Title

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Journal

Psychiatry Research, 360

ISSN

0165-1781

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Publication Date

2026-06-01

DOI

10.1016/j.psychres.2026.117112

Published in final edited form as:

Psychiatry Res. 2026 June ; 360: 117112. doi:10.1016/j.psychres.2026.117112.

Association between premenstrual syndrome and postnatal depression in women with recurrent major depressive disorder

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Ethic statement

All participants provided written informed consent. This procedure was approved by the institutional review boards of all participating hospitals and conducted in accordance with standard research practices in Korea.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the authors used ChatGPT for draft translation and coding for data analysis. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

CRediT authorship contribution statement

Jeong Hun Yang: Writing – original draft, Methodology, Investigation, Conceptualization. **Yong Min Ahn:** Investigation, Data curation. **Sooyeon Min:** Investigation, Data curation. **Yoojin Song:** Investigation. **Heon-Jeong Lee:** Investigation, Data curation. **Seunghee Won:** Investigation, Data curation. **Kyu Young Lee:** Investigation. **Do Hoon Kim:** Investigation. **Ji Hyun Baek:** Formal analysis. **Kyoung-Sae Na:** Formal analysis. **Eun-Jeong Joo:** Formal analysis. **So Hee Lee:** Formal analysis. **Christopher Hyung Keun Park:** Investigation. **Woojae Myung:** Investigation. **So Young Yoo:** Investigation. **Jaesub Park:** Investigation. **Won-Hyoung Kim:** Data curation. **Moon Soo Lee:** Data curation. **Jung Jae Lee:** Data curation. **Sung Joon Cho:** Data curation. **Seok Woo Moon:** Data curation. **Ji-Woon Jeong:** Data curation. **Young Min Choe:** Data curation. **Joo Yun Song:** Data curation. **Kenneth S. Kendler:** Data curation. **Sang Jin Rhee:** Writing – review & editing, Resources, Project administration. **Dongyun Lee:** Writing – review & editing, Resources, Project administration. **Jonathan Flint:** Investigation.

Declaration of competing interest

The authors declare no conflicts of interest.

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Abstract

Postnatal depression (PND) represents a major mental health concern with significant implications for mothers and children. Premenstrual syndrome (PMS) has been suggested as a potential risk factor for PND, although its role among women with recurrent major depressive disorder (MDD) remains unclear. Using data from the Korean Mood Disorder Genetic Study-Depression (KOMOGEN-D), an analysis of 2309 women with recurrent major depressive disorder and at least one childbirth experience was conducted to investigate the association between PMS and PND.PMS was defined by self-reported premenstrual emotional symptoms, and PND was defined as a depressive episode within 6 months postpartum. Logistic regression analysis was performed. Women with PMS demonstrated significantly higher rates of PND than those without PMS (45.5% vs. 22.5%, $p < 0.001$). Younger age (odd ratio [OR]: 0.93, 95% confidence interval [CI]: 0.93–0.94, $p < 0.001$), younger age at menarche (OR: 0.84, 95% CI: 0.8–0.87, $p < 0.001$), PMS (OR: 2.87, 95% CI: 2.4–3.45, $p < 0.001$), childhood sexual abuse (OR: 1.65, 95% CI: 1.33–2.04, $p < 0.001$), and a family history of MDD (OR: 1.76, 95% CI: 1.48–2.1, $p < 0.001$) were associated with PND. A positive association was observed between PMS symptom burden and PND incidence. Women with PND also exhibited earlier onset of depression, longer illness duration, and higher trauma exposure. These findings identify PMS as a marker of a clinically meaningful vulnerability profile within recurrent MDD, underscoring the need for tailored screening and intervention strategies across the reproductive life cycle.

Keywords

Premenstrual syndrome; Postnatal depression; Major depressive disorder; Psychosocial factors; KOMOGEN-D

1. Introduction

Postnatal depression (PND), also known as postpartum depression, represents a significant mental health concern affecting a substantial proportion of new mothers worldwide (Ohsuga et al., 2024). The global prevalence of PND was found to be approximately 17.22% (95% CI 16.00–18.51) in the meta-analysis of PND(Wang et al., 2021). PND remains associated with serious consequences for mothers and children, including impaired maternal-infant bonding and developmental issues among offspring (Misri and Kendrick, 2008; Moehler et al., 2006). Early identification of women at risk for PND remains a clinical priority.

A prior history of major depressive disorder (MDD) represents the primary risk factor associated with PND, with odds ratios (ORs) for developing PND ranging from 2.7

(Johansen et al., 2020) to 9.23 (Chojenta et al., 2016). Multiple psychosocial factors contribute to PND risk, including perinatal anxiety, marital conflict, lack of partner support, stressful life events, unplanned pregnancy, and adverse birth outcomes; none demonstrate an effect size comparable to MDD. Premenstrual syndrome (PMS) is also reported to increase PND risk. A recent meta-analysis that pooled data from 19 studies reported that women with a pre-pregnancy history of PMS had more than double the odds of developing postpartum depression compared to those without PMS (pooled OR: 2.20, 95% confidence interval [CI]: 1.81–2.68) (Cao et al., 2020).

While these findings consistently support the association between PMS and PND in general populations, the existing literature has largely overlooked a clinically important subgroup: women with recurrent MDD. Recurrent MDD, defined as the occurrence of two or more major depressive episodes, represents a distinct clinical entity characterized by greater genetic loading, more pronounced neurobiological alterations, and higher susceptibility to future depressive episodes compared to single-episode depression(Burcusa and Iacono, 2007; Monroe and Harkness, 2011). Given that both PMS and PND are hypothesized to arise from heightened sensitivity to hormonal fluctuations, women with recurrent MDD may represent a uniquely vulnerable population in whom these reproductive mood phenomena converge. However, previous studies examining the PMS–PND association have typically included heterogeneous samples from the general population or primary care settings, without stratifying by depressive illness course. Consequently, whether PMS confers additional risk for PND beyond the already elevated baseline risk in women with recurrent MDD remains unknown. This gap is clinically significant because women with recurrent MDD constitute a high-risk group for perinatal mood episodes, yet targeted screening strategies based on premenstrual symptom profiles have not been established for this population.

It is also important to distinguish between PMS and premenstrual dysphoric disorder (PMDD). PMS refers to a broad range of recurrent physical and emotional symptoms occurring during the luteal phase of the menstrual cycle, whereas PMDD, recognized in the DSM-5 as a distinct depressive disorder, represents a more severe and functionally impairing form characterized by prominent affective symptoms. (2013) PMDD requires prospective symptom confirmation across at least two menstrual cycles and evidence of marked functional impairment, criteria that are not applied to PMS. While both PMS/PMDD and MDD involve depressive symptoms, they differ in their temporal pattern: PMS/PMDD symptoms are confined to the luteal phase and remit after menstruation, whereas MDD episodes are not cycle-dependent. Nevertheless, shared vulnerability to hormonal fluctuations and overlapping neurobiological pathways suggest that these conditions may reflect a common susceptibility to affective dysregulation.

These observations raise questions regarding the independent association of MDD and PMS with PND, possible interactions that may modify risk, and the involvement of additional contributing factors. The largest and most recent investigation addressing this issue, an analysis of >1 million women in the Swedish Medical Birth cohort (2024), identified a bidirectional link between premenstrual disorders and perinatal depression (Yang et al., 2024). Previous studies have suggested that psychiatric disorders, including MDD,

may influence the relationship between PMS and PND (Pilver et al., 2013). Another proposed explanation posits that PMS increases the likelihood of developing MDD or other psychiatric conditions (Hartlage et al., 2001), as indicated by attenuation of associations after adjustment for psychiatric comorbidities in earlier cohort analyses.

In addition to PMS itself and prior depression, multiple psychosocial and biological factors may moderate the risk of PND among women with PMS. Childhood sexual abuse (CSA) has been linked to both PMS and PND, suggesting that early life trauma may sensitize women to reproductive hormonal fluctuations and intensify mood vulnerability (Yang et al., 2022). A hereditary predisposition to psychiatric disorders has also been associated with both PMS and postpartum depression, likely reflecting genetic or familial vulnerability (Jaholkowski et al., 2023; Zacher Kjeldsen et al., 2022). Social support plays a crucial buffering role; women with stronger interpersonal support report lower risk for perinatal depression, whereas low support remains consistently associated with higher symptom severity (Zyrek et al., 2024). Furthermore, earlier age at menarche has been associated with heightened risk for both PMS and PND in several studies (Lancaster et al., 2022; Lu et al., 2021), possibly due to prolonged exposure to cyclical hormonal changes or early psychosocial stressors related to puberty. These findings provide theoretical and empirical support for examining these factors as potential moderators of the PMS–PND relationship. To the best of our knowledge, studies examining the relationship among PND, PMS, and MDD within a cohort of women with recurrent MDD are scarce. This gap in the literature was addressed through an analysis of data from the Korean Mood Disorder Genetic Study-Depression (KOMOGEN-D), a case–control study investigating the genetic basis of recurrent MDD. Few studies have examined the relationship between PMS and PND in East Asian populations, and no large-scale investigation has been conducted in Korea. The KOMOGEN-D dataset, which includes >6000 Korean women with recurrent MDD and corresponding controls, provides a unique opportunity to explore this association in a non-Western context.

In this context, the present study aims to analyze the association between PMS symptom severity and PND risk in a multivariate framework within a dataset of women with recurrent MDD, while identifying additional psychosocial and clinical factors that may independently contribute to PND risk in this high-risk population. By doing so, we seek to extend beyond simple correlation patterns in the existing literature and clarify how premenstrual symptom burden contributes to perinatal depressive outcomes through interaction with underlying depressive vulnerability.

2. Methods

2.1. Participants and study design

The KOMOGEN-D study was established as a large-scale investigation of recurrent major depressive disorder (MDD), aiming to recruit 10,000 women with a history of recurrent MDD in Korea. Recurrent MDD was defined as having a history of at least two major depressive episodes (MDEs), and all cases were clinically confirmed, increasing the likelihood of underlying genetic predisposition. To reduce the probability of conversion to bipolar disorder, a minimum age of 30 years was required for inclusion in the patient group, and only individuals whose first MDE occurred between the ages of 14 and 50 were eligible.

Eligibility criteria required that all four grandparents of both patients and controls be of Korean descent, and individuals with a history of psychosis, bipolar disorder, intellectual disability, cognitive impairment, dementia, or current prescription of cognitive enhancers, as well as those with past or present alcohol or substance use disorders, were excluded. Patients were recruited from outpatient clinics and inpatient wards at participating hospitals nationwide, as well as referred from private psychiatric clinics and community mental health centers when they met inclusion criteria. After a board-certified psychiatrist confirmed the diagnosis of recurrent MDD, trained interviewers conducted standardized structured clinical interviews to collect study data. (Min et al., 2026)

Data from 2309 women with recurrent MDD and at least one childbirth experience were available in the KOMOGEN-D study. PND was assessed within the structured clinical interview by trained interviewers. Participants who reported at least one childbirth were asked whether they had experienced a depressive episode lasting two weeks or longer within six months of childbirth, accompanied by symptoms previously endorsed in the major depressive episode section of the interview (yes/no). For those who responded affirmatively, additional information was collected, including the number of postnatal depressive episodes, the duration of the longest episode (minimum 2 weeks), the age at first postnatal depressive episode, and the shortest interval between childbirth and depression onset (maximum 26 weeks).

PMS was defined based on self-reported emotional symptoms before menstruation. Participants were classified as having PMS if they reported moderate or higher intensity in at least one of the four core symptoms: fatigue, depression, irritability, and mood swings. Each symptom was rated on a 4-point severity scale (none, mild, moderate, severe). This definition, validated in large-scale epidemiological studies such as the Australian Longitudinal Study of Women's Health, demonstrated high validity and practicality for predicting long-term depression, and was considered appropriate for large population-based studies (Hou et al., 2023). At the time of the KOMOGEN-D assessment, PMS was evaluated retrospectively based on participants' recall of premenstrual symptoms rather than at a prospective prenatal or postpartum timepoint. It should be noted that the PMS classification in this study was based on self-reported symptom severity without assessment of functional impairment, and therefore captures a broader spectrum of premenstrual symptomatology than would be identified by formal PMS or PMDD diagnostic criteria. A flowchart illustrating the participant selection process and study design is presented in Fig. 1.

Current psychological distress levels were measured using the depression items from the Symptom Checklist-90 (Hafkenscheid, 1993), with each item rated from 0 (not at all) to 4 (very much). The total score served as a continuous indicator of overall psychological distress.

Childhood sexual abuse (CSA) was assessed using structured interview items adapted from Kendler et al. (Kendler et al., 2004)., who originally developed these items for the Virginia Adult Twin Study to examine the relationship between CSA, stress sensitivity, and major depression in women. CSA was defined as any unwanted sexual experience occurring before the age of 18 and was classified as present when one or more of the following were

reported: sexual demands, genital contact, exposure to sexual acts, sexual coercion, or sexual intercourse. In that study, CSA was shown to produce long-lasting increases in sensitivity to the depressogenic effects of stressful life events, with a dose-response relationship between CSA severity and depression risk.

Family history of MDD was self-reported by asking whether the participant had a parent or sibling diagnosed with MDD. Family history was assessed using adaptations from the Family History Research Diagnostic Criteria (Endicott J et al., 1975), previously validated and field-tested in the VATSPSUD (Kendler et al., 2004) and CONVERGE study (Docherty et al., 2017)

Social support was measured by the number of emotionally supportive close individuals, with response questions branching based on marital status. The final variable represented the number of emotionally close individuals as a continuous variable quantifying the level of social support (Janevic et al., 2004)

2.2. Statistical analysis

The distribution of continuous variables was assessed using the Shapiro-Wilk test. Every continuous variable was non-normally distributed, and the variables were summarized as median (interquartile range [IQR]) and compared using the Mann-Whitney U test. Categorical variables were expressed as frequencies and percentages and compared using chi-square tests.

The analysis procedure began with a comparison of demographic and clinical characteristics according to the presence or absence of PMS and PND, followed by an examination of the trend in PND incidence according to the sum of severity subscale of PMS symptoms. Subsequent analyses included univariate and multivariate logistic regression models incorporating major psychosocial factors and medical history-related variables to identify predictors of PND. Covariates for the multivariate regression model were selected based on statistical significance ($p < 0.05$) in univariate logistic regression analyses, consistent with established covariate screening procedures (Liu et al., 2023). In the multivariate logistic regression analyses, multicollinearity among predictor variables was assessed using variance inflation factors (VIF); a VIF value exceeding 5 was considered indicative of problematic multicollinearity.

All analyses were performed using R statistical software (version 4.3.1), and the main analyses utilized packages such as dplyr, writexl, gmodels, broom, DiagrammeR, ggplot2, and openxlsx. All analyses employed two-tailed tests, and p-values <0.05 were considered statistically significant.

3. Results

3.1. Sample characteristics

A total of 2309 women with recurrent MDD and at least one prior childbirth were included in this analysis. The PMS-positive group consisted of 1274 women, and the PND-positive group consisted of 813 women.

3.2. Comparisons by PMS and PND status

As shown in Table 1, participants with a history of PMS had a higher rate of experiencing PND than those without PMS (45.5% vs. 22.5%), and the number of major depressive episodes was higher among those who experienced PND. Additionally, the age of onset of depressive episodes was earlier among those with PND (31.90 vs. 34.95). Participants with PMS were younger, had an earlier age at menarche, had fewer close interpersonal relationships, and had a higher prevalence of a family history of MDD. A higher proportion of participants also reported experiencing childhood sexual trauma.

Table 2 shows that the PND-positive group was younger than the PND-negative group and had a longer duration of depressive episodes and a higher number of episodes. Additionally, the age of onset of depressive episodes was earlier in the PND-positive group. The prevalence of a family history of MDD and the prevalence of childhood sexual trauma were also higher in this group.

3.3. Relationship between PMS severity and PND

Fig. 2 visualizes the relationship between PMS total severity (sum of severity of each PMS symptom) and the predicted probability of PND using a logistic regression model. The graph shows a gradual increase in the predicted probability of PND as PMS total severity increases. The regression line indicates that as PMS total severity rises, the probability of PND also increases, with this relationship being statistically significant. According to the regression analysis, for each unit increase in PMS Total Severity, the probability of PND increases by approximately 0.15379. The p-value of <2e-16 confirms that this relationship is highly significant and not due to chance. These results suggest a positive relationship between PMS total severity and the risk of PND.

3.4. Factors associated with PND

According to Table 3, PMS (OR: 2.87, 95% CI: 2.4–3.45, $p < 0.001$), CSA (OR: 1.65, 95% CI: 1.33–2.04, $p < 0.001$), and a family history of MDD (OR: 1.76, 95% CI: 1.48–2.1, $p < 0.001$) showed significant positive associations with PND, whereas age (OR: 0.93, 95% CI: 0.93–0.94, $p < 0.001$) and age at menarche (OR: 0.84, 95% CI: 0.8–0.87, $p < 0.001$) exhibited significant negative associations. The number of socially close relationships was not statistically significant (OR: 0.95, 95% CI: 0.89–1, $p = 0.08$). In a multivariate logistic regression analysis of statistically significant variables, age (OR: 0.95, 95% CI: 0.94–0.96, $p < 0.001$), PMS (OR: 2.08, 95% CI: 1.71–2.53, $p < 0.001$), and a family history of MDD (OR: 1.49, 95% CI: 1.24–1.8, $p < 0.001$) remained significant. All variables' VIF values were within the range of 1 to 2, and multicollinearity of concern was not suspected.

4. Discussion

This study examined the association between PMS and PND in 2309 women with recurrent MDD from the KOMOGEN-D cohort. The principal finding was that PMS remained a significant independent predictor of PND (adjusted OR: 2.08, 95% CI: 1.71–2.53) after controlling for age, childhood sexual abuse (CSA), family history of depression, and age at menarche. A positive association was also observed between PMS symptom severity

and PND incidence. In addition, family history of depression and younger age were independently associated with PND, whereas CSA, age at menarche, and social support lost statistical significance after multivariate adjustment.

4.1. PMS as an independent predictor of PND

The robust association between PMS and PND observed in this study is consistent with a large body of prior evidence. A meta-analysis of 19 studies reported a pooled OR of 2.20 (95% CI: 1.81–2.68) for the association between PMS history and postpartum depression (Cao et al., 2020), and a nationwide Swedish register-based study of over one million women demonstrated a bidirectional link between premenstrual disorders and perinatal depression (OR 4.76, 95% CI [4.52,5.01]; $p < 0.001$) (Yang et al., 2024). Our adjusted OR of 2.08 is comparable to these estimates, reinforcing the consistency of this association across different populations and study designs.

Notably, the present study extends prior findings by demonstrating that PMS remains a significant predictor of PND even within a high-risk cohort of women with recurrent MDD. Previous studies examining the association between PMS/PMDD and perinatal depression have been conducted primarily in general population or clinical samples without restricting the study population to women with recurrent MDD (Gastaldon et al., 2022; Pereira et al., 2022). Pereira et al. (2022) noted that existing studies have not adequately considered the association with potential confounding variables, including history of depression throughout life. By focusing exclusively on women with recurrent MDD, our study addresses this gap and demonstrates that PMS confers additional predictive value for PND above and beyond the already-elevated baseline risk attributable to recurrent depression. The severity and breadth of premenstrual symptoms may reflect a graded pattern of risk for postpartum mood disturbance. Although a formal nonlinear dose-response analysis was not conducted, the observed trend is consistent with earlier hypotheses suggesting that greater PMS severity is associated with increased affective instability (Yang et al., 2024).

Several mechanisms may underlie this association. PMS and PND may share a common neurobiological substrate involving heightened sensitivity to fluctuations in gonadal steroid hormones. PMS has been characterized not as a condition arising from abnormal hormone levels but rather from differential neural responsiveness to normal hormonal fluctuations (Huo et al., 2007; Schweizer-Schubert et al., 2020). Similarly, PND has been hypothesized to occur in women who are particularly sensitive to the dramatic perinatal changes in estrogen and progesterone levels (Schiller et al., 2015). This shared hormonal sensitivity model is further supported by genetic evidence showing overlapping polygenic liability between premenstrual disorders and major psychiatric disorders (Jaholkowski et al., 2023). Additionally, genome-wide association studies of postpartum depression have identified significant genetic correlations between PPD and MDD, with cell-type enrichment analyses implicating GABAergic neurons as a convergent mechanism (Guintivano et al., 2023). GABAergic dysfunction, particularly altered sensitivity of GABA-A receptors to allopregnanolone, a neuroactive metabolite of progesterone, has been proposed as a convergent pathway linking PMS, PND, and MDD (Schweizer-Schubert et al., 2020).

4.2. Family history of depression

Family history of depression remained independently associated with PND (adjusted OR: 1.49, 95% CI: 1.24–1.80) in the multivariate model. This finding is consistent with a systematic review and meta-analysis by Zacher Kjeldsen et al. (2022) (Zacher Kjeldsen et al., 2022), which reported that a family history of any psychiatric disorder significantly increased the risk of postpartum depression (pooled OR: 2.08, 95% CI: 1.67–2.59). Although the effect size in our study was somewhat smaller, this likely reflects the fact that our sample was restricted to women with recurrent MDD, in whom genetic and familial vulnerability is already elevated, thereby attenuating the additional effect of family history.

The persistence of family history as a significant predictor in this high-risk cohort suggests that familial transmission of depression operates through multiple pathways beyond the shared genetic architecture indexed by the recurrent MDD diagnosis itself. These may include epigenetic modifications related to early-life stress exposure, intergenerational transmission of maladaptive parenting behaviors, or family-level psychosocial adversity that increases vulnerability to affective episodes during reproductive transitions.

4.3. Age

Younger age at the time of assessment was independently associated with increased PND risk in our study (adjusted OR: 0.95, 95% CI: 0.94–0.96). It is important to note that the age variable in this study reflects the participants' age at the time of the KOMOGEN-D assessment, not their age at childbirth or at the onset of PND. This distinction limits direct comparison with prior studies that have examined maternal age at delivery as a risk factor for PPD. For example, Bottino et al. (2012) reported that younger maternal age at delivery was significantly associated with PPD (OR=0.96 per year, $p = 0.019$) in a cross-sectional study of 811 mothers, interpreting this finding through an evolutionary framework suggesting that diminishing reproductive potential with advancing age may reduce susceptibility to PPD. (Bottino et al., 2012) Conversely, Silverman et al. (2017), in a population-based study of over 700,000 women, reported that PPD risk increased with advanced maternal age among all women (RR=1.25, 95% CI: 1.13–1.37), although among women without a depression history, younger age was a significant risk factor (RR=2.14, 95% CI: 1.79–2.57).(Silverman et al., 2017)

Because the age variable in our study represents the age at assessment rather than at delivery, the observed association most likely reflects a recall bias artifact inherent to the retrospective design. Women who were younger at the time of assessment were more likely to have experienced childbirth and any associated PND more recently, resulting in more vivid recall and higher reporting rates. In contrast, older participants may have experienced PND decades earlier, leading to under-reporting due to the passage of time. This interpretation is supported by the observation that age of onset of depression was also significantly earlier in the PND-positive group, suggesting a temporal relationship between younger current age, more recent reproductive events, and PND reporting. Therefore, the association between younger current age and PND in this study should be interpreted with caution and does not necessarily imply that younger maternal age at delivery is a risk factor for PND in this population. Future studies using age at delivery rather than age at assessment would be

necessary to properly evaluate the role of maternal age in PND risk among women with recurrent MDD.

4.4. Factors not independently associated with PND after multivariate adjustment

CSA was significantly associated with PND in univariate analysis (OR: 1.65, 95% CI: 1.33–2.04) but lost significance in the multivariate model (OR: 1.12, 95% CI: 0.89–1.41). This finding is partially consistent with the mixed evidence reported in the literature. In a systematic review of 43 studies, Alvarez-Segura et al. (2014) reported that the association between maternal lifetime abuse and perinatal depressive symptoms persisted after adjusting for confounding factors in the majority of studies (80%).(Alvarez-Segura et al., 2014) However, the review also identified several studies in which the association between childhood abuse and postpartum depression was not significant, particularly after controlling for confounders such as social support, or when abuse was limited to physical or sexual types without emotional abuse. Similarly, Sorbo et al. (2014), in a prospective study of 53,065 women, found that adult abuse remained strongly associated with PPD (adjusted OR: 1.8, 95% CI: 1.7–1.9) after full adjustment including child abuse, social support, and depression prior to pregnancy, although this study focused on adult rather than childhood abuse.(Sorbo et al., 2014)

Several factors may explain why CSA lost significance in our multivariate model. First, the aforementioned studies examined broader definitions of abuse (lifetime abuse or adult abuse), whereas our study focused specifically on childhood sexual abuse. The effect of CSA on PPD may be more distal and indirect compared to the effects of recent or ongoing adult abuse. Second, and most importantly, our study sample consisted exclusively of women with recurrent MDD, a population in which the variance attributable to early adversity may already be captured by the recurrent MDD diagnosis itself. In contrast, most prior studies were conducted in general population samples where the independent contribution of abuse to perinatal depression would be more readily detectable. Third, CSA may exert its influence on PND indirectly through intermediate pathways such as the development of MDD or PMS, both of which were included in our multivariate model. Kendler et al. (2004) demonstrated that CSA increases stress sensitivity in women with a dose-response relationship between CSA severity and susceptibility to depressive episodes, suggesting that CSA may predispose women to both PMS and recurrent MDD, which in turn increase PND risk.(Kendler et al., 2004) Future studies employing mediation analysis would be necessary to formally test these indirect pathways.

Age at menarche was strongly associated with PND in univariate analysis (OR: 0.84, 95% CI: 0.80–0.87) but was no longer significant after multivariate adjustment (OR: 0.96, 95% CI: 0.91–1.01, $p = 0.08$). Earlier menarche has been associated with both PMS and PND in prior studies (Lancaster et al., 2022; Lu et al., 2021), possibly reflecting prolonged lifetime exposure to cyclical hormonal fluctuations. The attenuation in our multivariate model suggests that the effect of menarche age on PND may be mediated through PMS; that is, women with earlier menarche are more likely to develop PMS, and it is the PMS itself, rather than menarche timing per se, that drives PND risk. This interpretation is consistent

with findings by Lu et al. (2021), who reported that pubertal timing was associated with premenstrual disorders in young adulthood. (Lu et al., 2021)

The number of close social relationships did not reach statistical significance even in univariate analysis (OR: 0.95, 95% CI: 0.89–1.00, $p = 0.08$). This contrasts with population-based studies that have consistently identified social support as a protective factor against PND (Zyrek et al., 2024). Notably, Alvarez-Segura et al. (2014) also reported that in several studies of abused women, a lack of social support emerged as a significant contributor to depressive symptoms, suggesting that social support may serve as an important buffer. The discrepancy in our study may be attributable to the clinical characteristics of our sample. Women with recurrent MDD may exhibit uniformly reduced social functioning and smaller social networks compared to general population samples, resulting in restricted variance that limits the ability to detect a protective effect of social support. Additionally, the measurement of social support in this study was limited to the number of close relationships, which may not adequately capture qualitative aspects of social support such as perceived emotional availability or partner-specific support that have been more consistently associated with PND outcomes(Zyrek et al., 2024).

4.5. Strengths and limitations

The strength of this study lies in its precise analysis of the relationship between PMS and PND in a large, well-characterized dataset of women with recurrent MDD. Multivariate analysis controlling for multiple covariates provided higher interpretive power compared to previous studies that have not controlled for recurrent MDD status. The large sample size ($N = 2309$) and the use of clinician-confirmed diagnoses of recurrent MDD through standardized structured clinical interviews strengthen the reliability of the findings.

However, several limitations should be acknowledged. First, the cross-sectional design prevented the determination of causal relationships between PMS and PND. PMS and PND were both assessed retrospectively, precluding establishment of temporal precedence. Second, reliance on retrospective self-report may have introduced recall bias, especially for childhood trauma, age at menarche, and the occurrence of PND. Although the PND assessment was conducted within a structured clinical interview with reference to the participant's reported major depressive symptoms, it was based on retrospective recall without prospective confirmation or a validated PND-specific screening instrument, which may have led to underreporting of milder episodes or overreporting due to retrospective attribution. Third, PMS was defined based on self-reported premenstrual emotional symptoms without prospective daily symptom tracking and without assessment of functional impairment, which may not fully align with formal diagnostic criteria for PMS or PMDD. The exposure variable in this study may therefore be more accurately characterized as premenstrual symptoms rather than premenstrual syndrome in the strict clinical sense. Fourth, the sample included only women with recurrent MDD, which restricts the generalizability of the findings to broader clinical or community populations. The absence of a non-MDD comparison group precludes conclusions about whether the PMS–PND association differs between women with and without recurrent MDD. Furthermore, because the premenstrual symptom questionnaire did not assess whether symptoms fully

remitted after the onset of menses, we cannot distinguish between pure PMS — in which symptoms are confined to the luteal phase — and premenstrual exacerbation (PME) of the underlying recurrent MDD. Given that all participants had recurrent MDD, it is plausible that a substantial proportion of PMS-positive women in this study experienced PME rather than pure PMS. The pathophysiology and clinical implications of these two conditions may differ(Schweizer-Schubert et al., 2020), and future studies should incorporate assessments of symptom remission after menses to differentiate between these subtypes. Finally, unmeasured confounders such as medication use, obstetric complications, breastfeeding status, and hormonal levels may have influenced the results.

4.6. Conclusion

In conclusion, this study demonstrated that PMS is independently associated with PND in women with recurrent MDD, with the association persisting after adjustment for age, family history of depression, childhood sexual abuse, and age at menarche. These findings support the clinical relevance of assessing premenstrual symptom history as part of prenatal risk stratification in women with recurrent depression. Future prospective studies with hormonal biomarker assessments and mediation analyses are warranted to elucidate the biological and psychosocial pathways linking PMS and PND.

Acknowledgments

We extend our sincere gratitude to our nationwide partners and collaborators, and the dedicated interviewers whose contributions were essential to this research.

Funding

The project is funded by the National Institutes of Health (U01MH126798) and Wellcome Trust (200176/A/15/Z).

Data statement

The datasets generated ana analyzed during the current study are not available.

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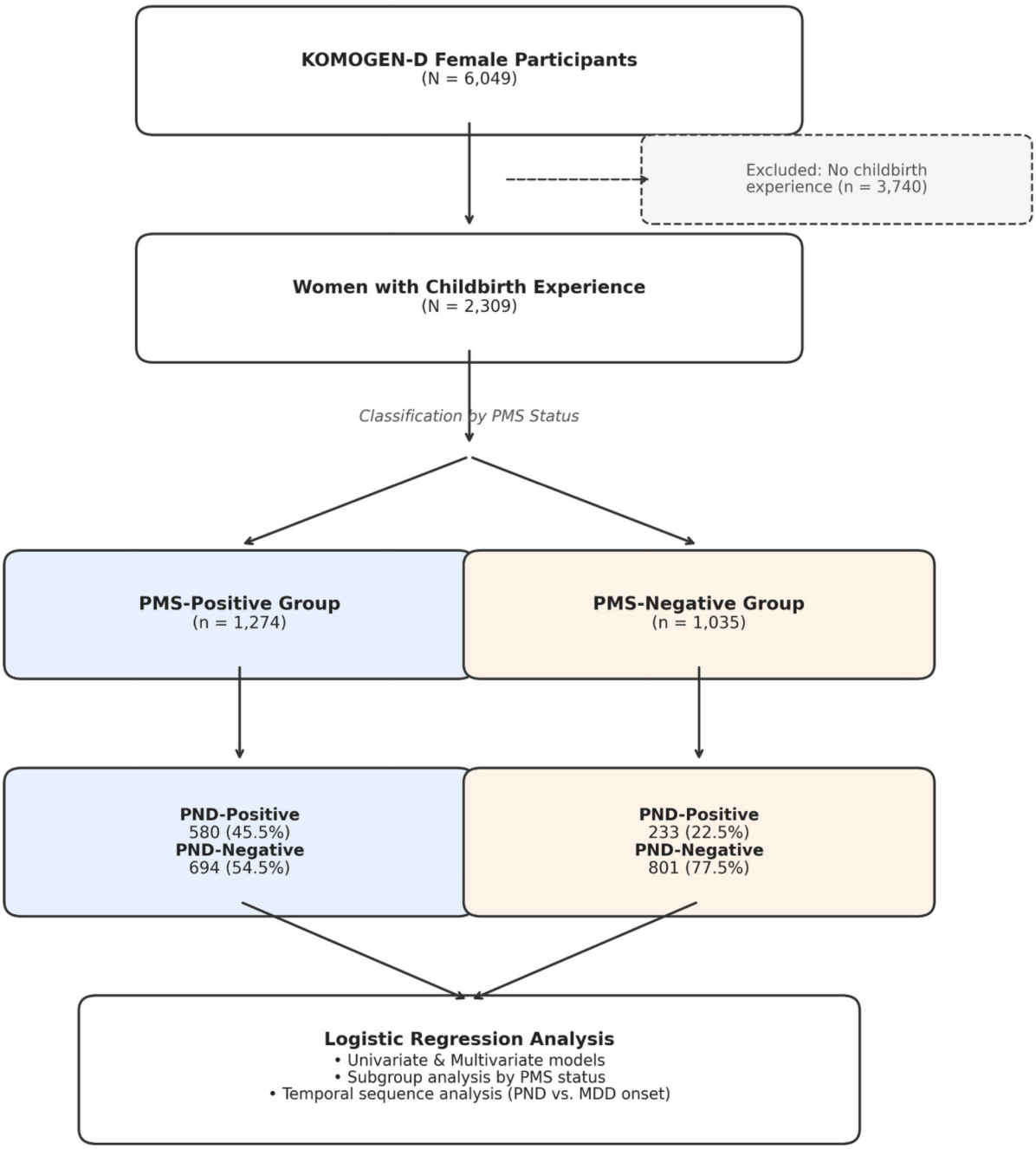

Fig. 1.

Flowchart of participant selection and study design. Of 6,049 female participants in the Korean Mood Disorder Genetic Study-Depression (KOMOGEN-D), 2,309 women with recurrent major depressive disorder and at least one childbirth experience were included. PMS, premenstrual syndrome; PND, postnatal depression; MDD, major depressive disorder.

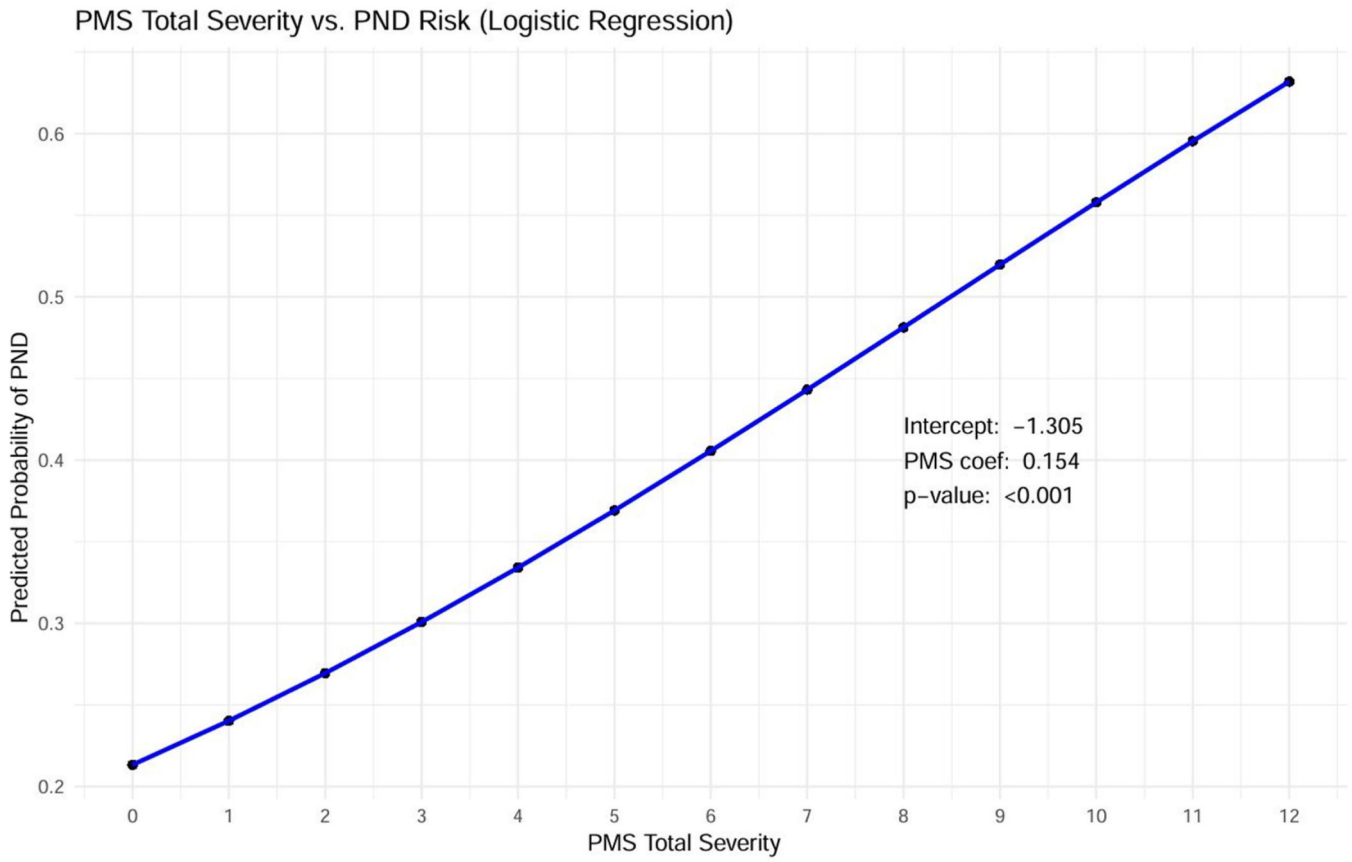

Fig. 2.

Predicted probability of postnatal depression (PND) according to premenstrual syndrome (PMS) total severity score. PMS, premenstrual syndrome; PND, postnatal depression.

Table 1

Demographic and clinical characteristics according to PMS status.

Variable	Category		No PMS (n = 1035)	PMS (n = 1274)	Statistic	p-value	Test
Age			59.00 [52.00–65.00]	52.00 [44.00–59.75]	887,893	<0.001	U
Number of births			2.00 [2.00–2.00]	2.00 [1.00–2.00]	724,878.5	<0.001	U
Length of longest depressive episode			52.00 [16.00–156.00]	52.00 [20.50–156.00]	591,446	0.020	U
Number of depressive episodes			3.00 [2.00–3.00]	3.00 [2.00–3.00]	626,187.5	0.026	U
Age of onset of depression			36.00 [27.00–44.00]	32.00 [25.00–40.00]	774,817.5	<0.001	U
Postnatal depression	0	No	801 (77.5%)	694 (54.5%)	131.23	<0.001	χ^2
	1	Yes	233 (22.5%)	580 (45.5%)			
Number of postnatal depressive episodes†			1.00 [1.00–1.00]	1.00 [1.00–2.00]	60,280	0.002	U
Length of postnatal depressive episodes†			12.00 [4.00–24.00]	16.00 [4.00–48.00]	57,965.5	0.010	U
Age of first postnatal depressive episode†			28.00 [25.00–32.00]	29.00 [25.00–32.00]	64,945	0.385	U
Shortest period between childbirth and depression†			2.00 [0.40–4.00]	2.00 [1.00–8.00]	62,454.5	0.087	U
Age at first menstruation			14.00 [13.00–16.00]	14.00 [13.00–15.00]	755,976.5	<0.001	U
Number of close relationships			2.00 [2.00–3.00]	2.00 [1.00–3.00]	449,926	<0.001	U
Family history of depression (parents and siblings)	0	No	579 (55.9%)	554 (43.5%)	34.96	<0.001	χ^2
	1	Yes	456 (44.1%)	720 (56.5%)			
Number of DSM-5 criteria for MDD			8.00 [7.00–9.00]	8.00 [8.00–9.00]	592,890	<0.001	U
SCL total score			36.00 [27.00–50.00]	46.00 [34.00–58.00]	476,816	<0.001	U
Childhood sexual trauma: if any	0		889 (86.6%)	981 (77.2%)	32.98	<0.001	χ^2
	1		137 (13.4%)	290 (22.8%)			
Education level	Above bachelor	Master or Ph.D.	36 (3.5%)	57 (4.5%)	69.81	<0.001	χ^2
	Bachelor	Bachelor degree	173 (16.7%)	302 (23.7%)			
	Junior middle	Junior middle school	153 (14.8%)	131 (10.3%)			
	Non-primary	Non-preschool/primary	215 (20.8%)	141 (11.1%)			
	Senior middle	Senior middle school	372 (35.9%)	482 (37.8%)			
	Technical junior	Technical school or junior college	86 (8.3%)	161 (12.6%)			
Employment	Disabled	Permanently disabled	44 (4.3%)	31 (2.4%)	22.29	0.001	χ^2
	Keeping house	Keeping house/staying at home	473 (45.7%)	560 (44%)			

Variable	Category		No PMS (n = 1035)	PMS (n = 1274)	Statistic	p-value	Test
	Laid off	Temporarily laid off or sick leave	50 (4.8%)	79 (6.2%)			
	Retired	Retired from a paid job	76 (7.3%)	60 (4.7%)			
	School-other	Going to school or other	58 (5.6%)	108 (8.5%)			
	Unemployed	Unemployed	28 (2.7%)	41 (3.2%)			
	Working	Working for pay	306 (29.6%)	395 (31%)			

Continuous variables: median [IQR] (Mann-Whitney U test). Categorical variables: n (%) (Chi-square test).

U = Mann-Whitney U test; χ^2 = Chi-square test.

†Among participants with postnatal depression only (No PMS n = 233; PMS n = 580).

Table 2

Demographic and clinical characteristics according to PND status.

Variable	Category		No PND (n = 1496)	PND (n = 813)	Statistic	p-value	Test
Age			58.00 [50.00–64.00]	51.00 [43.00–57.00]	830,947	<0.001	U
Number of births			2.00 [2.00–2.00]	2.00 [1.00–2.00]	619,050.5	0.425	U
Length of longest depressive episode			52.00 [16.00–156.00]	60.00 [24.00–156.00]	503,753.5	<0.001	U
Number of depressive episodes			3.00 [2.00–3.00]	3.00 [2.00–4.00]	515,024.5	<0.001	U
Age of onset of depression			37.00 [29.00–44.00]	29.00 [22.00–35.00]	851,774.5	<0.001	U
Number of postnatal depressive episodes‡			NA	1.00 [1.00–2.00]			
Length of postnatal depressive episodes‡			NA	12.00 [4.00–48.00]			
Age of first postnatal depressive episode‡			NA	29.00 [25.00–32.00]			
Shortest period between childbirth and depression‡			NA	2.00 [1.00–6.00]			
Premenstrual syndrome	0	No	694 (46.4%)	341 (41.9%)	131.23	<0.001	χ^2
	1	Yes	802 (53.6%)	472 (58.1%)			
Age at first menstruation			14.00 [13.00–16.00]	14.00 [13.00–15.00]	732,633	<0.001	U
Number of close relationships			2.00 [1.00–3.00]	2.00 [1.00–3.00]	393,814.5	0.076	U
Family history of depression (parents and siblings)	0	No	808 (54%)	325 (40%)	40.96	<0.001	χ^2
	1	Yes	688 (46%)	488 (60%)			
Number of DSM-5 criteria for MDD			8.00 [7.00–9.00]	8.00 [7.00–9.00]	570,323	0.010	U
SCL total score			39.00 [29.00–52.25]	46.00 [34.00–60.00]	475,588.5	<0.001	U
Childhood sexual trauma: if any	0		1254 (84.2%)	616 (76.3%)	20.69	<0.001	χ^2
	1		236 (15.8%)	191 (23.7%)			
Education level	Above bachelor	Master or Ph.D.	48 (3.2%)	45 (5.5%)	77.96	<0.001	χ^2
	Bachelor	Bachelor degree	263 (17.6%)	212 (26.1%)			
	Junior middle	Junior middle school	212 (14.2%)	72 (8.9%)			
	None-primary	Non-preschool/primary	280 (18.7%)	76 (9.3%)			
	Senior middle	Senior middle school	557 (37.2%)	297 (36.5%)			
	Technical junior	Technical school or junior college	136 (9.1%)	111 (13.7%)			
Employment	Disabled	Permanently disabled	53 (3.5%)	22 (2.7%)	19.09	0.004	χ^2
	Keeping house	Keeping house/staying at home	703 (47%)	330 (40.6%)			

Variable	Category		No PND (n = 1496)	PND (n = 813)	Statistic	p-value	Test
	Laid off	Temporarily laid off or sick leave	78 (5.2%)	51 (6.3%)			
	Retired	Retired from a paid job	93 (6.2%)	43 (5.3%)			
	School-other	Going to school or other	113 (7.6%)	53 (6.5%)			
	Unemployed	Unemployed	40 (2.7%)	29 (3.6%)			
	Working	Working for pay	416 (27.8%)	285 (35.1%)			

Continuous variables: median [IQR] (Mann-Whitney U test). Categorical variables: n (%) (Chi-square test).

‡Data available for PND group only.

Table 3

Logistic regression results for factors associated with PND.

Predictor	Univariate regression		Multivariate regression		
	OR (95% CI)	p-value	OR (95% CI)	p-value	VIF
Premenstrual syndrome	2.87 (2.4–3.45)	<0.001	2.08 (1.71–2.53)	<0.001	1.05
Childhood sexual abuse	1.65 (1.33–2.04)	<0.001	1.12 (0.89–1.41)	0.34	1.04
Family history of depression	1.76 (1.48–2.1)	<0.001	1.49 (1.24–1.8)	<0.001	1.01
Number of close social relationships	0.95 (0.89–1)	0.08			
Age	0.93 (0.93–0.94)	<0.001	0.95 (0.94–0.96)	<0.001	1.23
Age at menarche	0.84 (0.8–0.87)	<0.001	0.96 (0.91–1.01)	0.08	1.17