Are highly educated gravida more likely to be depressed?—— Exploring the causal relationship between educational attainment and postpartum depression: Evidence based on a two sample Mendelian Randomization approach

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Abstract. Postpartum depression (PPD) refers to a psychiatric disorders that afflicts women subsequent to childbirth, which represents a substantial global health concern with a prevalence that demands attention. Therefore, it is important to address this condition to reduce the disease and economic burden it causes. However, the pathogenesis of postpartum depression (PPD) remains unclear. Recent studies have suggested that educational attainment may play a role, indicating a need for further exploration. To elucidate this potential link, this study employs a two-sample Mendelian Randomization (TSMR) analysis, leveraging years of schooling (YOS) as a proxy variable, to rigorously investigate the causal relationship between educational attainment and the onset of postpartum depression. MR analyses performed by the IVW method indicated that educational attainment may has a negative causal effect on postpartum depression (OR: 0.52, 95% CI: 0.45–0.61, P=2.78e-18) in the European population. The results of the MR analyses suggest that a higher level of education is a protective factor for postpartum depression. Therefore, advocating for the equitable dissemination of education and enhancing women's educational attainment becomes imperative to safeguard their physical and mental health.

Keywords: Causal relationship; Two Sample Mendelian Randomization (TSMR); Epidemiology; Postpartum depression; Year of schooling.

1. Introduction

Postpartum depression stands as a prevalent psychological disorder and a significant mental health concern among women following childbirth, exerting a substantial impact on the well-being of postpartum individuals globally. The pooled prevalence of postpartum depression on a global scale was estimated to be 17.7% (95% CI: 16.6-18.8%). Low- and middle-income countries exhibit a much higher morbidity[1]. Additionally, the attack rate of postpartum depression was recorded at 12% (95% CI: 0.04-0.20%) among healthy mothers without a prior history of depression[2]. Moreover, research indicates that the COVID-19 pandemic has exacerbated depression and anxiety manifestations in postpartum women due to decreased social support and physical activity[3]. Therefore, it is imperative to conduct further research. Postpartum depression is characterised by prolonged emotional depression, decreased self-esteem, lack of confidence in life, as well as physical symptoms such as poor sleep and decreased appetite in postpartum women. It is worth noting that 19.3% of women experience self-harm ideation[4]. Postpartum depression can impair maternal-infant interaction by reducing maternal attachment and sensitivity, and promoting poor parenting practices, which can have adverse effects on children's development[5]. Therefore, the increasing prevalence and disease burden of postpartum depression is a serious concern that requires attention. Exploring modifiable risk factors to reduce the incidence rate of postpartum depression is significant for improving women's health and promoting public health.

Although significant progress has been made in diagnosing and treating postpartum depression, the causes of this condition have not been fully elucidated. The pathogenesis of postpartum depression is believed to result from the interaction of biological and psychosocial factors. Biological factors include reproductive hormones, such as progesterone, and genetic factors. Psychosocial factors mainly include stressful life events, family relationships, education, and social
support, etc[6]. Education can affect lifestyle by influencing cognition and income, which can further impact physical and mental health. In recent years, research has increasingly examined the impact of educational attainment on the risk of various diseases[7], indicating its significant role in disease development. Therefore, we consider educational attainment as a modifiable risk factor for postpartum depression. While observational studies have indeed demonstrated a correlation between education and postpartum depression prevalence[8], there is currently no direct study that evaluates the causal relationship between educational attainment and postpartum depression, and we cannot determine the causality from the results of these observational studies. The main reason for this is that educational attainment serves as a socio-economic exposure variable, rendering it unsuitable for validation through clinical trials. Furthermore, it is crucial to consider that the relationship between postpartum depression and education level may also be influenced by confounding factors and reverse causality.

Due to the long incubation period between exposure and results, and the unsuitability of educational attainment for clinical trials, it is not feasible to use RCT to study this issue. Instead, Mendelian Randomization (MR) analysis can overcome limitations by avoiding bias, confounding factors, and reverse causality, and is helpful for analysis due to its high level of evidence and convenience[9]. The MR method has been extensively utilized in various studies to establish causal relationships, including those between education and diseases like lung cancer, chronic kidney disease, and coronary heart disease[10]. However, there is a lack of research on the relationship between education and postpartum depression. This study aims to investigate whether higher educational attainment can mitigate the risk of postpartum depression. Therefore, we employed TSMR analysis to investigate the causal association between educational attainment and postpartum depression.

2. Methods

2.1 Study design

The present investigation conducted a TSMR analysis to elucidate the causal nexus between educational attainment and postpartum depression, as illustrated in Figure 1. The instrumental variables (IVs) employed in this inquiry were single nucleotide polymorphisms (SNPs) screened from GWAS. These SNPs can serve as an alternative to exposure, and their random allocation can simulate randomized controlled trials. This allows for the innate IV to be independent from confounding factors such as BMI and age, resulting in higher levels of evidence. educational attainment, measured by years of schooling, was selected as the exposure, while postpartum depression was selected as the outcome. Additionally, the MR design must satisfy three assumptions: (1) Correlation assumption: genetic instruments must be highly correlated with exposure factors (P < 5 × 10-8). (2) Independence assumption: genetic instruments must be strictly independent from confounding factors. (3) Exclusivity assumption: genetic instruments only influence outcomes through risk factors and are not directly linked to outcomes[11].

Fig. 1 The flow chart of TSMR.
2.2 Data sources

The IV of years of schooling was selected from the GWAS dataset of Okbay et al. [12], in which 3,037,499 sample size and 10,675,380 SNPs were contained. IV related to postpartum depression was obtained from FinnGen, includes 11,711 Ncases and 214,996 Ncontrols (Table.1). All the public source data we studied has obtained ethical approval from their institutional review committee.

<table>
<thead>
<tr>
<th>Exposure- Years of schooling</th>
<th>Total population</th>
<th>Cases/Controls</th>
<th>Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome- Postpartum depression</td>
<td>3,037,499</td>
<td>NA</td>
<td>European</td>
</tr>
<tr>
<td></td>
<td>226,707</td>
<td>11,711/214,996</td>
<td>European</td>
</tr>
</tbody>
</table>

2.3 Selection of the Genetic IVs

We use a p-value threshold of $5 \times 10^{-8}$ to identify SNPs associated with Years of schooling and exclude those with linkage disequilibrium (within 10000 kb or $r^2 > 0.001$), therefore 603 SNPs are selected as IV, to achieve higher reliability, among which 2 SNPs are dropped for $F <10$[13]. 582 SNPs are extracted from outcome, among which 32 SNPs are dropped after harmonization, remaining final 550 SNPs for the next two-sample MR analysis.

2.4 TSMR Analysis

In the two-sample Mendelian randomization (MR) analysis, we employed the IVW method as the primary approach to validate the causal association between educational attainment and postpartum depression. Furthermore, to bolster the reliability of our estimates across various scenarios, we employed supplementary methodologies including MR Egger, weighted median method, weighted mode, and simple mode[14]. If the estimation results of IVW and these auxiliary methods are inconsistent in the study, a more stringent tool p-value threshold could be set, however, the direction of the $\beta$ value needs to be consistent among all the methods above.

2.5 Sensitivity Analysis

The sensitivity analysis encompassed both heterogeneity and horizontal pleiotropy assessments. Heterogeneity was evaluated through the MR Egger heterogeneity test, where the bias on causal effect estimation could only be disregarded if $P>0.05$. Should remarkable heterogeneity emerge ($P<0.05$), the random effects IVW method would be employed for the MR analysis. Horizontal pleiotropy was evaluated using the MR Egger regression method, considering weak genetic pleiotropy negligible when $P>0.05$. Additionally, the presence of horizontal pleiotropy could be depicted through a funnel plot. Should horizontal pleiotropy be evident, MR-PRESSO could be utilized for evaluation and correction. Subsequent to outlier removal, reanalysis was conducted. Finally, reliability was corroborated via the leave-one-out method[15]. Data analyses were performed utilizing the TwoSampleMR package. (R version: 4.2.1).

3. Results

3.1 TSMR Results

In MR analyses performed by the IVW method, we found that in the European population, educational attainment was significantly associated with postpartum depression (OR: 0.52, 95% CI: 0.45 – 0.61, $P=2.78e-18$) , as shown in Figure 2. Other MR methods (MR-Egger, weighted median method, weighted model) also show an overall consistent and significant protective effect of EA on
the risk of postpartum depression (Figure 2). The scatter plot of TSMR further illustrates that different methods have the same decreasing trend as well (Figure 3). 550 SNPs related to education explained 2.75% of the variance in education level, and the F statistics were greater than 10, suggesting a low likelihood of weak instrumental bias[16].

<table>
<thead>
<tr>
<th>Method</th>
<th>N.SNP</th>
<th>OR (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR Egger</td>
<td>550</td>
<td>0.433 (0.278–0.674)</td>
<td>2.31e-04</td>
</tr>
<tr>
<td>Weighted median</td>
<td>550</td>
<td>0.497 (0.410–0.603)</td>
<td>1.32e-12</td>
</tr>
<tr>
<td>Inverse variance weighted</td>
<td>550</td>
<td>0.524 (0.453–0.606)</td>
<td>2.78e-18</td>
</tr>
<tr>
<td>Simple mode</td>
<td>550</td>
<td>0.688 (0.313–1.510)</td>
<td>3.51e-01</td>
</tr>
<tr>
<td>Weighted mode</td>
<td>550</td>
<td>0.512 (0.272–0.985)</td>
<td>3.89e-02</td>
</tr>
<tr>
<td>MR-PRESSO Raw</td>
<td>550</td>
<td>0.524 (0.453–0.606)</td>
<td>3.31e-17</td>
</tr>
<tr>
<td>MR-PRESSO Outlier-corrected</td>
<td>549</td>
<td>0.534 (0.463–0.617)</td>
<td>9.40e-17</td>
</tr>
</tbody>
</table>

Fig. 2 Forest Plots of TSMR Results.

Fig. 3 Scatter plot of TSMR.

3.2 Sensitivity Analysis

The MR-Egger regression method showed insufficient evidence to confirm the existence of horizontal pleiotropy among IVs (intercept=0.0022, P=0.37) (Table 2). MR Egger heterogeneity test indicated the presence of heterogeneity (Q=754.15, P=1.058124e-08) (Table 2). The MR-PRESSO method detected abnormal values (rs34488670, rs7356921), after removing the abnormal SNPs, MR analysis showed that there was no significant change in the results (IVW, β =-0.64, 95% CI: (-0.79, -0.50), P=3.51E-18) (Table 3). Heterogeneity still exists (P=9.05e-09) (Table 2).

The leave-one-out analysis, where each instrument (SNP) was sequentially excluded to assess sensitivity, revealed that no single instrument was significantly driving the overall effect of education on postpartum depression. Additionally, the funnel plot exhibited good symmetry (Figure 4). These findings from the leave-one-out analysis and funnel plot suggest the absence of horizontal pleiotropy in the results. In conclusion, our study furnishes compelling evidence affirming a protective causal association between higher educational attainment and postpartum depression.

<table>
<thead>
<tr>
<th>Method</th>
<th>Cochran’s Q</th>
<th>P-Value</th>
<th>Egger intercept</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before MR Egger</td>
<td>754.1541</td>
<td>1.058124e-08</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Table 3. TSMR results after MR-PRESSO

<table>
<thead>
<tr>
<th>Method</th>
<th>N.SNP</th>
<th>P-value</th>
<th>OR(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR Egger</td>
<td>549</td>
<td>0.000234</td>
<td>0.433063</td>
</tr>
<tr>
<td>Weighted median</td>
<td>549</td>
<td>1.10E-11</td>
<td>0.499415</td>
</tr>
<tr>
<td>IVW</td>
<td>549</td>
<td>3.51E-18</td>
<td>0.524499</td>
</tr>
<tr>
<td>Simple mode</td>
<td>549</td>
<td>0.374577</td>
<td>0.708185</td>
</tr>
<tr>
<td>Weighted mode</td>
<td>549</td>
<td>0.045936</td>
<td>0.527626</td>
</tr>
</tbody>
</table>

Fig. 4 Funnel plots of TSMR Results

4. Discussion

Postpartum depression is a prevalent emotional disorder and mental health disorder among pregnant women. It has a significant negative impact on maternal physical and mental health, as well as the development of family relationships, with a high morbidity and mortality rate. Therefore, research into modifiable risk factors for postpartum depression, as well as the development of positive public health policies for the prevention, are of vital importance to improve maternal health and female health.

Through a comprehensive literature review, it was revealed that this study stands as the pioneering MR investigation to explore the causal association between educational attainment and postpartum depression. Our findings underscore a significant protective effect, indicating that individuals with higher educational attainment exhibit a diminished risk of experiencing postpartum depression (OR: 0.52, 95% CI: 0.45 – 0.61, P=2.78e-18). This observation aligns with prior research suggesting a heightened risk of postpartum depression associated with lower educational attainment, while conversely, higher levels of education serve as a protective factor against the condition.[17]. Our findings are consistent with these observations and with the results of systematic reviews. On the contrary, another study did not find an association between educational
attainment and postpartum depression[18]. However, it is important to note that the MR analysis was conducted solely on a European population. As such, the generalisation of our findings to other populations and ethnicities, given the varying incidence of postpartum depression, levels of economic development, and cultural environments in the observational and prospective studies mentioned above, may not be appropriate. Nonetheless, our findings remain of significant reference value.

We utilised MR and selected genetic tools from a summary GWAS dataset to identify data supporting the causal relationship between educational attainment and the reduction of postpartum depression prevalence. The MR analysis is optional and recommended in revealing causal effects between educational attainment and complex diseases due to the genetic traceability of education as a genetic phenotype[19]. For this study, we selected common education-related SNPs as IVs, and included only those SNPs that met the research criteria after a series of conditional screenings. The MR Egger regression outcomes revealed that horizontal pleiotropy did not exert effect on the study data. These findings bolster the validity of the evidence supporting a causal effect of educational attainment (EA) on postpartum depression (PPD). Leveraging the MR methodology has allowed for mitigation of the influence of conventional confounding factors and other limitations inherent in observational research on the study outcomes. Furthermore, this approach proves invaluable in assessing the causal relationships between risk factors and outcomes, providing a more robust foundation for informed decision-making in clinical and public health settings[20]. In addition, our research utilised widely accepted and selected EA IVs, along with the latest aggregate dataset published by GWAS, to elucidate the causal impact of EA on postpartum depression and revealed a significant correlation (p=5e-8). Moreover, sensitivity analysis, incorporating the IVW method, MR Egger method, and weighted median method, consistently reaffirmed the robustness of our findings.

However, how EA affects the risk of postpartum depression through potential genetic and epidemiological mechanisms has not been elucidated. Research has shown that compared to men, women's level of depression in adulthood is more dependent on education[21]. Additionally, studies conducted in two areas of Lebanon have shown that educational attainment may mediate the effect on the incidence rate of postpartum depression through cesarean delivery[22]. In another study, it was stated that education leads to postpartum depression by influencing pregnant women's perception of discrimination during pregnancy[23]. These are all possible causes of postpartum depression. Moreover, educational attainment is an important indicator to measure individual socio-economic status [24]. People with lower socioeconomic status have a higher risk of psychiatric disorders such as depression, anxiety disorders, schizophrenia, and posttraumatic stress disorder [25]. Postpartum depression is also a special subtype of depression. At the same time, people with low education level face various social problems, which may be accompanied by violence and abuse, low socio-economic status, vitamin D deficiency (malnutrition), and lack of social support, all of which are risk factors leading to postpartum depression [26]. There is also an observational study that shows that the disparities in healthcare service will be aggravated due to lower educational attainment and other socio-economic conditions, thereby increasing health gap[27]. And it is widely acknowledged that individuals with a higher socioeconomic status have greater access to a range of resources, including beneficial social connections, healthcare services, enhanced health literacy, and reduced family and work-related stress [28], which are also important contributing factors for the formation of healthy behaviors and lifestyles [29], resulting in the reduction of survival stress and the development of good mental health status [30]. In conclusion, highly educated female groups usually have higher socioeconomic status, a harmonious living environment, healthy lifestyle patterns, superior accessibility to healthcare services, and good social support also further reduce the risk of postpartum depression.

This study demonstrates the causal impact of high educational attainment on reducing the risk of postpartum depression. Therefore, when developing public health policies and preventive screening measures that focus on maternal and women's health, low educational attainment should be considered as a risk factor for high-risk groups of postpartum depression. Developing policies to
improve public educational attainment, including antenatal education, may prevent the onset of postpartum depression[31].

5. Strengths and limitations

Notably, our study has the following important strengths: First, we are the first MR study on the causal association between educational attainment and postpartum depression, and the genotypic grouping of participants in the MR study design was based on the principle of randomization, so the MR method also avoids the possibility of reverse causality and potential confounders that are common in observational studies. Second, the sample size of the GWAS summary dataset we included is the largest(3.3 million) in the EA study so far, and with the statistical considerations made in the use of instrumental variants (F-statistic >10), we had sufficient statistical power to be able to perform the assessment of potential causal effects with certain accuracy (96%)[32].

Of course, several limitations must be considered in our study. First of all, the participants selected in the summary GWAS dataset are all from high-income countries in Europe, so we need to include people from countries with different economic development levels and geographical locations to validate the generalizability of our findings. Secondly, the educational attainment information for some of the populations in the summary GWAS dataset was collected in a self-reported way, and those who self-reported educational attainment information and those who did not may have different characteristics, so the effects of measurement bias and selection bias need to be considered in the clinical analysis. Thirdly, although no horizontal pleiotropy was detected in our study, heterogeneity was found in the results, which may have introduced potential bias.

6. Conclusion

The findings from our study, employing the TSMR method, strongly support a causal relationship between educational attainment and postpartum depression. Specifically, our results indicate that individuals with higher levels of educational attainment exhibit a lower incidence of postpartum depression, suggesting that higher education serves as a protective factor against PPD. These results underscore the significance of education in promoting women's mental health and well-being, particularly during the postpartum period. It highlights the importance of integrating educational interventions and support programs into public health initiatives aimed at preventing postpartum depression and promoting overall mental health among women. Moreover, our findings emphasize the necessity of prioritizing screening for postpartum depression and enhancing mental health support services during pregnancy and gestation. By recognizing the role of education as a protective factor against PPD, medical institutions and policymakers can implement targeted interventions and policies to address this issue effectively.

In summary, our study contributes to the growing body of evidence highlighting the crucial link between education and mental health outcomes, particularly in the context of postpartum depression. It underscores the need for comprehensive strategies that integrate education, healthcare, and support services to safeguard the mental well-being of women during and after pregnancy.

Data Availability Statement: The data is available under reasonable request to the corresponding author.

Conflict of interest: The authors declare that no possible conflict of interest existed during the research.
References


