mode	15	–1.152	0.316	0.075	1.330	0.139
	Weighted mode	15	–0.881	0.415	0.119	1.439	0.187
Education/Household income	MR-Egger	147	0.067	1.069	1.023	1.116	3.090×10^{-3}
	Weighted median	147	0.086	1.090	1.077	1.104	9.169×10^{-45}
	IVW	147	0.091	1.095	1.085	1.105	2.805×10^{-87}
	Simple mode	147	0.097	1.102	1.063	1.142	3.718×10^{-7}
	Weighted mode	147	0.094	1.098	1.062	1.135	1.646×10^{-7}

OR, odds ratio; CI, confidence interval; PPD, postpartum depression; IVW, inverse variance weighting; IVs, instrumental variables.

Table 2. Heterogeneity was tested using the Cochrane Q statistic.

Exposure/Outcome factor	Methods	Q	Q_df	Q_p-value
Education/PPD	MR-Egger	99	96.72177	0.546
	IVW	100	96.81564	0.572
Household income/PPD	MR-Egger	13	12.35466	0.499
	IVW	14	20.89616	0.104
Education/Household income	MR-Egger	145	245.8951	3.386×10^{-7}
	IVW	146	248.0728	2.799×10^{-7}

Q, Cochrane's Q statistic.

within the scope of the above three MR analyses. However, the results of the MR-PRESSO analysis (Table 3) indicate that, within the scope of the three MR analyses mentioned above, none of the IVs used exhibited significant horizontal pleiotropy. It is particularly important to note that while the MR-PRESSO method suggests the presence of horizontally pleiotropic IVs in the association between education and household income, the specific IVs with pleiotropy could not be identified.

4. Discussion

Through the application of MR analysis, we identified a significant association between education and PPD. Specifically, women who spend more time in education have a lower risk of developing PPD. Additionally, an increase in household income plays an important mediating role in the association between time spent on education and PPD.

A cohort study involving 90,194 pregnant women demonstrated that those with a brief period of education were more likely to develop PPD compared to those with a longer period of education [14]. Another retrospective study also found that a lower level of education was a significant predictor of PPD [23]. In this study, household income accounted for 56.67% of the total effect in the association between education and PPD, underscoring the importance of household income in this association. Education level is a key measure of socio-economic status, and pregnant women from families with lower socio-economic status have a significantly higher risk of PPD [24,25]. In empirical studies, years of schooling are usually used as a proxy for educational attainment. Modern theories of human capital highlight education to be an important factor in increasing individual incomes and contributing to a country's economic development, as confirmed by several social surveys [26–28]. Socio-economic status is typically measured by level of education, income, and occupation, with education level often serving as a more reliable indicator than income or occupation [14,29]. After childbirth, the costs of childcare and basic living expenses increase substantially. Women with low incomes, who are concerned about their family's financial situation, are nearly four times more susceptible to PPD than those with higher income levels [30]. Increasing the number of years of education en-

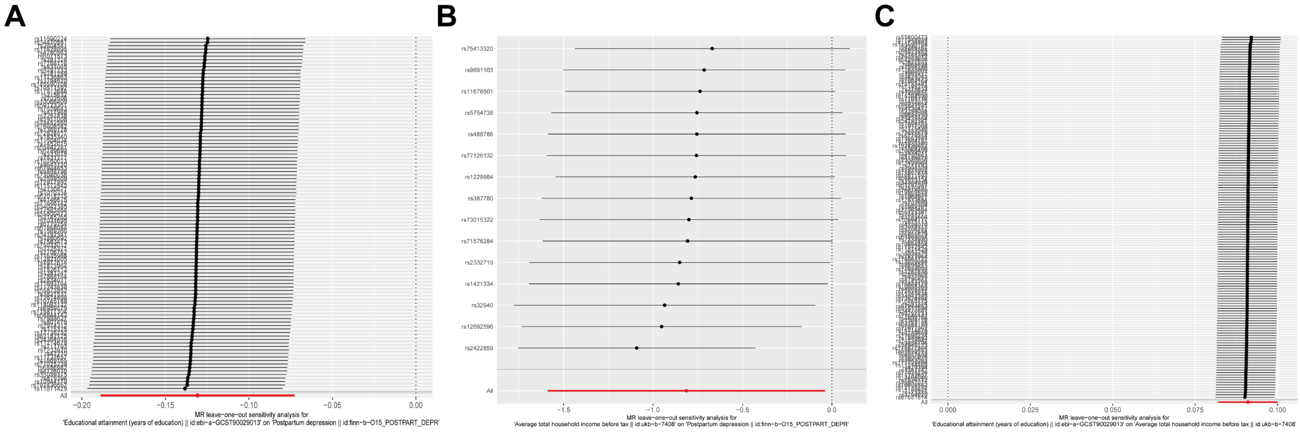

Fig. 2. Leave-one-out sensitivity analysis of the association effect of exposure on outcome. (A) Education and PPD. (B) Household income and PPD. (C) Education and household income.

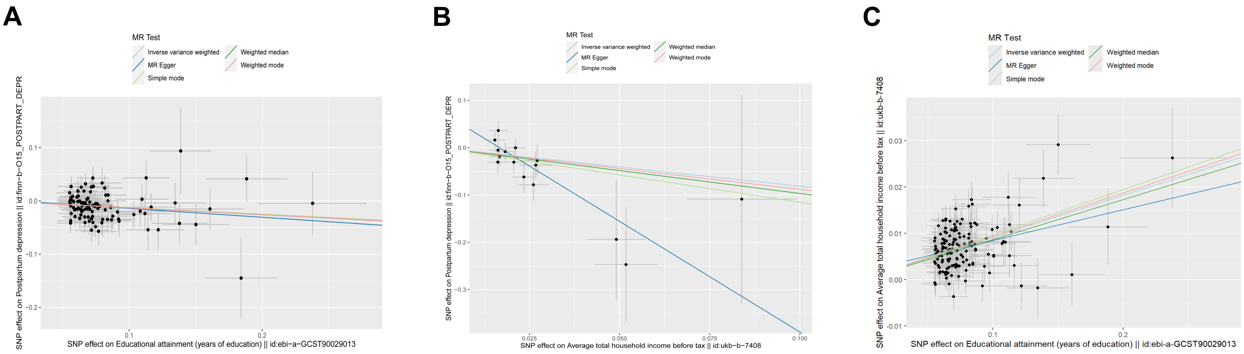

Fig. 3. MR-Egger intercept analysis to analyze horizontal pleiotropy of single-nucleotide polymorphisms (SNPs). (A) Education and PPD. (B) Household income and PPD. (C) Education and household income.

hances overall improvement of knowledge and skills, enabling women to cope with stressful situations more effectively and optimistically. However, further investigation is needed to determine whether this relationship is consistent across diverse contexts, including variations in countries and social health care policies.

In China, the prevalence of maternal PPD is notably high, representing a significant public health challenge. However, due to the heterogeneity of the disease and the diversity of the scales, PPD is still underdiagnosed, underrecognized, and inadequately treated [31,32]. Access to education and the acquisition of knowledge and skills can help women to improve their baseline cognitive level, develop a healthy mindset and a positive attitude towards life, and become more competitive at work [33–35]. Such women can bring more income, exert a positive and active influence on their families, raise the next generation with both virtue and talent, and promote the healthy development of society [36]; they can also provide the market with high-quality talents, promote the optimization of the industrial structure, and contribute to overall socio-economic development [37]. Consequently, it is important to reduce the incidence of PPD by increasing the number of years of female education, which in turn increases household income and improves the state of female mental health.

In this study, the MR analysis revealed a significant negative association between years of education and PPD. Specifically, the promotion of female education and the increase in female educational attainment can effectively decrease the incidence of PPD.

Limitations

This study has several limitations. First, all participants included in this study were drawn from a European population. While this reduces population heterogeneity and enhances the credibility of the results, additional research is required to determine whether these findings generalize to other ethnicities. Second, in the mediational two-sample MR analysis we conducted, we did not account for the effects of other potential confounders, such as age, on the outcome, nor did we assess their role in the association. However, MR analysis, akin to a randomized controlled trial, is minimally influenced by confounders after strict quality control of IVs. Third, the p-value of the MR-Egger intercept test in the analysis of household income and PPD is less than 0.05, and there is significant horizontal

Table 3. Pleiotropy testing using Cochrane's Q test and MR-PRESSO.

Exposure/Outcome factor	MR-Egger regression method			MR-PRESSO method						
	Egger intercept	SE	*p*-value	MR analysis	Causal estimatee	SD	T-Sat	*p*-value	RSSobs of Global Test in MR-PRESSO results	*p*-value of the Global Test in the MR-PRESSO results
Education/PPD	0.003	0.009	0.760	Raw Outlier-corrected	–0.126 NA	0.029 NA	–4.328 NA	3.540×10^{-5} NA	100.858	0.549
Household /PPD	0.078	0.027	0.012	Raw Outlier-corrected	–0.820 NA	0.384 NA	–2.134 NA	0.050 NA	24.172	0.149
Education/Household income	0.002	0.009	0.864	Raw Outlier-corrected	0.091 NA	0.005 NA	19.878 NA	9.448×10^{-44} NA	256.715	1.000×10^{-4}

MR-PRESSO, MR Pleiotropy RESidual Sum and Outlier; NA, not available; RSSobs, residual sum of squares observed.

pleiotropy in the MR-PRESSO analysis of education and household income, which raises concerns about the reliability and validity of the research conclusions. Nevertheless, we rigorously screened SNPs to ensure they served as valid IVs. Additionally, we utilized the MR-PRESSO method to examine IVs for potential horizontal pleiotropy, but no specific IVs exhibited the issue. We also employed the Weighted Median Estimator, a robust method that is less sensitive to invalid IVs, for validation. The results of the weighted median analysis indicated that the association effect remained statistically significant. Both primary analysis methods (IVW and Weighted Median) yielded statistically significant results with consistent directional outcomes. This indicates that, despite concerns about pleiotropy, the primary findings of the MR analysis remain robust. However, the interpretation and further analysis of each association should be approached with caution.

5. Conclusions

This study reveals the associations between education level, household income, and PPD from a genetic perspective. We also analyze the indirect effect of household income on the relationship between education level and PPD. The results offer a theoretical basis for the screening and prevention of PPD, indicating that special attention should be given to the education level and household income of pregnant and postpartum women at high risk of PPD. However, since all GWAS datasets used in this study were derived from European populations, the interpretation of the associations between education level, household income, and PPD is limited. Whether these conclusions can be generalized to other populations (e.g., Asian populations) requires further validation through prospective cohort studies or GWAS data from other ethnic groups in the future.

Availability of Data and Materials

The datasets used in this study are available in public databases, and the data analysis process can be obtained from the corresponding author. GWAS data on education (ebi-a-GCST90029013), household income (ukb-b-7408), and PPD (finn-b-O15_POSTPART_DEPR) used in our study were obtained from the IEU GWAS Open Project (https://gwas.mrcieu.ac.uk/).

Author Contributions

WQ, JX, HW, RJ and HQ designed the research study. WQ, JX, HW, RJ and HQ performed the research study. WQ and JX analyzed the data. HW performed the data visualization. RJ and HQ conducted supervision and review the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study used data from published public data and all original research was ethically approved. Therefore, no ethical approval was required for this study.

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Conflict of Interest

The authors declare no conflict of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used deepseek in order to check spell and grammar. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

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