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Uncovering The Relationship Between Opioid Use And Postpartum Depression: Evidence From A Two-Sample Mendelian Randomization Study

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UNCOVERING THE RELATIONSHIP BETWEEN OPIOID USE AND POSTPARTUM DEPRESSION:
Evidence from a Two-Sample Mendelian Randomization Study

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Abstract

**Background and Objective:** Opioid use during pregnancy is a significant public health concern that has been associated with adverse maternal and fetal outcomes. This study aims to investigate the association between the genetic liability for prescription opioid medication and postpartum depression (PPD) using a Two-Sample Mendelian Randomization (MR) approach. By reducing the risk of residual confounding found in traditional observational studies, we can comprehend how MR can further improve our understanding of this issue.

**Design, setting, and participants:** We conducted a 2-sample MR using summary statistics from genome-wide association studies (GWAS) to determine associations of prescription opioid use with PPD. Selected relevant single nucleotide polymorphisms from GWASs have a threshold \( P \) less than \( 5 \times 10^{-6} \) and \( R^2 \leq 0.001 \). The GWAS data comprised participants of European ancestry included in the UK Biobank and FinnGen biobanks. We performed sensitivity analyses to assess bias due to genetic pleiotropy.

**Main outcomes and measures:** Postpartum depression

**Results:** The primary analysis included 78,808 participants with a record of prescription opioid use, 13,657 participants with PPD, and 236,178 without PPD. Per doubling in the genetically predicted population prevalence of opioid use, the odds of developing PPD increased by 12\% (OR = 1.12, [95\% CI] = [1.05, 1.20], \( p = 0.002 \)). This finding was further validated by sensitivity analyses controlling for genetically predicted cofounders.

**Conclusions and relevance:** The findings of these robust MR analyses additionally demonstrate a potential causal association between opioid use and PPD when considering traditional observational studies suggesting a relationship between opioid use and PPD. While replication is necessary, these findings may inform further investigation of the opioid epidemic related to maternal mental health.
Acknowledgments

Thank you to my friends, family, advisors, and colleagues for supporting me through this journey. I hope you see how much I have grown through this work.
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Introduction

Opioid use during pregnancy is a significant public health concern associated with adverse maternal and fetal outcomes (Krans et al., 2015). In 2019, approximately 7% of women reported using opioid pain relievers during pregnancy (Ko et al., 2019). However, when examining usage longitudinally, there has been a 131% increase in opioid-related diagnoses at delivery between 2010 and 2017 (Hirai et al., 2021). In addition to the growing prevalence of use among pregnant women (Epstein et al., 2013), there is growing evidence that it may contribute to the development of postpartum depression (PPD) (Holbrook et al., 2012).

Observational studies have suggested that opioid use during pregnancy may be associated with an increased risk of PPD. For instance, a retrospective chart review of 125 pregnant women in the Philadelphia metropolitan area enrolled in a substance abuse program, primarily using opioids, found a high prevalence of PPD within their sample (Holbrook et al., 2012). Furthermore, an analysis of cross-sectional data from the Maternal Opioid Treatment: Human Experimental Research (MOTHER) study found that among 174 pregnant women who were dependent on opioids, 65% received a diagnosis of at least one mental health disorder. Specifically, 40% were diagnosed with anxiety, 33% with severe depression, and 49% with mood disorders (Benningfield et al., 2010). While informative, observational results from examining opioid use and PPD studies may be limited by confounding due to sociodemographic factors, mental health conditions, discrepancies in diagnosis criteria, and other unmeasured variables that may influence the relationship between opioid use and PPD.

Mendelian randomization (MR) is an approach that can provide causal evidence for the effect of an exposure on an outcome. MR can reduce confounding and reverse causation by utilizing genetic variants as instrumental variables randomly assigned at conception. This is because alleles are randomly allocated and are not influenced by behavior or other diseases, reducing the risk of confounding and
reverse causation (Davey Smith et al., 2014). Rosoff et al. conducted the first MR study associating opioid use and major depression using case-control GWAS data from the UK Biobank (UKB) containing 54% women with a mean (SD) age of 56.5 (8.1) years predominantly of European ancestry. They utilized Two-Sample MR and found suggestive evidence for a causal effect between opioid use and depression was discovered (Rosoff et al., 2021). While the Rosoff study provides evidence for a relationship between prescription opioid use and major depression using genetic instruments, the results were unspecified to women, pregnancy, and the postpartum period which is of interest to the current study.

In summary, opioid use during pregnancy is a growing public health concern that may contribute to developing PPD. Previous studies have been limited by confounding (Holbrook et al., 2010; Benningfield et al., 2010), lack of specificity to prescription opioid use (Benningfield et al., 2010), and depression in the postpartum (Rosoff et al., 2021), highlighting the gap in research between these conditions. The current study aims to bridge this gap by using two-sample MR to investigate the causal association between opioid use and PPD and its implications for maternal and child health.

Methods

Study Design

A two-sample Mendelian Randomization study (Figure 1) was conducted to assess the association between genetically determined opioid pain medication use and the risk of PPD in individuals of European ancestry. Two-sample MR is a method that uses genetic variants as instrumental variables to estimate the causal effect of an exposure on an outcome. To ensure valid causal inference in MR, the following assumptions for a valid instrument must first be met:

1. Instrument-relevance: The genetic variant(s) used as an instrument should be strongly associated with the exposure of interest, in this case, opioid use. Genetic variants should be a
valid instrument and explain a substantial proportion of the variation in the exposure. Violating this assumption can lead to weak instruments, which may result in imprecise or biased estimates of the causal effect (Burgess et al., 2017; Sheehan et al., 2011).

2. Instrument exclusion: The genetic variant(s) used as an instrument should not be associated with any confounders of the exposure-outcome association. If the genetic variant is associated with any potential confounders, the MR estimate may be biased (Burgess et al., 2017; Sheehan et al., 2011).

3. Independence: The genetic variant(s) used as an instrument should be independent of other pathways that may influence the outcome. Specifically, genetic variants should not be associated with other factors that may influence the outcome except through the exposure. The MR estimate may be biased due to potential pleiotropic effects if the genetic variant is associated with other pathways. (Burgess et al., 2017; Sheehan et al., 2011).
Datasets

Genetic instruments for opioid pain medication use were extracted from summary statistics in the Wu et al. study, a case-control GWAS using data from the UKB, including 78,808 study participants of European ancestry from the United Kingdom (Table 1). The Anatomical Therapeutic Chemical Classification System defined opioid pain medications as containing the active ingredient of opioids (i.e., morphine, oxycodone, codeine, fentanyl, pethidine, and tramadol). The duration of use to be classified as a prescription opioid user was undefined as usage was ascertained through self-report via interviews.
SNPs that were strongly associated (p-value < \(5 \times 10^{-6}\)) with opioid use and uncorrelated (10,000 kilobase pairs apart and \(R^2 \leq 0.001\)) were selected as genetic instruments.

For our outcome, PPD, we used GWAS summary statistics from FinnGen release 8, which included 249,835 participants of European ancestry from the Finnish population (Table 1). This dataset defined PPD cases as ICD-10 codes F32, F33, and F53.0, while controls were defined as having a registered delivery. There were 13,657 and 236,178 cases and controls.

In addition to the primary analysis of the association between opioid use and the risk of PPD, we conducted sensitivity analyses where we accounted for potential genetic correlation with traits related to opioid use (see below). Social confounders were considered by addressing potential genetic pleiotropy through traits related to opioid use. The GWAS data on the site-specific pain conditions were extracted from the UKB (Elsworth et al., 2017), pregnancy complications were from FinnGen release 8, and GWAS data for other pain medications were from UKB (Wu et al., 2019) (Table 1).

Population stratification was avoided by evaluating one ancestry group (European) for both exposure and outcome. Data on the genetic risk of opioid use and genetic risk of PPD was not available for other genetic ancestry groups.

**Statistical Analysis**

The Wald ratio for each SNP was calculated by dividing the SNP-PPD association by the SNP-opioid use association. This assumes that the only effect of the SNP on the risk of PPD is through its effect on the exposure (Sanderson et al., 2022). An inverse-variance weighted (IVW) analysis was used as the main analysis to assess the effect across all SNPs for opioid use exposure. MR Egger, weighted median, and weighted mode were used as sensitivity analyses to validate the results of the IVW by investigating potential violations of the key assumptions in MR analysis. MR Egger accounts for directional pleiotropy and evaluates whether the genetic instruments satisfy the exclusion restriction.
assumption (Burgess et al., 2017). Weighted median and weighted mode analyses are used when some genetic variants used as instruments violate the MR assumptions. They provide consistent estimates if at least 50% of the instruments are valid. These sensitivity analyses help to ensure that the MR findings are not driven by violations of the underlying assumptions (Bowden et al., 2016; Hartwig et al., 2017).

Multivariable MR (MVMR) analyses were conducted to evaluate the effect of opioid medication use while accounting for other genetically correlated traits. One set of multivariate MR analyses evaluated the effect of genetically predicted opioid medication use and a site-specific pain condition (i.e., back, neck/shoulder, knee, hip, headache, and abdominal/stomach) simultaneously. MVMR considering site-specific pain conditions was conducted to control for opioid use caused by these conditions. Additionally, MVMR was performed using pregnancy complications as an exposure (i.e., ectopic pregnancy and cesarean section) and non-opioid medication use (i.e., anilide, salicylic acid, and derivatives NSAIDs).

To further validate our findings, we evaluated the association between opioid use and the risk of PPD using a separate dataset for the outcome. This dataset was from an Australian cohort in 2018 with 20,689 participants aged between 28 and 58 years and 75% female (case/control = 3,804/6,134). The cases in this study consisted of women who had registered in the Australian Genetics of Depression Study (AGDS), had given birth to at least one live baby, and satisfied the PND diagnosis criteria, which could be a high diagnostic test score, a prior diagnosis of PND by a healthcare provider, or a minimum of 2 weeks of perinatal depression (Kiewa et al., 2022). Finally, the findings from the main dataset (UKB) and this dataset were meta-analyzed using fixed effects.

The possibility of reverse causation where genetically predicted PPD was associated with the outcome of genetically predicted opioid use was considered. The final sensitivity analyses reversed the exposure and outcome variables to evaluate genetically predicted PPD against genetic susceptibility to
opioid use. This was done to determine the magnitude of association for the reverse relationship to
determine if the causal pathway was unidirectional.

Software

All analyses were conducted using R (version 4.2.3) and the TwoSampleMR (version 0.5.6), and
metafor (version 3.8-1) packages.

Ethical Approval

Only summary-level data were used for this study, and approval from the institutional review
board was not required. The summary-level data were drawn from studies with relevant ethical
approvals.

Table 1. Source of exposure genome-wide association study summary data (adapted from Rosoff et al.)

<table>
<thead>
<tr>
<th>Trait</th>
<th>Data Sources</th>
<th>First Author (Year)</th>
<th>Type</th>
<th>Number of cases/controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid use</td>
<td>UKB</td>
<td>Wu (2019)</td>
<td>Exposure</td>
<td>22,982/55,826</td>
</tr>
<tr>
<td>Back</td>
<td>UKB</td>
<td>Elsworth (2018)</td>
<td>Exposure</td>
<td>80,588/36,816</td>
</tr>
<tr>
<td>Knee</td>
<td>UKB</td>
<td>Elsworth (2018)</td>
<td>Exposure</td>
<td>76,910/20,979</td>
</tr>
<tr>
<td>Stomach/abdominal</td>
<td>UKB</td>
<td>Elsworth (2018)</td>
<td>Exposure</td>
<td>21,711/17,200</td>
</tr>
<tr>
<td>Ectopic Pregnancy</td>
<td>FinnGen</td>
<td>Kurki (2023)</td>
<td>Exposure</td>
<td>5,052/135,962</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>FinnGen</td>
<td>Kurki (2023)</td>
<td>Exposure</td>
<td>10,937/84,558</td>
</tr>
<tr>
<td>Salicylic Acid Use</td>
<td>UKB</td>
<td>Wu (2019)</td>
<td>Exposure</td>
<td>61,583/50,427</td>
</tr>
<tr>
<td>NSAID Use</td>
<td>UKB</td>
<td>Wu (2019)</td>
<td>Exposure</td>
<td>74,150/90,370</td>
</tr>
</tbody>
</table>
Results

Main Analysis

The primary analysis investigated the relationship between univariate genetically predicted opioid use and genetically predicted PPD. The exposure of opioid use utilized 26 independent variants ($F = 31.8$, [95% CI] = [30.0, 32.4], variance explained = 0.914%) from the UKB sample containing 22,982 cases and 55,826 controls. The outcome of PPD had a sample of 13,657 cases and 236,178 controls from the FinnGen biobank. Univariate Two-Sample MR analysis showed that per doubling in the genetically predicted prevalence of opioid use, the IVW OR for PPD was 1.12 ([95% CI] = [1.05, 1.20], $p = 0.002$) (Table 2) (Figure 2).

Weighted mode and weighted median estimates produced for the main univariate analysis were consistent with the calculated IVW but were less precise (Weighted mode: OR = 1.14, [95%CI] = [0.97, 1.34], $p = 0.129$; Weighted median: OR = 1.14, [95%CI] = [1.03, 1.25], $p=0.008$). The MR Egger estimate differed substantially from the IVW and lacked significance and precision (MR Egger: OR = 1.01, [95%CI] = [0.82, 1.24], $p = 0.957$).

Sensitivity analyses

In the sensitivity analyses, we first investigated whether the effect of opioid use on PPD changed when directly accounting for site-specific pain conditions. When adjusting opioid use for site-specific pain conditions, the effect of opioids on PPD was almost identical to the primary univariate analysis.
Additionally, MVMR analyses controlling for pregnancy complications of ectopic pregnancy and C-section showed opioid use having a weaker effect on the PPD outcome with less statistical significance than the main analysis (Ectopic pregnancy: OR = 1.08, [95% CI] = [1.00, 1.17], p = 0.067; C-section: OR = 1.09, [95% CI] = [1.01, 1.18], p = 0.043). MVMR analyses were done to evaluate the effect of opioid use when directly accounting for potential genetic correlation with the use of other pain medications. The effect estimates for anilide use were similar to the main analysis (OR = 1.12, [95%CI] = [1.01, 1.25], p = 0.033). Salicylic acid and NSAID use both produced smaller and non-significant OR values compared to the univariate effect estimate (Salicylic acid: OR = 1.05, [95%CI] = [0.96, 1.14], p = 0.289; NSAID: OR = 1.09, [95%CI] = [0.99, 1.20], p = 0.077).

We conducted a reverse causality analysis to investigate if PPD was a predictor of opioid use. The IVW OR suggested an increased odds of opioid use per doubling of the genetically predicted prevalence of PPD. However, the wide confidence interval, which included the null value, and large P value, rendered this result non-significant (OR = 1.17, 95% CI = [0.93, 1.47], p = 0.176).

**Meta-Analysis**

We replicated the main univariate analysis using opioid use exposure data from the UKB and PPD outcome data from the ADGS cohort in the Kiewa et al. study (2021). The IVW OR estimates produced from this replication were similar to the main analysis using FinnGen outcome data but were not significant (OR = 1.15, [95%CI] = 0.961, 1.38], p = 0.126).

In the meta-analysis, we combined the OR estimates from the main univariate analysis and the replication analysis using ADGS cohort data to obtain a pooled estimate of the causal effect of opioid use on PPD (Figure 4). The meta-analysis used a fixed effects model and revealed a significant
association between opioid use and PPD, with a pooled OR of 1.13 (95% CI = [1.06, 1.19], p<0.001). The study weights in the meta-analysis were 86.5% for the main analysis and 13.5% for the replication cohort.

Figure 2. Scatter plot of opioid use and PPD MR

This scatter plot shows the association between the exposure, opioid use, (horizontal axis) and the outcome, PPD (vertical axis). Each point on the plot represents a genetic variant included in the analysis. The point-bars represents 95% confidence intervals. The slope of the regression line represents the causal effect estimate of the exposure on the outcome, as estimated using the selected MR method. The intercept of the MR Egger regression line represents the potential pleiotropic effects of the genetic variant on the outcome that are not mediated by the exposure.
Figure 3. Forest plot of MR analyses

Figure 4. Meta-analysis using FinnGen and AGDS GWASs for PPD outcome
Discussion

In this two-sample MR, we observed a positive association between genetically predicted opioid use and the risk of PPD, indicating that opioid use may be a causal risk factor for PPD. Robust sensitivity analyses further supported this relationship. The effect of opioid use on PPD did not appear to be due to genetic correlation to pain conditions or pregnancy complications. Moreover, effect estimates remained consistent when replicated in an independent outcome cohort.

Opioid PPD MR estimates were similar in magnitude and direction for IVW, weighted median, and weighted mode analyses. This convergence of results across multiple MR methods provides confidence in the effect estimate obtained from the main univariate IVW analysis. The MR Egger analysis had a much lower point estimate that was non-significant (Figure 3) and a non-zero intercept on its regression line (Figure 2). The result from the MR Egger analyses indicates potential pleiotropy that yields a result closer to the null when accounted for. However, the confidence interval includes the point estimate from the IVW analysis and thus does not invalidate the central finding. This strengthens the validity of the MR analysis and provides more confidence in the effect estimate obtained from the previous method.

Confounding can be introduced in MR when the instrument(s) affect confounders and could exist between potentially genetically correlated traits. Our study conducted sensitivity analyses using MVMR to account for potential confounding factors such as pain conditions, pregnancy complications, non-opioid pain medications, and the causal relationship between opioid use and PPD. The MVMR results showed that the estimated OR for opioid use and PPD remained similar and significant after controlling for site-specific pain conditions. Examining the association between pregnancy complications and PPD showed estimated ORs slightly closer to null and 95% confidence intervals that included the point estimate from the main analysis. These results concur with the main analysis. The effect of opioid use, when directly accounting for potential genetic correlation with the use of other pain medications,
was similar for Anilide medications but weaker for salicylic acid and NSAIDs. These results also support findings from the main analysis as 95% confidence intervals included the OR from the main analysis and had relatively similar point estimates.

While the current study’s use of GWAS data to investigate the association between opioid use and PPD is novel, our results are consistent with the few observational investigations examining this association. For example, a retrospective chart review of 125 pregnant, primarily opioid-addicted women in the Philadelphia metropolitan area enrolled in a substance abuse program found that almost half had a PPD diagnosis (Holbrook et al., 2012). A cross-sectional analysis of the MOTHER study found that among 174 opioid-dependent pregnant women, 65% were diagnosed with at least one mental health disorder, of which 33% were severe depression (Benningfield et al., 2010). A systematic review of substance abuse and PPD in five observational cohorts consistently found high rates of PPD in substance-abusing pregnant women (Ross et al., 2009). While substance use was not specific to opioid use, the findings of this review align with similar observational trials. An important distinction between our study and the investigations above was the presence of known substance abuse in participants. While results from drug-addicted cohorts could inform research on the side effects of high-risk prescribed medications, confounding due to psychosocial elements of drug abuse can weaken findings, thus warranting further investigation. Our genetic-based methodology to evaluate standalone opioid use and PPD genetic instruments has brought more specificity to this topic while concurring with previous studies that describe the clinical profile of opioid-dependent pregnant women (Benningfield et al., 2010).

The results of this investigation also align with the Rosoff et al. study using similar genetic-based methods and exposure data to determine the relationship between prescription opioid use and major depression. The Rosoff IVW OR of 1.14 ([95% CI] = [1.06, 1.22], p < 0.001) is consistent with our OR
estimate of 1.12. This may suggest that PPD and major depression have a similar genetic basis or underlying biological basis that is comparably associated with opioid use.

The mechanism by which opioid use can contribute to PPD is not fully understood but may involve disruption of the maternal brain neurocircuit. Opioids, such as those used in buprenorphine maintenance treatment for opioid use disorder, can act on the periaqueductal gray (PAG) and other maternal brain regions, including the hypothalamus is critical for maternal behavior (Swain et al., 2019). Disruption of these regions can lead to deficits in maternal behaviors, including caregiving and aggression, associated with PPD (Swain et al., 2019).

The strengths of our study include extensive sensitivity analyses to assess the robustness of our findings. We attempted to assess potential biases, namely genetic pleiotropy, through correlated traits (i.e., pain conditions, pregnancy complications, non-opioid pain medications) and reverse causation. Another strength of our investigation was utilizing a replication cohort for our outcome GWAS to validate estimates obtained in the primary analysis. Analyzing one ancestry group increased the study's validity not only because of the reduction in the heterogeneity of genetic variants that produced more precise causal estimates but also because it reduced the risk of confounding due to population stratification. However, several limitations to our study should be considered. Despite its benefits in precision, our sample was limited to individuals of European ancestry, which may limit the generalizability of our findings to other populations. It is also unclear whether the genetic instruments for opioid use used in our study are specific to opioid use during pregnancy or reflect more general opioid use. There is also a significant limitation in diagnosing PPD within the GWASs. Despite using ICD-10 coding to ascertain cases, PPD is vastly underreported (Manso-Córdoba et al., 2020), and biobank data likely did not reflect all cases, potentially deflating our effect estimates.

The findings of our study can be considered within the context of maternal and child health promotion. While the magnitude of our findings is modestly suggestive, our study provides some
support for reducing prescription opioid usage to limit maternal mental health conditions. Healthcare providers should carefully weigh the risks and benefits of opioid use during pregnancy and consider alternative pain management strategies whenever possible. Moreover, it is essential to consider the socioeconomic disparities in postpartum opioid-related mortality, which are higher in patients with public insurance than those with private insurance (Suarez et al., 2023).

Further research is needed to understand the complex relationship between opioid use and PPD and to develop effective interventions to prevent and treat PPD in opioid-exposed women. This research would benefit from including multiple ancestry groups to replicate these findings. The temporality of which opioids are used (i.e., a trimester-specific exposure) and dosage should be considered in new prospective studies to assess a potential dose-response relationship at various stages with PPD. Moreover, delineating the biological mechanism linking opioid use and PPD could provide more insight into this topic and better inform future genetic studies. Overall, our study underscores the importance of a cautious approach to opioid use during pregnancy and highlights the need for ongoing efforts to promote maternal and child health.
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