frontiers | Research Topics

Women in psychiatry perinatal psychiatry 2023

Edited by
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Published in
Frontiers in Psychiatry

ISSN 1664-8714
ISBN 978-2-8325-5576-7
DOI 10.3389/978-2-8325-5576-7

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Women in psychiatry 2023: perinatal psychiatry

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Citation

Givrad, S., Hermann, A., Orsolini, L., eds. (2024). *Women in psychiatry 2023: perinatal psychiatry*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-5576-7

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frontiers | Frontiers in Psychiatry

TYPE Editorial
PUBLISHED 07 October 2024
DOI 10.3389/fpsyt.2024.1478300

OPEN ACCESS

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RECEIVED 09 August 2024
ACCEPTED 26 August 2024
PUBLISHED 07 October 2024

CITATION
Givrad S, Hermann A and Orsolini L (2024) Editorial: Women in psychiatry 2023: Perinatal psychiatry.
Front. Psychiatry 15:1478300.
doi: 10.3389/fpsyt.2024.1478300

Editorial: Women in psychiatry 2023: Perinatal psychiatry

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KEYWORDS

perinatal psychiatry, women's mental health, women's health, reproductive psychiatry, women researchers

Editorial on the Research Topic
Women in psychiatry 2023: Perinatal psychiatry

Sex and gender equity in mental health research should be a requisite of a civil and modern society. Mental health professionals, including psychiatrists, should have a social responsibility to advocate for a reduction in social, work, and clinical inequalities for all clinicians and researchers, including those related to sex and gender. An urgent call is needed regarding women's research priority areas, such as mental health issues throughout the reproductive life cycle. Despite advances in improving representation of women in research careers and publications, they are still underrepresented and underrecognized in leading academic roles, especially in mid and late-career (1). Many factors, such as long-standing biases, gender stereotypes as well as inequity in domestic and caretaking roles outside work, have contributed to women's underrepresentation in leading psychiatric research roles. The COVID-19 pandemic notably worsened this gap (2). Correcting long-standing inequities in career advancement for women conducting mental health research will require multiple approaches, including better investment in mentoring programs for women and further development of professional organizations to support the work of women researchers (1). Journals publishing mental health research also have an opportunity to advance this effort. In this Research Topic, Frontiers in Psychiatry highlights the work by and for women in psychiatry.

This Research Topic focuses on the work of women researchers in the field of perinatal psychiatry. There have been many clinical, advocacy, research, and educational activities in the field of perinatal psychiatry over the past decade. The perinatal period is a biologically, psychologically, and socially unique time with two-generational implications for health and disease. Perinatal mood and anxiety disorders (PMADs), for instance, are among the most common complications of pregnancy and can negatively impact the health of pregnant women and their offspring(s) and affect pregnancy and neonatal outcomes. Importantly, minorities, individuals in disadvantaged contexts, and those with medically complex pregnancies may experience remarkably higher rates of mental distress during this vulnerable time. As such, there remains a critical need for better research and understanding of biological and psychological processes and associated risk and protective factors, as well as the best models of delivery of clinical care and education for professionals and the general population.

Women in psychiatry 2023: perinatal psychiatry addresses these gaps and needs by representing a diverse international body of research in several areas of the field of perinatal psychiatry. A series of studies in this Research Topic focus on investigating risk factors for perinatal mental illness. Fish-Williamson and Hahn-Halbrook conducted a meta-analysis and meta-regression of 412 studies to better explore the association between nutritional factors and cross-national prevalence of postpartum depression (PPD) and, interestingly, found the overall prevalence of PPD to be higher than previously estimated. Furthermore, they found higher rates of PPD in countries with higher consumption of sugar-sweetened beverages. Liu et al. performed an observational research followed by a two-sample Mendelian randomization analysis to explore risk factors for PPD. The authors found a significant association between decreased levels of total bilirubin and the incidence of PPD. Albertini et al. investigated the prevalence of prenatal depression and its associated factors in low- and high-risk prenatal patients using a retrospective and prospective cross-sectional design. The authors found that epilepsy, unfavorable economic conditions, and living without a partner increased the risk of prenatal depression. However, they did not find any association between obstetric risk and the prevalence of prenatal depression, a finding that needs to be further investigated. Taking a more behavioral approach to better elucidate factors associated with PPD, Matsunaga et al. found that increased levels of rumination and decreased exposure to reward perception and behavioral activation were associated with higher rates of PPD, particularly in high-risk groups such as those with a history of mental illness. Their study was conducted during the COVID-19 pandemic, a period that led to increased isolation and rumination in the perinatal population. Therefore, the study showed clinical implications that could guide clinicians in providing perinatal population during large-scale stressful and/or traumatic events leading to isolation or higher levels of anxiety/rumination. Bonanni et al. ascertained whether couples who have twins are overly at higher risk for developing a mental illness by not identifying any significant differences in the psychological well-being among parents of twins and singletons through their retrospective study. Their study was performed in a setting in which mothers of twins automatically received psychological support and, hence, might also be representative of the beneficial role of psychological support. Quiray et al. carried out a qualitative study, using focus groups with doulas and interviews with doula clients, to investigate the role doulas can play in supporting perinatal mental health. Their study showed promising results, in particular, if doulas can be provided with appropriate support and training.

Two articles in this Research Topic focused on the role of artificial intelligence (AI) in perinatal psychiatry. In light of rapid developments in the use of AI in healthcare, Turchioe et al. discussed the importance of responsible AI (RAI) by using a patient-centered approach that is based on principles of autonomy, beneficence, justice, trust, privacy, and transparency. Patra et al. provided findings on natural language processing (NLP), one of the AI branches. Their study showed that NLP can guide patients to high-quality lay reading materials as cost-effective, readily available health education related to pregnancy health and PPD.

Acknowledging race/ethnicity as a social construct that influences health disparities, Beck et al. looked at trends in diagnosed behavioral and substance use disorders in 736,325 deliveries between 2008 and 2020. They identified an increase in the diagnosis of mental health disorders over the years, noting the greatest increase in the Asian population.

PMADs are the most common and best-studied mental disorders during the perinatal period. As such, we need more research elucidating the trajectory of other mental illnesses during this period. Sommerfeldt et al. addressed this need by studying the trajectory of eating disorders during pregnancy and the early postpartum period.

Lastly, Athan broadened the lens beyond traditional psychopathology by discussing psychological, social, cultural, and existential transitions experienced by women who are going to become mothers, known as 'matrescence'.

Hopefully, this initiative illustrates the excellent and qualified research work led and guided by women researchers in the field of perinatal psychiatry, and encourage future work for and by women scientists.

Author contributions

SG: Writing – original draft, Writing – review & editing. AH: Writing – review & editing. LO: Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Psychiatry

TYPE Systematic Review
PUBLISHED 15 June 2023
DOI 10.3389/fpsyt.2023.1193490

OPEN ACCESS

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RECEIVED 24 March 2023
ACCEPTED 02 May 2023
PUBLISHED 15 June 2023

CITATION
Fish-Williamson A and Hahn-Holbrook J (2023) Nutritional factors and cross-national postpartum depression prevalence: an updated meta-analysis and meta-regression of 412 studies from 46 countries.
Front. Psychiatry 14:1193490.
doi: 10.3389/fpsyt.2023.1193490

Nutritional factors and cross-national postpartum depression prevalence: an updated meta-analysis and meta-regression of 412 studies from 46 countries

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Background: Postpartum depression (PPD) is the most common complication associated with childbirth and can lead to adverse outcomes for both mothers and their children. A previous meta-analysis found that PPD prevalence varies widely across countries. One potential underexplored contributor to this cross-national variation in PPD is diet, which contributes to mental health and varies significantly around the world. Here, we sought to update the global and national estimates of PPD prevalence using systematic review and meta-analysis. Further, we examined whether cross-national variation in PPD prevalence is associated with cross-national variation in diet using meta-regression.

Methods: To estimate national rates of PPD prevalence, we conducted an updated systematic review of all papers reporting PPD prevalence using the Edinburgh Postnatal Depression Scale between 2016–2021 and combined our findings with a previous meta-analysis of articles published between 1985–2015. PPD prevalence and methods were extracted from each study. Random effects meta-analysis was used to estimate global and national PPD prevalence. To examine dietary predictors, we extracted data on sugar-sweetened beverage, fruit, vegetable, total fiber, yogurt, and seafood consumption from the Global Dietary Database. Random effects meta-regression was used to test whether between-country and within-country variation in dietary factors predicted variation in PPD prevalence, controlling for economic and methodological variables.

Results: 412 studies of 792,055 women from 46 countries were identified. The global pooled prevalence of PPD was 19.18% (95% confidence interval: 18.02 to 20.34%), ranging from 3% in Singapore to 44% in South Africa. Countries that consumed more sugar-sweetened beverages (SSBs) had higher rates of PPD (Coef. = 0.325, p = 0.044, CI:0.010–0.680); Moreover, in years when higher rates of sugar-sweetened beverages were consumed in a country, there were correspondingly higher rates of PPD in that country (Coef. = 0.129, p = 0.026, CI: 0.016–0.242).

Conclusion: The global prevalence of PPD is greater than previous calculations, and drastically varies by country. Sugar-sweetened beverage consumption explained some of the national variation in PPD prevalence.

KEYWORDS

postpartum depression (PPD), diet, sugar sweetened beverages (SSBs), added sugar, global, national, review—systematic, meta analyses

1. Introduction

Mental illness is a leading cause of death and a major public health concern for countries around the world (1). Mental illness in mothers is particularly concerning, as it is not only a leading cause of maternal death in several countries around the world, but it can interfere with parenting behavior and lead to a multitude of adverse physical and emotional child developmental outcomes (2–4). Children with depressed mothers, for example, are more likely to experience psychopathology, behavior issues, and have lower academic achievement (5–7). The adverse impact of maternal depression on offspring may persist into adulthood, raising lifelong risk for mental health, behavioral, and relational issues throughout the lifespan (8–10). In this way, mental health issues can pass down through generations, highlighting the need to understand and prevent maternal mental illness.

Although awareness and research into maternal mental health has increased dramatically in recent decades, rates of mental illness in mothers is still high (11, 12). The most common mental health disorder in mothers is postpartum depression (PPD), defined by the DSM-5 as depressive symptoms experienced in the first 6 months postpartum (13). A recent meta-analysis of 291 studies from 56 countries estimated the global postpartum depression rate to be 17.7%, although prevalence rates varied dramatically by county (11). The lowest rates of PPD were found in Singapore (3%), Nepal (7%), and the Netherlands (8%); while the highest rates were found in Hong Kong (30%), South Africa (37%), and Chile (38%) (11). Examining country-level factors that might explain why rates of PPD vary so dramatically between nations could provide insight into the etiology of PPD and help inform government-led prevention programs. In an initial attempt to do this, Hahn-Holbrook and colleagues (11) conducted a meta-regression that revealed that cross-national variation in PPD prevalence was explained, in part, by economic disparities, fertility rates, and women's access to quality health care resources. Differences in research methodology used across countries explained very little of the cross-national variation in PPD prevalence. Notably, significant cross-national variation in PPD prevalence remained unexplained, suggesting the need to explore other cultural variables (11, 14).

One potential underexplored contributor to cross-national variation in PPD is diet, as diets vary significantly around the world and certain foods such as vegetables, fruit, legumes, nuts, dairy products, fish, and olive oil, may be protective against depression (15). Indeed, scholars have posited that the high levels of PPD seen in the modern day may be due, in part, to evolutionary "mismatches" between our diets today and the diets that humans ate throughout most of human evolution (16). Some of these changes include a decrease in fiber, omega-3 fatty acids, and micronutrients, and an increase in added sugar (16). Thus, we sought to examine whether national variation in dietary patterns predict cross-national variation in postpartum depression. Several dietary factors that have been previously linked to depression risk were considered including yogurt, fiber, fruit, vegetables, omega-3 fatty acids, and sugar-sweetened beverages (SSBs).

1.1. Added sugars

High added sugar consumption can adversely affect physical health and lead to obesity, type II diabetes, cardiovascular disease, and mortality (17–19). Several studies have reported links between added sugar consumption and depression (20, 21). However, very few studies have sought to examine the link between sugar consumption and PPD specifically, although one study from Taiwan found that SSB consumption was associated with higher scores on the Edinburgh postpartum depression scale (EPDS) (22).

Several mechanisms have been proposed as to how sugar consumption may increase depression risk. One proposed mechanism is that sugar consumption causes an increase in certain gut bacteria that disrupt healthy brain function, specifically memory (23). A previous study found that issues in working memory may underlie problems with regulating emotions that lead to mood disorders such as depression (23). Another possible mechanism discussed in previous research is the hypothalamic-pituitary-adrenal (HPA) axis. For example, Harrell and colleagues (24) found that diets high in fructose have the potential to alter HPA function in rats, which was associated with increased risk for depressive-like symptoms (24). As fructose is the most common sweetener in processed foods, especially in SSBs, it is plausible that similar effects could be seen in humans (25). Given that SSBs are the main source of added sugar in diets around the globe (26–29), we sought to test whether countries that consume more SSBs have high higher rates of PPD.

1.2. Seafood

Several studies have also linked higher seafood consumption to reduced risk of depression, and postpartum depression specifically. For example, in a systematic review of six studies, Opie and colleagues (30) concluded that seafood consumption was protective against PPD (30). Another study by Hibbeln (31) examined this relationship at the national level and found that countries that consumed more seafood had lower rates of PPD (31), although national rates of PPD in this study were not derived by meta-analysis, calling into question their relatability. Authors of these studies have suggested that seafood may reduce PPD risk because it is high in omega-3 fatty acids, which can be depleted in mothers during pregnancy.

There are several mechanisms that have been theorized to explain how seafood consumption may reduce depressive symptoms and most focus on the role of omega-3 fatty acids. One important type of such acids is DHA, which is abundant in the brain and alters functions of neural systems that utilize dopamine and serotonin, which play a role in depression (32). Another explanation is that omega-3 fatty acids have anti-inflammatory properties and can reduce the production of pro-inflammatory cytokines that contribute to depressive symptoms (33). In addition, emerging research suggest that omega-3 fatty acids benefit the gut microbiome (34), which is also critical for mental health. Given the previously established connection between seafood consumption and depression, we aimed to explore if national

variation in seafood consumption predicted national variation in PPD prevalence using meta-analytically derived national PPD prevalence estimates.

1.3. Yogurt and Probiotics

Another dietary factor that varies by country is probiotic consumption, which introduces live microorganisms to the gut, altering the microbiome, which may have benefits for the prevention and treatment of depression (35). One of the pathways through which probiotic consumption is thought to reduce the risk of depression is through the gut-brain axis, the bidirectional system that directly and indirectly allows for microbes in the gut to communicate with the brain (36). Through this axis, microbes can affect the brain by regulating HPA functions, and reducing associated pro-inflammatory cytokines, both of which are heavily implicated in the etiology of depression (36). A recent systematic review concluded that probiotic consumption is a promising avenue for the prevention and treatment of depression, although the review did not focus on PPD specifically (37).

Given that there is significant overlap between major depression and PPD, several studies have examined the effectiveness of probiotic consumption for PPD prevention. For example, a randomized controlled trial found that women who received probiotic supplements during pregnancy ($N = 193$) reported significantly fewer symptoms of postpartum depression than women in the placebo group ($N = 187$) (38). These results are consistent with rodent models, in which administering probiotics improves depression-like symptoms in highly stressed rat mothers by altering gut microbiota composition, brain monoamines, oxidative stress, and reversing stress-induced changes in the HPA-axis and brain-derived neurotrophic factor (BDNF) (39). Probiotic supplementation is an effective way of distributing and controlling probiotics exposure in experimental research, however, to examine the effects of probiotics on PPD from a global perspective, focusing on traditional foods containing probiotics may be more fitting.

Although there are many sources of probiotics in diets across the world, yogurt is one of the most ancient and most popular (40, 41). References to yogurt consumption for its health benefits date back to 6000 BC in Indian Ayurveda scripts, although it was not until the 1900s that these benefits were attributed to probiotics (40). Patterns of yogurt consumption vary greatly by country. For example, the majority of people in France consume yogurt every day, which is the case for only 6% of Americans. Research conducted in 15 countries showed that the largest amounts of yogurt were consumed in the Netherlands, France, Turkey, Spain, and Germany. The smallest amounts were consumed in Egypt, Colombia, Russia, Romania, and South Africa (42). In a cohort of 14,539 participants, high consumption of whole-fat yogurt was associated with lower rates of depression in women compared to those who did not consume as much yogurt (43). An additional study of 9,965 participants found that yogurt consumption had a protective effect on depression (44). Thus, it seems plausible that cross-national variation in yogurt consumption might explain some of the national variation in PPD prevalence.

1.4. Fiber

Fiber consumption also varies significantly by country, for example, Brazil's average fiber consumption (12.3 grams/day) is approximately half of Sweden's (23–25 grams/day) (45). Moreover, high fiber consumption has been found to reduce the risk of depressive symptoms (46, 47). One theory to explain this relationship is through the effect of fiber on the gut microbiota (46). Gut microbes can break down foods the human digestive system alone is not easily able to digest (e.g., insoluble fiber found in whole grains, nuts, and certain fruits and vegetables), creating a mutually beneficial relationship (48). Non-human animal studies suggest that fiber consumption may lead to microbiota-driven modification of gene expression and increased production of neurotransmitters that may protect against depressive symptomatology (47). In addition to its benefits for the microbiome, fiber also has anti-inflammatory properties thought to help reduce depression risk (47). Specifically, consuming a diet high in fiber may lower inflammation by modifying the pH and permeability of the gut, and reducing inflammatory compounds that can alter neurotransmitter concentrations and influence depressive symptoms (47).

To the authors' knowledge, no human studies have examined the relationship between insoluble (or any) fiber consumption and postpartum depression risk. However, one rodent study found that high intake of dietary fiber supplements alleviates depression-like symptoms postpartum in female mice (49). Therefore, it seems possible that dietary fiber consumption could play a role in PPD such that countries that consume less fiber have higher rates of PPD.

1.5. Fruits and vegetables

Several studies have found that mothers who consume diets that include plenty of fruits and vegetables have a lower risk of developing PPD (15, 30, 50). Fruits and vegetables contain high levels of fiber, and so it is perhaps not surprising that diets rich in fruits and vegetables are both associated with decreased inflammation, which is a known risk factor for PPD (51, 52). Additionally, as fiber is the key food source for may beneficial gut-bacteria, adequate fruit and vegetable intake is associated with higher bacterial diversity in the gut microbiome (53), which may be protective against PPD (53). In line with the view that fruit and vegetable consumption may be protective against PPD, a cross-sectional survey of 939 women found that higher consumption of fruits and vegetables was associated with lower likelihood of reporting PPD symptoms (54). Thus, it seems feasible that countries that consume more fruits and vegetables may have lower rates of PPD than countries that consume fewer fruits and vegetables.

1.6. The current study

The aims of the current study were four-fold. First, we sought to update the global and national estimates of PPD prevalence provided by Hahn-Holbrook et al. (11) by conducting a systematic review and meta-analysis of studies published between 2016 and

2021. The second aim was to conduct a meta-regression to examine whether the dramatic differences in PPD prevalence by country can be explained by cultural variation in dietary factors like sugar, yogurt, fiber, fruit and vegetable, and seafood consumption. We hypothesized that countries with higher yogurt, fiber, fruit, vegetable, and seafood consumption, on average, would report lower levels of PPD. Moreover, we predicted that countries with higher SSB consumption would report higher levels of PPD. Given that diets in a country can and do change overtime, the third aim of this study was to explore if changes in a country's diet over time corresponded to changes in prevalence rates of PPD over time (hereafter termed within-country variation in PPD). We predicted that, in years when countries consumed more sugar and less yogurt, fiber, fruits, vegetables, and seafood, studies within those countries would report higher levels of PPD. Finally, a fourth study aim was to explore the extent to which methodological differences across studies contributed to variation in PPD prevalence across studies and across countries.

2. Methods

2.1. Research design

This study was carried out in a six-step process. First, we conducted a systematic review of studies reporting PPD prevalence published since the meta-analysis published in 2018 by Hahn-Holbrook and colleagues. Following PRISMA guidelines (55), we extracted information on PPD prevalence and methodological variables from each article. Second, this new dataset was merged with Hahn-Holbrook and colleagues (11) dataset, giving us a database of studies reporting PPD prevalence using the EPDS scale published between 1985 and 2021. Third, we used meta-analysis to estimate an updated global rate of PPD prevalence, as well as updated PPD prevalence estimates by country. Fourth, we conducted a meta-regression to explore the extent to which methodological variation predicted variation in PPD prevalence reported across studies. Fifth, using our meta-analytically derived PPD prevalence estimates for each country, we used meta-regression to test the extent to which national variation in rates of PPD could be explained by cultural variation in dietary factors. In these analyses, we statistically controlled for methodological conventions used across countries and national GDP, as the previous meta-analysis by Hahn-Holbrook et al. (11) identified national poverty as the strongest predictor of cross-national variation PPD. Finally, we conducted a meta-regression to explore whether within-country (mean-centered) variation in dietary consumption patterns across time predicted within-country (mean-centered) variation in rates of PPD across time.

2.2. Search strategy and study selection criteria

In order to update the global and national estimates of PPD prevalence provided by Hahn-Holbrook et al. (11), who included articles published between January 1, 1985 to December 31st 2015, we followed the same search and methodological strategies. To identify new potentially eligible articles published between January 1, 2016 and July 26, 2021, we searched PubMed, PsychINFO, and CINAHL using a combination of the following MeSH terms in the abstract: ("postpartum depression" or "postnatal depression") and ("incidence" or "prevalence"). Additionally, we used the measures and instruments qualifier "Edinburgh Postnatal Depression Scale". The Edinburgh Postpartum Depression Scale (EPDS) is a 10-item self-report, widely-used tool specially designed to measure PPD. We chose to focus on studies that used the EPDS specifically, as this is overwhelmingly the most commonly used tool to measure postpartum depression; 70% of studies that measure PPD use the EPDS (11). Moreover, this measure has been specially designed and validated to detect depressive symptoms in the postpartum period. Other self-report depression scales can be problematic to use in the postpartum period as they contain items about weight gain/loss and sleep changes, which are normal in the postpartum period. Clinical interviews for depressive status typically produce lower prevalence rates than self-report measures. However, we chose to focus on studies reporting prevalence using the gold-standard self-report measure (rather than clinical interviews) given that clinical interviews are rarely conducted in low-income countries given the increased cost and participant burden. We further narrowed our search by only including studies of human females published in English. The exact Boolean searches used for each database are provided in Supplementary material.

To be included in this meta-analysis, studies were required to report PPD prevalence using the EPDS on samples of mothers $\leq$1 year postpartum with a sample size over 20 (56). To address the important issue of the timing of depression postpartum, we coded studies in terms of when in the postpartum period that depression was assessed, allowing us to examine this variable using meta-regression. We also excluded studies reporting PPD prevalence in samples unlikely to be representative of the general population (e.g., studies that exclusively recruited special populations like women with a history of depression, adolescent mothers, mothers seeking treatment for depression, mothers of high-risk infants, etc.).

See Figure 1 for a PRISMA flow diagram reporting identification and selection of studies for this updated meta-analysis. Of the 601 studies that our updated search produced, 407 abstracts were reviewed, and 125 full text articles were assessed for eligibility. Of these, 104 studies published between January 2016 and July 2021 met our inclusion criteria. These studies were coded for methodological and PPD prevalence, and then this dataset was merged with the from Hahn-Holbrook et al. (11), resulting in a full dataset of 412 studies that could be included in this updated meta-analysis.

2.3. Data extraction

The following methodological variables were coded from each study: PPD prevalence, total sample size, EPDS cutoff score employed, and the timeframe postpartum in which PPD was assessed. To get one estimate of PPD prevalence per study, data from longitudinal studies reporting PPD in the same women at multiple time points were merged by averaging the PPD prevalence

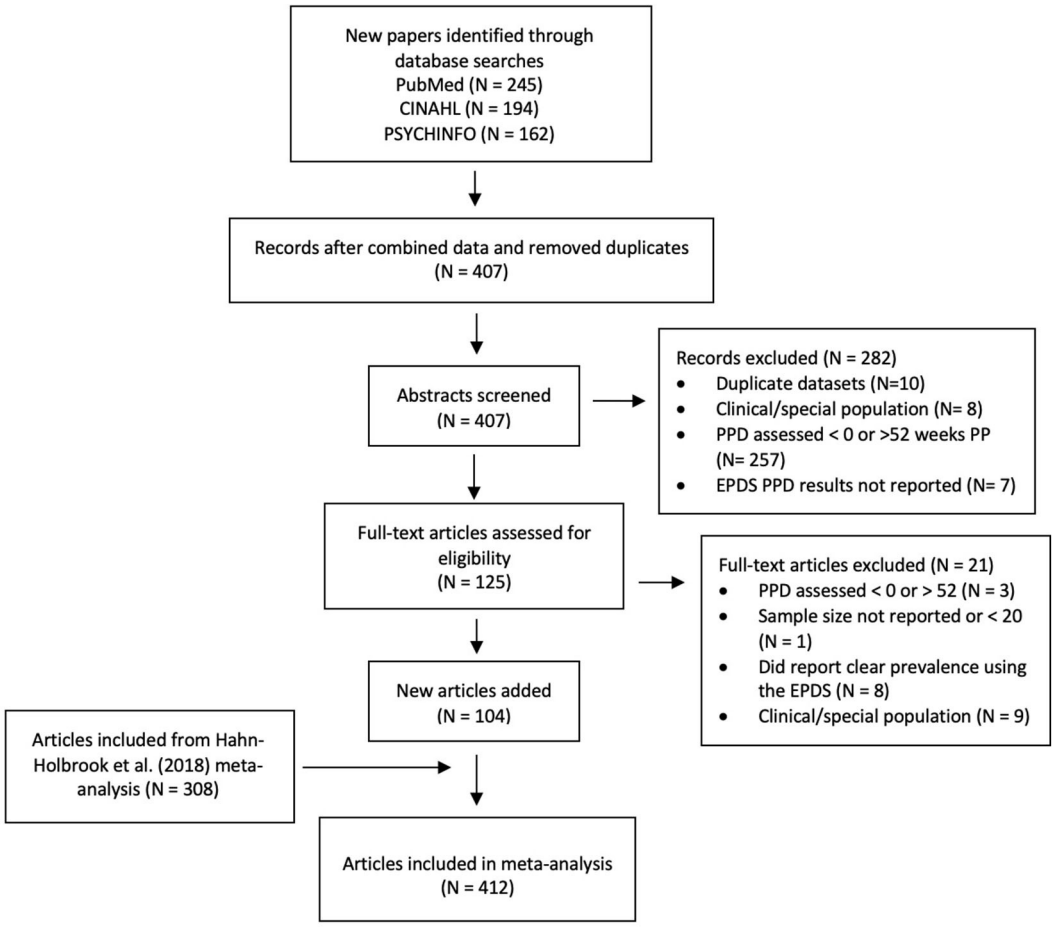

FIGURE 1
PRISMA flow diagram reporting identification and selection of studies for the meta-analysis.

over the time points weighted by the sample size at each time point. Also, if multiple prevalence rates were reported in the same study using different EPDS cutoffs, the prevalence rate from the lowest EPDS cutoff was chosen by default. This decision could cause a bias toward higher estimates of PPD incidence; therefore, we also used meta- regression to estimate PPD prevalence at the standard recommended EPDS cutoffs for possible (9/10) and probable (12/13) PPD (56). To investigate whether studies including women earlier or later in the postpartum period report higher PPD prevalence, we coded the range of the timeframes postpartum during which PPD was assessed and used this score to predict PPD prevalence in meta-regression.

2.4. Methodological variables

Previous studies indicated that some of the differences in PPD prevalence found across studies and between countries can be explained, in part, by methodological differences (11, 57). For example, it is possible that scientists in some countries use lower PPD cutoffs scores more often than scientists in other countries, leading to the appearance of cross-national variation in PPD, when really it is just that some countries set lower symptom thresholds than others. To investigate the role of methodological differences in cross-national PPD prevalence, national averages for each study N, EPDS cutoff score, age of baby at start of data collection, length of assessment window, and year published were included in meta-regression models.

2.5. Dietary factors

This study examined several dietary factors that have been associated with depression in previous research, namely: fiber, yogurt, seafood, SSBs, vegetables, and fruit. To assess national rates of dietary consumption, we used estimates collected by the Global Dietary Database (GDD) (58). The database is part of the Global Nutrition and Policy Consortium, an initiative based at the Tufts Friedman School of Nutrition Science and Policy. GDD data was collected through nationally representative surveys when available, and, when national surveys were not available, multiple smaller surveys that encompassed people from different parts of the country were aggregated. For countries with no surveys available,

sources such as the WHO Infobase were used (58). We used the national consumption of foods measured in terms of grams per day, excluding dietary supplements (e.g., pills). Dietary fiber includes intake from all food sources, including fruits, vegetables, grains, legumes, and pulses. Yogurt data includes total intake of all types of yogurts and fermented milk. Seafood includes the total daily intake of fish and shellfish. SSB data includes intake of any beverage with added sugars having ≥ 50 kcal per 8 oz or 236.5 g of added sugar per serving, including commercial or homemade beverages, soft drinks, energy drinks, fruit drinks, punch, lemonade, and frescas. The SSB variable excludes fruit and vegetable juices with no added sugar, and non-caloric artificially sweetened beverages. Fruit includes total intake of fresh, frozen, cooked, canned, or dried fruit, and excludes fruit juices and salted or pickled fruits. Vegetables include total intake of fresh, frozen, cooked, canned, or dried vegetables, and excludes vegetables juices, salted or pickled vegetables, starchy vegetables such as potatoes, and legumes such as beans. Given that dietary patterns in a country can and do change over time, food consumption in the GDD is reported in yearly intervals. This within-country variation in food and beverage consumption was taken into account in our analysis by mean-centering food consumption within each country, giving us a variable that captures whether consumption of each food was higher or lower in a given year than the country's national average.

2.6. National GDP

Previous research has identified Global Domestic Product (GDP) per capita as a significant predictor of cross-national PPD prevalence (11). As GDP may relate to national dietary habits, we wanted to statistically adjust for this factor in models testing the association between PPD and dietary factors. National GDP data (in adjusted US dollars) were obtained from the World Bank (59).

2.7. Data analytic strategy

Following recommendations for meta-analysis of prevalence (60), we used a double-arcsine transformation of the PPD prevalence data before calculating the study weights and 95% confidence intervals (CIs) to avoid undue influence of weights obtained for studies with low or high prevalence (prevalence close to 0 or 1). To test for heterogeneity in the data, both the Cochran Q test statistic and the I^2 statistic were conducted (61). The same procedure was followed to create meta-analytically derived national estimates of PPD prevalence based solely on the studies available from each country. Meta-analytic estimates of PPD prevalence could not be calculated in countries with fewer than two studies ($N = 21$) (62). All meta-analyses were conducted using the program MetaXL and the "prev" command (60).

Three sets of meta-regressions were performed, the first addressing which methodological factors predicted variation in PPD across all studies, regardless of the nation in which the study was conducted. The second addressed methodological and dietary predictors of PPD variation across nations. The third addressed methodological and dietary predictors of PPD variation within-nations across time. All meta-regression analyses were performed in STATA 14 (63) using the "metareg" command with random-effects models (because all tests indicated significant heterogeneity). To obtain the standard errors needed to weight studies (or nations) for meta-regression in STATA, we transformed the 95%-CIs provided by MetaXL using the following formula (upper 95% CI—lower 95% CI)/3.92.

Funnel plots were used to test whether papers were more or less likely to be published if they had higher or lower PPD prevalence. Results were considered statistically significant if p-values were under 0.05. Effect sizes are reported as unstandardized coefficients and R^2 values obtained in meta-regression models.

3. Results

3.1. Meta-analysis of global PPD prevalence

792,055 women from 412 studies were included in this meta-analysis. Table 1 presents the data extracted from the 103 new studies published since the Hahn-Holbrook and colleagues (11) meta-analysis. The updated global pooled prevalence of PPD across all 412 studies was 19.18% (95% CI: 18.02 to 20.34%). There was a significant degree of heterogeneity between studies ($Q = 40{,}688.45$, $p = 0.00$, $I^2 = 99\%$). Adjusting for the recommended EPDS cut-offs yielded a global PPD prevalence of 19.9% (CI: 18.31 to 21.49%) for possible PPD (EPDS cutoff of 10) and 18.28% (CI: 16.56 to 19.9%) for probable PPD (EPDS cutoff of 13). There was no evidence of publication bias as a function of PPD prevalence rate reported in studies (see Figure 2).

3.2. Meta-regression of between-study variation

Table 2 presents the results of the meta-regression testing the extent to which methodological variables predict variation in PPD prevalence across studies. We found that studies with smaller sample sizes tend to report higher levels of PPD prevalence (Coef. = −0.117, $p = 0.019$; CI: −0.215 to −0.019). Studies that used lower EPDS cutoff scores reported significantly higher PPD prevalence (Coef. = −0.105, $p = 0.44$; CI: −0.207 to −0.003). Studies with a longer window of PPD assessment tended to report higher levels of PPD (Coef. = 0.161, $p = 0.003$, 95% CI: 0.056 to 0.266). No other methodological variables predicted between-study variation in PPD. Together, methodological variables accounted for 4.63% of the variance in PPD prevalence between studies [$F[5, 374] = 4.68$, $p < 0.05$].

3.3. Meta-analyses of national PPD prevalence

See Figure 3 for meta-analytically derived estimates of PPD prevalence in 46 countries. National sample sizes

TABLE 1 New studies included in this meta-analysis published January 2016–July 2021.

Reference	*n*	Depression prevalence (%)	Cut-off used	Postpartum assessment (weeks)	Country
Ogbo et al. (64)	17,564	0.03	13	0–6	Australia
Azad et al. (65)	376	0.39	10	0–52	Bangladesh
Abuchaim et al. (66)	205	0.31	10	0–9	Brazil
Avilla et al. (67)	287	0.13	11	4–6	
Corrêa et al. (68)	3,060	0.20	11	4–14	
Farías-Antúnez et al. (69)	3,838	0.28	10	52	
Halal et al. (70)	2,222	0.28	13	13	
Lei et al. et al. (27)	10,223	0.26	13	26–52	
Lorentz et al. (71)	50	0.35	10	0–26	
Dennis et al. (72)	97	0.08	10	1–8	Canada
Emerson et al. (73)	46,863	0.13	10	6–12	
Falah-Hassani et al. (74)	522	0.24	10	1–8	
Gan et al. (75)	2546	0.11	10	6	China
Guo et al. (76)	438	0.22	9.5	6	
Huang et al. (77)	241	0.10	9.5	0–26	
Li et al. (78)	240	0.16	12	1–4	
Liang et al. (79)	864	0.30	10	6–12	
Liu et al. (80)	1,204	0.23	13	6	
Liu et al. (81)	882	0.07	11	0–4	
Long et al. (82)	242	0.13	13	26	
Peng et al. (83)	1,325	0.27	10	2–8	
Peng et al. (84)	4,813	0.12	10	6	
Shi et al. (85)	213	0.16	12	0	
Wang et al. (86)	1,126	0.12	13	2–8	
Xiong et al. (87)	468	0.56	10	6	
Zhou et al. (88)	288	0.10	9	0–8	
Zhou et al. (89)	228	0.26	13	4	
Ding et al. (90)	308	0.12	10	6	
Stylianides et al. (91)	543	0.28	12	6	Cyprus
Fiala et al. (92)	3,233	0.11	13	6–26	Czechia
Ahmed et al. (93)	257	0.34	13	9–26	Egypt
Meky et al. (94)	170	0.04	14	8–16	
Adamu et al. (95)	618	0.23	13	0–6	Ethiopia
Dadi et al. (96)	916	0.09	6	2–8	
Dadi et al. (97)	866	0.09	13	26	
Wubetu et al. (98)	308	0.16	13	0–6	
Fritel et al. (99)	1,413	0.13	10	16–35	France
Koutra et al. (100)	1,037	0.14	13	8	Greece
Ana et al. (101)	1,406	0.32	13	0	India
Badiya et al. (102)	347	0.09	10	0–13	

(Continued)

TABLE 1 (Continued)

Reference	*n*	Depression prevalence (%)	Cut-off used	Postpartum assessment (weeks)	Country
Jha et al. (103)	1,004	0.17	10	0	
Joshi et al. (104)	300	0.19	10	0–50	
Murry et al. (105)	284	0.22	12	6–8	
Nurbaeti et al. (106)	283	0.20	13	4–13	Indonesia
Nurbaeti et al. (107)	166	0.20	12	4	
Abdollahi et al. (108)	1,910	0.19	12	13	Iran
Ezzeddin et al. (109)	325	0.35	13	13–35	
Afshari et al. (110)	505	0.39	12	2–26	
Iranpour et al. (111)	360	0.35	13	0–13	
Daoud et al. (112)	1,128	0.10	10	6–26	Israel
Mazor et al. (113)	120	0.33	10	0	
Bruno et al. (114)	110	0.05	10	13–26	Italy
Clavenna et al. (115)	2,706	0.05	13	8–12	
Cozzolino et al. (116)	105	0.19	10	0–52	
Ostacoli et al. (117)	163	0.44	11	0–3	
Cui et al. (118)	80,872	0.09	9	4	Japan
Honjo et al. (119)	86,490	0.09	9	4	
Iwata et al. (120)	2,709	0.12	9	4–26	
Matsumura et al. (121)	90,194	0.13	9	4–26	
Okubo et al. (50)	1,316	0.08	9	8–40	
Muchanga et al. (122)	82,489	0.14	9	0–5	
Shibata et al. (123)	258	0.15	9	0	
Suzuki et al. (124)	809	0.14	9	4	
Takehara et al. (125)	1,306	0.12	9	0–12	
Zejnullahu et al. (126)	247	0.21	12	6	Kosovo
Inthaphatha et al. (127)	428	0.32	10	6–8	Lao People's Democratic Republic
Badr et al. (128)	150	0.19	13	0	Lebanon
Radzi et al. (129)	387	0.80	10	0–52	Malaysia
Abdul et al. (130)	458	0.20	13	4–13	Maldives
Suárez-Rico et al. (131)	293	0.39	13	4–12	Mexico
Bhusal et al. (132)	346	0.17	13	4–14	Nepal
Chalise et al. (133)	242	0.17	12	0–26	
Maharjan et al. (134)	330	0.15	13	0–12	
Sulyman et al. (135)	483	0.22	13	0	Nigeria
Shakeel et al. (136)	643	0.09	10	14	Norway
Qandil et al. (137)	97	0.33	11	1–25	Palestine
Labrague et al. (138)	165	0.16	10	6	Philippines
Drozdowicz-Jastrzebska et al. (139)	84	0.12	12	0	Poland
Jaeschke et al. (140)	434	0.15	13	6–12	
Maliszewska et al. (141)	546	0.33	8	0	

(Continued)

TABLE 1 (Continued)

Reference	*n*	Depression prevalence (%)	Cut-off used	Postpartum assessment (weeks)	Country
Nasr et al. (142)	174	0.39	13	0–24	Saudi Arabia
Almutairi et al. (143)	113	0.26	15	1–6	
Alzahrani et al. (144)	217	0.17	13	8–10	
Mokwena et al. (145)	406	0.57	13	0–52	South Africa
Fan et al. (146)	1,349	0.12	9	1–4	Sri Lanka
Khalifa et al. (147)	223	0.06	12	13–35	Sudan
Eckerdal et al. (148)	3,888	0.13	12	6	Sweden
Roumieh et al. (149)	1,105	0.28	13	4–7	Syria
Lin et al. (150)	474	0.16	13	26	Taiwan
Lin et al. (151)	344	0.08	10	6–8	
Lin et al. (152)	180	0.09	7	4	
Bay et al. (153)	550	0.25	13	0–4	Turkey
Bolak Boratav et al. (154)	87	0.48	12	13–26	
Çelik et al. (155)	63	0.43	13	8	
Demirel et al. (156)	461	0.31	13	2–52	
Dikmen-Yildiz et al. (157)	858	0.26	13	4–26	
Sahin et al. (158)	497	0.05	13	4–6	
Yilmaz et al. (159)	530	0.25	13	8–52	
Alhammadi et al. (160)	504	0.33	10	1–26	United Arab Emirates
Emerson et al. (73)	43	0.12	10	9–26	USA
Kothari et al. (161)	249	0.04	12	2–26	
Magliarditi et al. (162)	970	0.12	10	0	
Soffer et al. (163)	1,113	0.07	10	6	
Do et al. (164)	116	0.28	12	0–52	Vietnam

TABLE 2 Between study predictors of postpartum depression prevalence.

	Coeff.	P-value	95% CI	
Study *N*	−0.117	0.019	−0.215	−0.019
EPDS cutoff score	−0.105	0.044	−0.207	−0.003
Age of baby at start	−0.174	0.001	−0.277	−0.071
Assessment window	0.161	0.003	0.056	0.266
Year published	−0.022	0.664	−0.096	0.079

ranged from 332 to 353,444 women. National estimates of PPD ranged from 3% in Singapore, 8% in Netherlands, and 11% in Switzerland, to 32% in Vietnam, 38% in Chile, and 44% in South Africa. Meta-analysis suggested that there was significant heterogeneity in PPD prevalence between nations ($Q = 8{,}130.37$ $p < 0.00$, $I^2 = 99\%$), suggesting the need for meta-regression to explain cross-national variation in PPD prevalence.

3.4. Meta-regression of predictors of between-country variation

See Table 3 for the results of a meta-regression in which national averages of methodological variables, along with economic and dietary factors, were entered together to predict cross-national variation in PPD prevalence. Of the methodological variables, only the timing of the start of the assessment window predicted cross-national variation in PPD prevalence, with nations that tended to measure PPD earlier in the postpartum reporting higher PPD levels (Coef. $= -0.413$ $p = 0.037$; CI: -0.800 to -0.027). Methodological variables alone (when dietary and economic factors were removed from the model) accounted for 10.88% of the total between-country variation in PPD prevalence. GDP did not predict cross national PPD prevalence when methodological and dietary factors were included in the model. In terms of dietary factors, SSB consumption emerged as the only significant dietary factor that predicted cross-national PPD prevalence. This effect remained statistically significant when methodological, economic, and other dietary factors were included in the model. Specifically, countries that consumed more SSBs had higher levels of PPD (Coef. = 0.345,

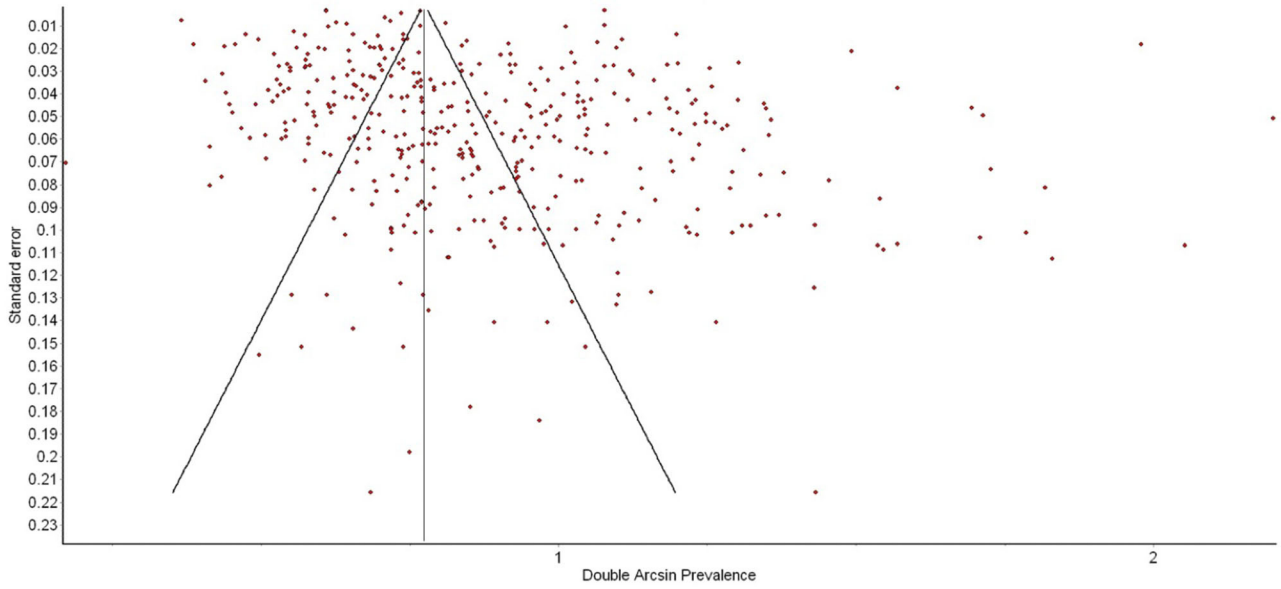

FIGURE 2
Funnel plot of postpartum depression (PPD) prevalence as a function of prevalence estimate standard error. There was no evidence of publication bias.

$p = 0.044$; CI:0.010 to 0.680). SSB consumption alone accounted for 11.42% of between-study variation in PPD prevalence (see Figure 4).

3.5. Meta regression of within-country variation

Given that this study includes research on PPD conducted over 40 years, it is important to consider the fact that dietary patterns within a country can change dramatically over time. For example, daily SSB consumption in Japan was approximately 109 grams per person, per day in 1997 but has decreased to about 86 grams in 2018, representing a 21.1% decrease over time. Therefore, we examined whether postpartum depression rates tended to be higher in a country in years when they ate more or less of certain foods. To do this, we matched the year that the PPD study was published to the dietary behavior in that country for that given year. Then, to isolate within-country variation, we created country specific z-scores that mean-center the dietary intake for each country over time, with higher scores representing more consumption of a dietary factor relative to that country's average consumption over-time. We then used these country mean-centered scores to predict country mean-centered variation in PPD (see Table 4 for results). We found that, in years when countries consumed more SSBs, studies within that country tended to report higher levels of PPD (Coef. = 0.129, $p = 0.026$; CI:0.016 to 0.245. In terms of methodological variables, when studies within a country measured PPD earlier and using a lower EPDS cutoff, compared to the county's average, the studies tended to report higher PPD.

4. Discussion

This study represents the largest meta-analysis and meta-regression on postpartum depression prevalence in the literature to date. We found that the unadjusted global prevalence rate of PPD in studies utilizing the EPDS scale is 19.18% (95% CI: 18.02 to 20.34%). Adjusting for the recommended EPDS cutoffs yielded a prevalence of 19.9% for possible PPD ($\geq$10) and 18.28% for probable PPD ($\geq$13). These estimates are slightly higher than the previous calculation by Hahn-Holbrook et al. (11), which found a global PPD prevalence of 17.7% (95% CI: 16.6–18.8%) (11). One explanation for this discrepancy is that the current study adds new data with a higher proportion of studies from relatively low- and middle-income countries, that tend to report higher rates of PPD (57). Between South Africa, which has the highest PPD prevalence rate (44%), and Singapore, which has the lowest PPD prevalence rate, there is a 41% difference. Considering there are many low-income countries missing from this analysis, it is plausible that global PPD is even more prevalent than our findings suggest. While several methodological variables predicted cross-national variation in PPD, specifically the timing of assessment and EPDS cutoff used, the strongest individual predictor in this study was SSB consumption.

Our meta-regression revealed that SSB consumption predicted PPD prevalence both between-countries and within-countries. Specifically, countries that consumed more SSBs, on average, had higher rates of PPD prevalence. This finding alone could be attributed to other cultural differences that co-vary with SSB consumption, although this effect was still significant when methodological factors and GDP were included in the model. However, we also found that, within the same country, in years with

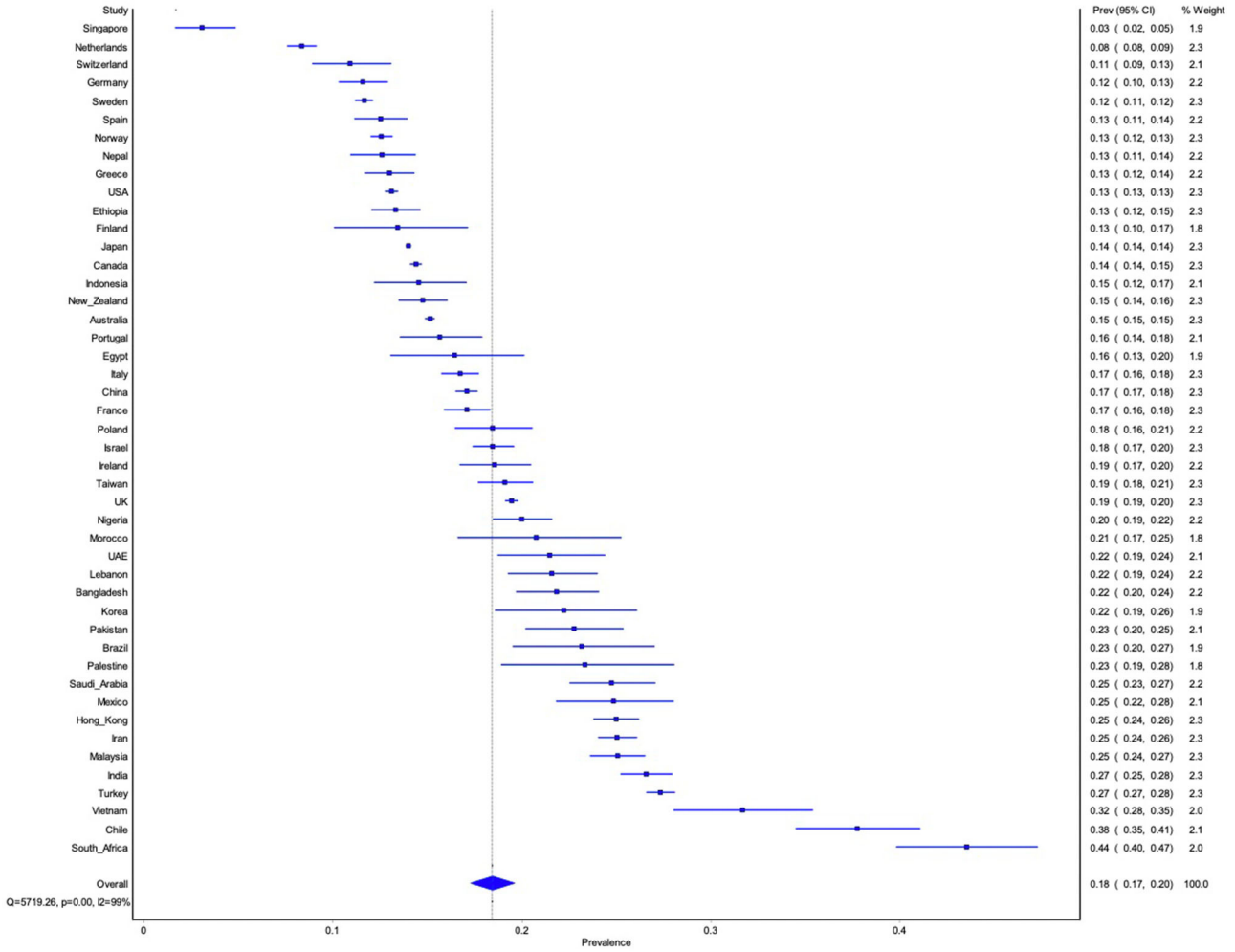

FIGURE 3
Forest plot of between-country variation in PPD prevalence.

higher SSB consumption, studies tended to report higher rates of PPD in that country. This within-country finding lends credence to the hypothesis that it is SSB consumption, and not some other cultural factor, that contributes to higher rates of PPD.

The current study did not find a statistically significant association between seafood consumption and cross-national PPD prevalence, contradicting a previous report by Hibbeln and colleagues (31). Specifically, the previous study correlated DHA in the milk of breastfeeding mothers to PPD rates by country ($N = 23$), and found that countries that consumed more seafood tended to have lower rates of PPD prevalence (31). There are several possible reasons for the discrepancy between our current findings and this previous report. For example, the current study examines twice the number of countries ($N = 46$) and includes countries with more diverse economic conditions. Additionally, the current study used meta-regression which weighted countries and studies, and controlled for methodological variables and GDP, while Hibbeln (31) did not control for these confounding variables. Although our findings were not significant, the effect we found was in the same direction as Hibbeln (31). Additionally, Hibbeln (31) was published over two decades ago, and it is possible that breastfeeding women were not discouraged from consuming certain seafood in the same way they are now due to concerns surrounding mercury poisoning (165). Future directions focusing on PPD and seafood consumption, particularly seafood high in omega-3 fatty acids, is warranted. In addition to seafood consumption, we found no relationships between fiber, yogurt, fruit, and vegetable consumption and national PPD prevalence. Despite these null results at the cross-national level, we encourage researchers to continue to examine the relationship between these dietary factors and PPD.

4.1. Implications

Our results have several important implications for research and policy to prevent PPD. For example, our research suggests that policies that help reduce SSB consumption may help reduce

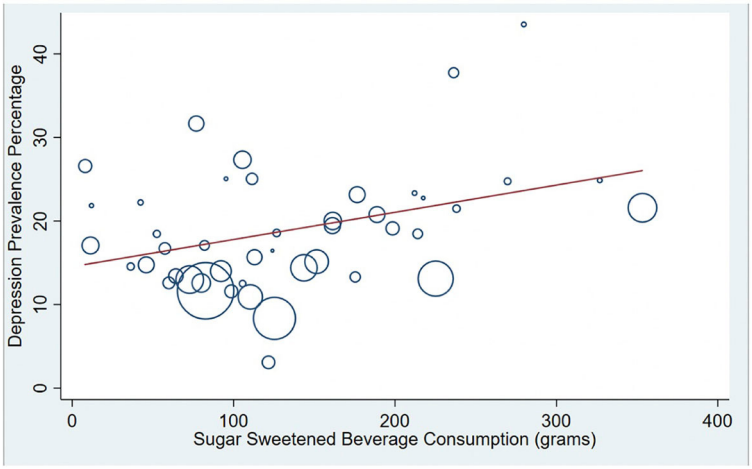

FIGURE 4
Correlation between National PPD prevalence and National Sugar Sweetened Beverage (SSB) consumption. Bubble plots are presented showing the significant positive association between SSB consumption and national postpartum depression (PPD) prevalence (R-squared = 11.4%). Countries with larger bubbles had larger sample sizes and were weighted accordingly in meta-regression models.

TABLE 3 Between-country predictors of postpartum depression prevalence.

	Coeff.	P-value	95% CI	
Study *N*	1.335	0.434	−2.121	4.790
Age of baby at start	−0.413	0.037	−0.800	−0.027
Assessment window	−0.144	0.589	−0.684	0.396
EPDS cutoff score	0.220	0.524	−0.480	0.919
GDP	−0.238	0.318	−0.719	0.243
Fiber consumption	0.016	0.935	−0.376	0.408
Yogurt consumption	−0.017	0.933	−0.434	0.400
Seafood consumption	−0.103	0.513	−0.425	0.218
SSB consumption	0.344	0.044	0.010	0.679
Vegetable consumption	0.064	0.747	−0.338	0.465
Fruit consumption	−0.160	0.416	−0.559	0.238

TABLE 4 Within-country variation in dietary and methodological factors predicting within-country variation of postpartum depression prevalence across time.

	Coeff.	P-value	95% CI	
Study *N*	−0.165	0.002	−0.271	−0.059
EPDS cutoff score	−0.259	0.000	−0.366	−0.153
Age of baby at start	0.018	0.787	−0.112	0.148
Assessment window	0.126	0.023	0.017	0.234
Year of publication	−0.082	0.245	−0.219	0.056
Fiber consumption	−0.001	0.982	−0.125	0.122
Yogurt consumption	−0.034	0.650	−0.179	0.112
Seafood consumption	0.070	0.260	−0.052	0.193
SSB consumption	0.129	0.026	0.016	0.243
Vegetable consumption	−0.078	0.287	−0.223	0.066
Fruit consumption	−0.067	0.367	−0.214	0.079

All variables were Z scored and mean centered.

PPD prevalence. There are several existing policies shown to reduce SSB consumption at the national and regional level. For example, implementing a "sugar tax" at the national level disincentivizes the consumer from purchasing SSB by increasing the overall price. Therefore, causing a loss in SSB revenues and encouraging SSB companies to reduce the sugar in their product so that it does not qualify as a high-sugar product. In addition, the extra tax revenue from this strategy can then be used to offset the health care costs associated with sugar-related disease (166). Currently, 45 countries in the world have some type of sugar tax, however, in the US, sugar taxes are in place in only a few cities. Due to the availability of cross-national and within-country sugar consumption data, future research could explore whether implementing sugar taxes changes national rates of depression. While a sugar tax is a good start, more aggressive policies and behavioral health campaigns focusing on limiting SSB consumption may also be necessary. For example, interventions could focus on limiting the consumption of common ingredients in most SSBs. In the last 50 years, the use of high fructose corn syrup has increased dramatically, largely due to the fact that it is inexpensive and manufacturing friendly (167). National and local policies to reduce the use of high fructose corn syrup may be a viable step to improve maternal mental health. However, all types of added sugar are low in nutrient density, and

high fructose corn syrup is just one factor in a massive global issue. Therefore, while focusing on types of added sugars in policymaking may lead to some health improvement, reducing consumption of all sugar types would be most impactful.

In addition to gaining a deeper understanding of the impact caused by different types of sweeteners, future work on this topic should focus on identifying additional cultural factors that may further explain variance in national PPD prevalence. For example, environmental and lifestyle factors such as exercise, obesity, partner support, and mindfulness practices, which have been linked to PPD, in individual studies might also be linked to PPD on the national level (168–171). Future research could also focus on micronutrients, such as vitamin D, that previous research have shown play an important role in mental health (172).

4.2. Limitations

Although this study had several strengths, including the large number of studies representing populations with varied lifestyles, economic backgrounds, and diets, our results should be considered alongside several important limitations. First, our study focused on a widely used self-report PPD measure instead of clinical interviews. Self-report PPD measures tend to yield higher estimates than clinical interviews, and therefore, the estimates in this study are likely higher than if we had used studies that conducted interview-based methods. However, given that interview methods are less common than self-report measures, especially in low-income countries, we felt that it was important to utilize a more representative measure. We also felt that potentially overestimating PPD would be safer than underestimating PPD, given its detrimental consequences. We use is nationally representative, and some countries estimates are much more reliable than others. We urge readers to consider the 95% confidence intervals when considering our national PPD prevalence estimates. More research reporting PPD prevalence is essential for providing more accurate prevalence estimates that. Secondly, collecting accurate nutrition data is notoriously challenging. This is why we used the Global Dietary Database, which has the most comprehensive empirical data on dietary intake across and within nations (173). Even so, it is difficult to identify inaccuracies within it. Thirdly, when using aggregate data, it is important to remember the ecological fallacy- that analyses based on area-level averages can yield very different conclusions than those that would be obtained from an analysis at the individual level (174).

5. Conclusion

PPD is common globally, however, there is significant cross-national and within-country variation. While certain methodological variables may contribute to this variation, SSB consumption may also be a risk factor. Future research is warranted to test whether policy that reduces SSB consumption at the national level may help to reduce PPD prevalence.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

AF-W conducted the review, meta analysis, and meta regression, as well as wrote the manuscript. JH-H oversaw all analysis, edited the manuscript, and provided guidance. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1193490/full#supplementary-material

FIGURE S1
Forest plot of between-study variation in PPD prevalence.

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Appendix

Search Syntax

CINAHL 7/26/21 Here is the Boolean search that yields 195 records: Boolean search

(IN edinburgh postnatal depression scale) AND (AB (postpartum depression OR postnatal depression)) AND (AB (incidence OR prevalence))

With the additional limiters:

(1) Narrow to start 2016

(2) Narrow it to English articles only

(3) Narrow it to Humans only

(4) Narrow it to females only

PSYCHINFO 7/26/21 Here is the Boolean search that yields 162 records:

AB (incidence or prevalence) AND AB (postnatal depression or postpartum depression) AND

TM edinburgh postnatal depression scale Here are the limiters:

Date: start 2016

∗ Language: English

∗ Population: Female

PUBMED 7/26/21

Here is the Boolean search that yields 245 records: ((“postpartum depression”[All Fields] OR “postnatal depression”[All Fields]) AND “prevalence”[All Fields]) AND “edinburgh postnatal depression scale”[All Fields] AND ((“2015/01/01”[PDAT]) AND “humans”[MeSH Terms])

frontiers | Frontiers in Psychiatry

TYPE Brief Research Report
PUBLISHED 20 November 2023
DOI 10.3389/fpsyt.2023.1258887

OPEN ACCESS

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RECEIVED 14 July 2023
ACCEPTED 25 October 2023
PUBLISHED 20 November 2023

CITATION
Patra BG, Sun Z, Cheng Z, Kumar PKRJ, Altammami A, Liu Y, Joly R, Jedlicka C, Delgado D, Pathak J, Peng Y and Zhang Y (2023) Automated classification of lay health articles using natural language processing: a case study on pregnancy health and postpartum depression.
Front. Psychiatry 14:1258887.
doi: 10.3389/fpsyt.2023.1258887

Automated classification of lay health articles using natural language processing: a case study on pregnancy health and postpartum depression

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Objective: Evidence suggests that high-quality health education and effective communication within the framework of social support hold significant potential in preventing postpartum depression. Yet, developing trustworthy and engaging health education and communication materials requires extensive expertise and substantial resources. In light of this, we propose an innovative approach that involves leveraging natural language processing (NLP) to classify publicly accessible lay articles based on their relevance and subject matter to pregnancy and mental health.

Materials and methods: We manually reviewed online lay articles from credible and medically validated sources to create a gold standard corpus. This manual review process categorized the articles based on their pertinence to pregnancy and related subtopics. To streamline and expand the classification procedure for relevance and topics, we employed advanced NLP models such as Random Forest, Bidirectional Encoder Representations from Transformers (BERT), and Generative Pre-trained Transformer model (gpt-3.5-turbo).

Results: The gold standard corpus included 392 pregnancy-related articles. Our manual review process categorized the reading materials according to lifestyle factors associated with postpartum depression: *diet*, *exercise*, *mental health*, and *health literacy*. A BERT-based model performed best (F1 = 0.974) in an end-to-end classification of relevance and topics. In a two-step approach, given articles already classified as pregnancy-related, gpt-3.5-turbo performed best (F1 = 0.972) in classifying the above topics.

Discussion: Utilizing NLP, we can guide patients to high-quality lay reading materials as cost-effective, readily available health education and communication sources. This approach allows us to scale the information delivery specifically to individuals, enhancing the relevance and impact of the materials provided.

KEYWORDS

online health information, health communication, natural language processing, pregnancy, postpartum depression

1 Background and significance

Pregnancy is a vulnerable period that exposes patients to heightened anxiety, depression, and stress. One in seven birthing parents develops postpartum depression (PPD), a potentially life-threatening mental health condition and a much higher proportion of pregnant patients experience antenatal psychosocial stress (1, 2). Anxiety, depression, and stress lead to adverse maternal, infant, and family outcomes, disproportionately affecting disadvantaged families (1, 3). The negative impact can be mitigated by interventions from healthcare providers (4, 5). However, resource constraints, compounded with the sensitive nature of pregnancy and stigma against mental health, present a unique challenge in the prevention, screening, and management of mental health concerns in the clinical settings (1, 6). Disparities in the distance to healthcare, health literacy, socioeconomic status, and neighborhood characteristics further strangulate equitable access to clinical interventions during pregnancy (4, 7, 8).

In turn, patients resort to self-management to relieve stressors and resolve individual questions around pregnancy (9). Patients have grown to be active online information seekers (10–12), of which people of childbearing age are the most active members in the digital space in the US (13). Three-quarters of the US pregnant population is known to seek information about pregnancy health and birth online (14). However, a myriad of information and players with unspecified motives exist online, making it often difficult for lay audiences, particularly those with low health literacy, to comprehend and act appropriately (15, 16). Notably, the appropriateness of online content was identified as a barrier to user satisfaction and continued engagement among the pregnancy population (17, 18).

Our research is aimed to develop a platform to deliver personalized health education and communication materials. The Support Personalized prEgnancy Care with Artificial inteLligence (SPECIAL) platform (https://www.specialdayshealthinfo.com/) houses content on health education and communication developed by a commercial vendor. This study aimed to assess the feasibility of utilizing natural language processing (NLP) to repurpose publicly accessible lay reading materials from magazines and online sources as health education and communication content.

1.1 Related work

Numerous studies have explored strategies for evaluating online health information and utilizing it for health education, communication, and promotion (12, 19, 20). However, our approach in this study diverges from existing literature. We present an innovative method that streamlines the search for online lay articles and information based on relevance and topic, effectively alleviating the health literacy challenges and search burden experienced by patients. Studies most relevant to us are previous work in categorizing news from public datasets such as TagMyNews using various machine learning and optimization techniques (21). Likewise, there are studies on the classification of health-related information and news from social media, such as the extraction of information related to Zika virus, syndromic surveillance, and identifying misinformation from social media posts (22–25).

1.2 Objective

Extensive theoretical research and empirical evidence have consistently established the crucial role of health education and communication, particularly within the framework of social support, in determining health outcomes during pregnancy (9). As part of our ongoing study on preventing postpartum depression (PPD) through intervention development, we propose employing a machine learning approach to deliver health education and communication. This approach aims to assist patients in recognizing sources of support and enhancing their self-management abilities. Our objective is to develop an NLP model by curating relevant lay articles on pregnancy health that can serve as effective health education and communication materials for patients.

Our focus on lay articles stems from their accessibility and the ease with which patients can comprehend them, even without an advanced level of health literacy. In order to establish a scalable and sustainable approach, we hypothesize that NLP can be employed to identify current and credible reading materials pertaining to PPD from lay sources. By leveraging NLP techniques, we aim to provide patients with up-to-date and reliable resources related to PPD, thus enhancing their overall health literacy and empowering them to make informed decisions.

2 Materials and methods

2.1 Data construction

We identified articles from online sources such as Mayo Clinic, MedlinePlus, and American Pregnancy Association. We also collected medically reviewed articles from non-medical sources with easy accessibility and high recognition that are written with the lay population as the target audience. We looked for articles related to PPD risk factors and social support. Using Vaux's theory of social support (26), we centered the article classification around social support constructs and focused on articles and resources that serve as instrumental (diet, exercise), informational (health literacy), and emotional (wellness) support. Here, "informational" refers to articles that are related to pregnancy but do not fall into the previous three categories. We collected an initial set of articles by online search using keywords including *pregnancy diet*, *pregnancy exercise*, *pregnancy fitness*, *pregnancy yoga*, *pregnancy mental health*, *pregnancy anxiety*, *pregnancy mood swings*, *depression during pregnancy*, *mental wellbeing pregnancy*, *mental health AND pregnancy*, *pregnancy and mental issues*, *Perinatal mood and anxiety disorder (PMAD) in pregnancy*, *anxiety during pregnancy*, and *dealing with stress during pregnancy*. As we envisioned that the articles would be a preventative measure against PPD for pregnant readers, we intentionally excluded articles that mentioned PPD to avoid alerting patients to the potential disease risk (27).

Collected articles were then reviewed for selection following NIH recommendations on how to evaluate health information on

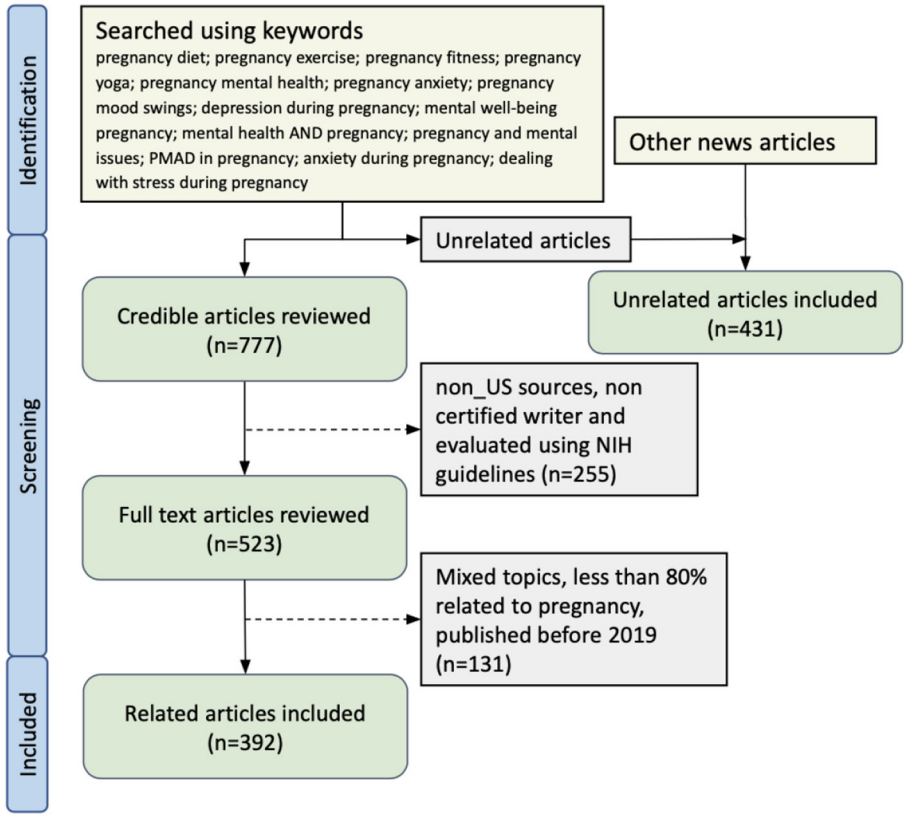

FIGURE 1
News articles inclusion criteria.

the internet (28). The recommendations focused on evaluating the ownership, purpose, and funding source of the website hosting the information; the evidence used to support the information; reviewers of the information (medically reviewed or not); the year of publication; consumer information collected by the site, and availability of monitoring for online interactions among consumers. Based on these criteria, we prioritized articles that were medically reviewed or published by a non-profit organization to serve as the corpus of the pipeline. Our content validation process also included a credibility check on the collected articles to avoid misinformation and conflicting information across sources. This secondary process excluded articles that were published by non-US sources, were not written by certified specialists holding degrees such as M.D. and Ph.D., and were not published by websites well-known to the general public. Finally, we excluded articles on mixed topics that contained less than 80% of content related to pregnancy, and we also excluded articles published before 2019 to ensure the timeliness of the information.

We identified 777 articles based on the above criteria from online searches. There were 523 credible articles left after the content validation step. Finally, we had 392 articles in our defined categories for training the NLP models. As a control, we also selected 431 articles that were not related to pregnancy. A list of unrelated news article topics is mentioned in Supplementary Table S5. The details of the article collection are shown in Figure 1 and counts of articles are provided in Table 1. Each article was reviewed by two annotators and the Cohen kappa metric for inter-rater reliability was 0.95. Any disagreement between reviewers was resolved by a third reviewer. During the review process, we identified the sources of the collected articles. Going forward, we will utilize these verified and authentic sources to gather pregnancy-related articles. To streamline the process, we have developed automated two web crawlers specifically tailored for each source, enabling efficient article collection.

TABLE 1 Characteristics of the dataset.

Tag	Categories	N	Avg # words	Avg # sentences
Related		392	1,231.44	59.41
	Diet	99	1,177.29	54.73
	Exercise	96	1,212.38	62.34
	Mental health	97	1,188.59	53.16
	Health literacy	100	1,347.48	67.41
Unrelated		437	1,343.51	61.37

2.2 Model development

We employed machine and deep-learning models to classify the collected articles. We concatenated the title and full-length

TABLE 2 Overall performances of RFs, gpt-3.5-turbo, and BERT models.

Models	Categories	Random forests			gpt-3.5-turbo			BERT		
		P	R	F	P	R	F	P	R	F
One-step (end-to-end)	Diet	0.910	0.919	0.915	0.793	0.970	0.873	0.981	0.966	0.973
	Exercise	0.946	0.906	0.926	0.711	1.000	0.831	0.953	0.979	0.965
	Mental health	0.916	0.784	0.844	0.485	0.979	0.648	0.951	0.943	0.945
	Health literacy	0.914	0.740	0.818	0.867	0.980	0.920	0.932	0.914	0.921
	Unrelated	0.902	0.977	0.938	1.000	0.599	0.749	0.970	0.954	0.962
	Macro	*0.917*	*0.865*	*0.888*	*0.771*	*0.906*	*0.804*	*0.957*	*0.951*	*0.953*
Two-step	Diet	0.876	0.928	0.899	0.932	0.970	0.951	0.918	0.971	0.943
	Exercise	0.890	0.938	0.909	0.795	0.969	0.873	0.910	0.953	0.927
	Mental health	0.832	0.889	0.856	0.688	0.979	0.808	0.888	0.897	0.892
	Health literacy	0.884	0.820	0.849	1.000	0.840	0.913	0.923	0.873	0.895
	Unrelated	0.957	0.937	0.947	0.966	0.854	0.906	0.957	0.937	0.947
	Macro	*0.888*	*0.902*	*0.892*	*0.876*	*0.922*	*0.890*	*0.919*	*0.926*	*0.921*

P, Precision; R, Recall; F, F1-score.
The macro-averaged values are italicized and the highest F1-scores are underlined.

text as the input. For both titles and full-length text, we removed stop words using the Natural Language Toolkit (NLTK) (29). We experimented with two approaches: an end-to-end approach and a two-step approach. The end-to-end approach treated articles as five topics: *diet*, *exercise*, *mental health*, *health literacy*, or *not related to pregnancy*. The two-step approach identified articles in two steps. The first stage classified articles based on whether or not they are related to pregnancy. Then, the second step classified a pregnancy-relevant article into four topics: *diet*, *exercise*, *mental health*, and *health literacy*.

2.2.1 Experimental settings

In this study, we used 5-fold cross-validation to obtain a distribution of the experimental metrics and reported the macro-averaged precision (P), recall (R), and F1-scores (F). In each of the five folds, we used one-fold (20%) as the hold-out test set and the remaining four folds (80%) as the training set. We leveraged the state-of-the-art Bidirectional Encoder Representations from Transformers [BERT (30)] and further fine-tuned the pertained model in downstream tasks. The model took a sequence of tokens with a maximum length of 512 and produced a 768-dimensional sequence representation vector. For text that is shorter than 512 tokens, we added paddings (empty tokens) to the end of the text to make up the length. For text that is longer than 512 tokens, we used the first 512 tokens as the input. Then, two fully connected layers are appended on top of the pooler output layer of the BERT model. Finally, a SoftMax layer is used to map the representation vector to the target label space. For the BERT model, we fine-tuned the "BioBERT" (31) model with the training data for 20 epochs with a learning rate of $2^{*}10^{-5}$ and batch size of 16. We adopted AdamW (32) as the optimizer and cross-entropy as the loss function. All BERT models were constructed on Amazon SageMaker with an NVIDIA T4 GPU with 128 GB of GPU memory. Pytorch (1.12.1) library was used to develop BERT models.

We compared the BERT model with the Generative Pre-trained Transformer model (GPT). We used the Dec 15, 2022 version of gpt-3.5-turbo to classify articles by question answering. Different questions corresponded to different classification methods and article types. For one-step approach, we asked gpt-3.5-turbo the question "Only give a one-word answer for which category this text belongs to: *pregnancy-related diet*, *pregnancy-related exercise*, *pregnancy-related mental health*, *pregnancy-related health literacy*, or *pregnancy-unrelated*." This allowed gpt-3.5-turbo to directly classify the articles into one of five categories. For the two-step method and the classification of pregnancy-related and pregnancy-topics, we first used the question "Only answer yes or no to the question: Is the following text related to pregnancy and not" to classify the articles as pregnancy-related or not. Further, for the pregnancy-related articles, we asked the question "Only give a one-word answer for which category this text belongs to: *diet*, *exercise*, *mental health*, or *health literacy*" to distinguish the pregnancy topics. We also compared the proposed BERT models with traditional machine learning methods. In particular, we experimented with Random Forests (RF) using TF-IDF features. We set the word frequency to be (<4) and capped the dimensionality to 1500 features. The number of trees in the forest was 200. Scikit-learn (1.0.2) library was used for the RF model.

3 Results

3.1 Overall performance

Table 2 shows the performance of RF, gpt-3.5-turbo, and BERT-based classifications using one-step and two-step approaches. In the case of the one-step approach, we observed that BERT obtained the best performance with a macro-averaged precision of 0.957, a recall of 0.951, and an F1-score of 0.953, which are 4.01, 8.60, and 6.50%

higher than those of RF, and 18.6, 4.6, and 14.9% higher than those of gpt-3.5-turbo, respectively. The BERT-based two-step approach achieved micro-averaged precision, recall, and F1-score of 0.919, 0.926, and 0.921, respectively. The RF-based two-step approach achieved macro-averaged precision, recall, and F1-score of 0.888, 0.902, and 0.892, respectively. The gpt-3.5-turbo-based two-step approach obtained macro-averaged precision, recall, and F1-score of 0.876, 0.922, and 0.890, respectively. When comparing the end-to-end model with the two-step approach, we found that the end-to-end BERT model performed better than the two-step BERT-based approach. However, the end-to-end gpt-3.5-turbo model is worse than its counterparts.

3.2 Classification by relevance to pregnancy

Figure 2 and Supplementary Table S1 show the binary classification performance comparison between RF, gpt-3.5-turbo, and BERT. We observed that BERT achieved the best performance with macro-averaged precision, recall, and F1-score of 0.975, 0.974, and 0.974, respectively for classifying pregnancy-related and unrelated articles. Detailed counts of BERT-based model such as true positive, false positive, and false negative of each fold can be found in Supplementary Table S2. RF and gpt-3.5-turbo showed lower F1-scores of 0.945 and 0.908 than BERT.

3.3 Classification by pregnancy topics

Figure 2 and Supplementary Table S3 show that the gpt-3.5-turbo model achieved the best performance with macro-averaged precision, recall, and F1-score of 0.973, 0.972, and 0.972, respectively. Detailed counts of gpt-3.5-turbo model such as the true positive, false positive, and false negative of each fold can be found in Supplementary Table S4. The performance of gpt-3.5-turbo was 3.53, 3.43, and 3.53% higher than that of RF and 0.52, 0.48, and 0.56% higher than that of BERT.

4 Discussion

Our pipelines demonstrated the ability of the NLP algorithm to identify pregnancy-related online health education materials. The end-to-end BERT model obtained better results than the two-step BERT by 3.22% in the F1-score. For RF, although the two-step approach increased the recall by 3.74%, the precision decreased by 2.95%. Similarly, the two-step approach using gpt-3.5-turbo increased the F1-score by 8.6%. BERT outperformed RF and gpt-3.5-turbo in all scenarios. While end-to-end had better performance than two-step, it lacks interpretability and requires retraining when new topics are added. In comparison, in the two-step approach, we only need to train the second one and there is flexibility in adding additional topics for articles.

In the binary classification of pregnancy-related articles, RF obtained a satisfactory F1-score. The performance of BERT in this task is not an obvious advantage; although it improved by 2.9% it required more time and computing cost. In addition, the type of input text had little effect on the performance of the model, and the title achieved high accuracy under extremely fast computation speed. In the classification of pregnancy topics, the performance advantage of BERT and gpt-3.5-turbo are significant. Despite the demonstrated performance of gpt-3.5-turbo in general question answering, we discovered that, due to the specialized needs of our questioning (related to pregnancy but does not mention postpartum depression), we needed a dedicated NLP model for our use case. Still, gpt-3.5-turbo demonstrated superior performance in pregnancy topic classification, thus showing its potential for use in the future.

We performed our experiments using 392 pregnancy-related articles, and the BERT-based system performed better in most cases. In the future, we plan to add more articles with additional categories related to pregnancy. We searched the articles for our experiments manually, and it is possible that our search did not retrieve all relevant articles. We plan to implement automated web crawlers to collect the articles from the identified sources more efficiently in the future.

4.1 Limitations

Here are two limitations of our study. First, we intentionally focused on articles from 2019 onwards as the gold standard to capture recent trends and understandings in health topics. While we acknowledge the potential relevance and value of articles published prior to 2019, our current model was designed with a specific timeframe in mind to ensure contemporary relevance. However, we will consider expanding our dataset to include older articles in future iterations or expansions of the model. Second, the BERT-based system has a limitation of accepting only 512 tokens as input from each document. One potential solution to this challenge is to divide the document into multiple chunks and feed them individually to the BERT-based system. However, since the system already outperformed all other systems in terms of performance, we decided not to pursue this approach in order to avoid complicating the development process.

5 Conclusion

Given the abundance of high-quality lay articles and the knowledge- and labor-intensiveness of creating patient education materials, we proposed that lay articles related to pregnancy could be categorized and repurposed into educational and communicational materials for patients through NLP models. We explored state-of-the-art BERT models and gpt-3.5-turbo in an effort to obtain superior performances in classifying these articles. Current work is underway to incorporate the model based on gpt-3.5-turbo into our research website to scale the volume and diversity of content the website can provide to patients with diverse backgrounds and needs. Future work involves an on-going pilot evaluation with patients to assess acceptability and technical feasibility.

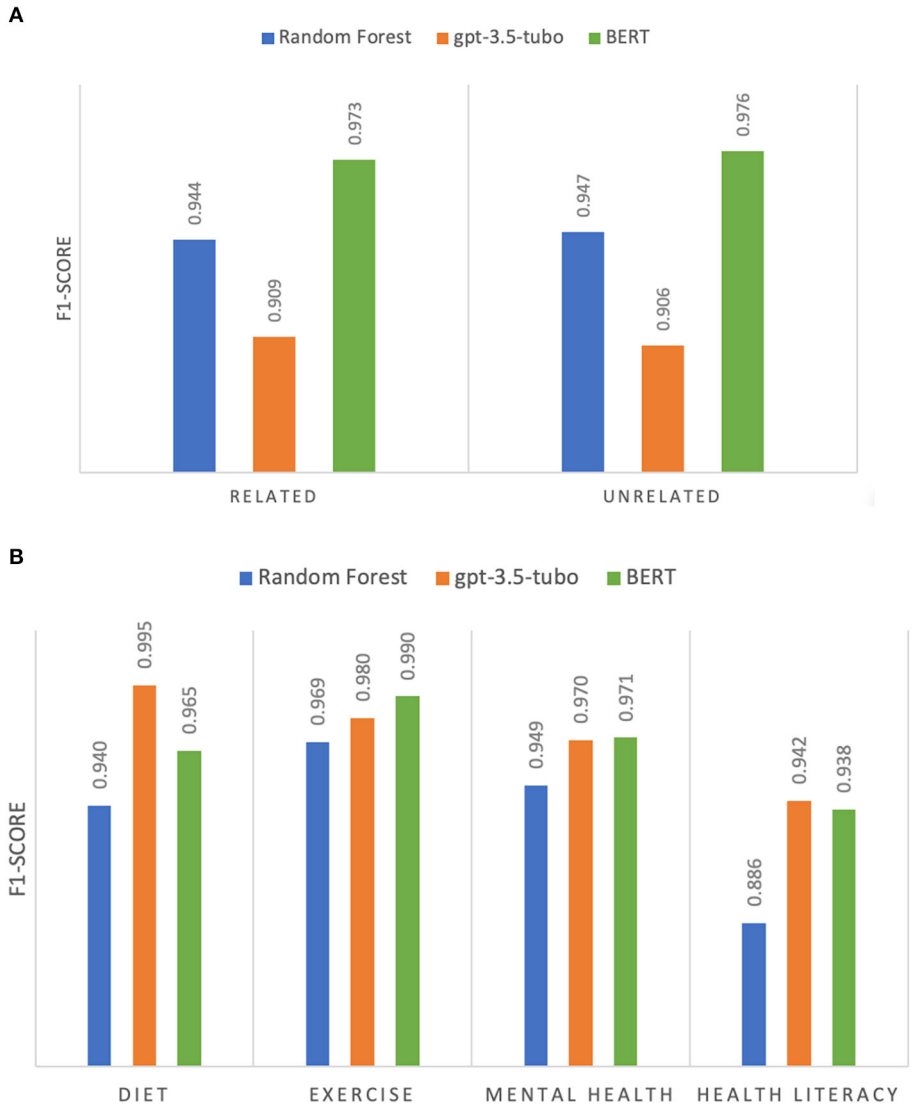

FIGURE 2
(A) F1-scores of the classification of pregnancy-relevant articles. **(B)** F1-scores of the classification of pregnancy topics.

Data availability statement

The original contributions presented in the study are publicly available. This data can be found here: https://github.com/brajagopalcse/AI_Driven_Patient_Education_Materials.

Author contributions

BP: Conceptualization, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Writing—original draft, Writing—review & editing, Data curation, Resources, Visualization. ZS: Data curation, Formal analysis, Software, Writing—review & editing, Validation. ZC: Data curation, Formal analysis, Software, Writing—review & editing, Validation. PK: Data curation, Formal analysis, Methodology, Project administration, Software, Validation, Writing—review & editing. AA: Data curation, Formal analysis, Writing—review & editing. YL: Data curation, Formal analysis, Software, Writing—review & editing, Validation. RJ: Conceptualization, Data curation, Writing—review & editing. CJ: Conceptualization, Data curation, Writing—review & editing. DD: Conceptualization, Data curation, Writing—review & editing. JP: Writing—review & editing, Supervision. YP: Investigation, Writing—review & editing, Supervision. YZ: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing—original draft, Writing—review & editing, Data curation, Validation.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This research is supported by the US Department of Transportation Center for Transportation, Environment, and Community Health, AWS Diagnostic Development Initiative Support (YP), and Amazon Research Award (YP).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1258887/full#supplementary-material

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frontiers | Frontiers in Psychiatry

TYPE Original Research
PUBLISHED 05 January 2024
DOI 10.3389/fpsyt.2023.1323779

OPEN ACCESS

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RECEIVED 18 October 2023
ACCEPTED 14 December 2023
PUBLISHED 05 January 2024

CITATION
Sommerfeldt B, Skårderud F, Kvalem IL, Gulliksen K and Holte A (2024) Trajectories of severe eating disorders through pregnancy and early motherhood.
Front. Psychiatry 14:1323779.
doi: 10.3389/fpsyt.2023.1323779

Trajectories of severe eating disorders through pregnancy and early motherhood

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Background: During pregnancy and early motherhood, risks of relapse and worsening are high for women with a history of eating disorders (EDs), as are adverse sequelae for their babies. However, systematic descriptions of the processes that these women undergo through pregnancy, birth, and early motherhood are lacking, as are good descriptions of the various trajectories these women follow through pregnancy and early motherhood. This study addresses both these knowledge gaps.

Methods: We used a longitudinal research interview design, recruiting a non-clinical sample of 24 women with a history of severe EDs from routine pregnancy controls in five public, local, family health care centers in Norway. The participants were interviewed twice, first during pregnancy and then 4–6 months after delivery. Data were analyzed according to grounded theory. The focus was on modeling the trajectories of EDs through pregnancy, birth, and early motherhood. All the participants were diagnosed (DSM-5) using the Eating Disorder Examination and then completed the Eating Disorder Examination Questionnaire.

Results: Five perceived trajectories through pregnancy and early motherhood were identified: "The mastering mother," in which an ED pathology seems to be absent through pregnancy and early motherhood; "The inadequate mother," in which the ED pathology worsens before pregnancy, through pregnancy, and early motherhood; "The overwhelmed mother," in which the ED worsens during pregnancy and early motherhood; "The depressed mother," in which the ED is put on hold during pregnancy, but worsens in early motherhood; and "The succeeding mother," in which the ED worsens during pregnancy, but reduces in early motherhood.

Discussion: ED trajectories through pregnancy and early motherhood vary greatly among women with a history of EDs. This may indicate different psychological dynamics through these phases. A model with five trajectories captures a large degree of the variation. The model may help clinicians' preparedness when dealing with these patients.

KEYWORDS

eating disorder, pregnancy, postpartum, protective factors, triggers, precursors

1 Introduction

Eating disorders (EDs) encompass behaviors such as restrictive eating, fasting, binging, and self-induced vomiting, as well as psychological traits such as distorted cognition and preoccupation with weight, body image, body, and food (1). In both anorexia nervosa (AN) and bulimia nervosa (BN), self-worth relies on body, shape, and weight (2).

Pregnancy and early motherhood are known to be vulnerable times for women with EDs (3–7). Reported prevalence during pregnancy is 5–8% (8, 9), increasing to 12.8% after birth (9), compared with 0.8% for AN and 2.8% for BN for comparable age groups in the general population (10). One assumption is that these differences are linked to profound and rapid changes in body appearance, body image, body functions, body sensations, and sense of self-identity during these phases in life (5, 11–13).

The distorted cognitions and behaviors associated with EDs have been observed to persist through pregnancy and postpartum (14, 15). Women who experience persistent ED pathologies through pregnancy and early motherhood also tend to report higher levels of anxiety and depression (8, 16, 17). Furthermore, postpartum depression seems to occur more frequently in women who have or have had an ED (16, 18). Taborelli et al. (19) examined retrospectively the transition from pregnancy to motherhood among women with a current ED. Recurrence of ED symptoms and depressive symptoms after birth were experienced by the subjects as a sign of their inadequacy as a mother (19).

EDs during pregnancy and early motherhood also seem to be a potential risk factor for the fetus (20–22). For instance, EDs are associated with increased risk of problems during labor and delivery, including higher risk of premature birth and cesarean delivery (23, 24), fetal distress (17), and resuscitation, low Apgar scores in newborns, and perinatal death (25).

Despite all this, the intersection between the ED pathology, pregnancy, and motherhood is little studied. Most studies have used questionnaire data (22), were retrospective (19), and/or used clinical hospital samples (1, 19). Although important, such studies have significant limitations. Some are likely to suffer from recall bias, selection bias, or, as in some questionnaire studies, are likely to give only quantitative, epidemiologically useful, but relatively superficial answers of limited clinical value (15, 26, 27).

Moreover, the available studies are limited to only one particular period of motherhood: pregnancy, postpartum, or early motherhood. For instance, Tierney et al. (1) investigated the experience of pregnancy among women with an ED and described their conflicting loyalties to their ED and their future baby's demands. The authors suggested that this conflict can cause women to question their mothering skills and deplete their already diminished self-esteem. Mason et al. (28) studied how women with AN have difficulty adapting to their new status and the emergence of a new relationship with their body during pregnancy. Others have found that women with EDs in the postpartum period report being highly distressed by breastfeeding and by the intensity of their body image and shape concerns (29).

No study has yet explored the psychological processes that these women go through or the possible different trajectories through pre-pregnancy, pregnancy, and early motherhood. Nor are there any prospective studies of the trajectories of ED pathologies through these phases of life.

Is it possible to identify a typical trajectory for such women? Are there some common traits, factors, or processes that the women themselves link to worsening, relapse, or maybe even improvement and recovery from their ED pathology through these phases? To treat this vulnerable group of women in a caring manner, it would be helpful to have a better understanding of how they experience the trajectory of their eating problems through pregnancy and early motherhood.

To start filling the gaps in the knowledge and provide clinicians with some insights, we used a longitudinal in-depth study design to closely follow a non-clinical sample of 24 women with a history of severe EDs through pregnancy and the first 6 months after birth. The participants were a non-clinical group, meaning that none of them were in treatment for their ED when they became pregnant and that they were recruited from a universal, public, routine pregnancy control, not a clinical treatment facility. Severity was conceptualized and defined using three components: persistent symptoms, long duration, and treatment history (more than 7 years). Weight was not used to determine severity because of the fluctuating weight of pregnant women. We aimed to identify possible common structural components in the women's narratives, as well as possible differences.

We had two research questions: (1) How do women with a history of severe EDs experience their ED pathology during the process from pregnancy to postpartum and (2) On the basis of these experiences, is it possible to identify different trajectories through pregnancy and early motherhood?

2 Materials and methods

2.1 Participants

This study is part of a larger study, "Mummy bodies." In "Mummy bodies," we comprehensively interviewed 24 women twice, first during pregnancy and then 4–6 months after delivery. Inclusion criteria were that the participants had a self-reported history of an ED, had been in treatment for a diagnosed ED within the past 10 years, and were pregnant at the time of the first interview. Exclusion criteria were any psychotic symptoms.

2.2 Setting and procedure

The participants were recruited from the general population through the universal, public, routine pregnancy controls at five local family health care centers in the Greater Oslo area in Norway. The services are free. The participation rate in the pregnancy controls at these centers is 95–98% (30).

Midwives and nurses at the health care centers were thoroughly informed about the project and its inclusion and exclusion criteria before being asked to invite potential participants. Social media, podcasts, and seminars were used to encourage and support the recruitment of participants. We did not know the degree to which the sample was representative of pregnant women with a history of EDs; moreover, the study did not differentiate between women with a current history of EDs and women who had previously suffered from EDs. The Eating Disorder Examination (EDE) and Eating Disorder Examination Questionnaire (EDE-Q) were used to qualify patients' current ED status.

Those interested in participating sent an email to the first author and then received further information about the study by email, accompanied by a written invitation to participate. The written invitation contained a detailed description of the research project, including its purposes and procedures. No one withdrew after having consented to give their contact information to the researcher.

After participation had been approved, the participant and interviewer arranged a time to meet. Then, the two semi-structured research interviews were conducted, with the participants completing the EDE-Q after each one (31). Further, the EDE was administered after each interview to make the ED diagnosis based on DSM-5 (32). All the information about the participants' ED history was based on self-reporting.

The aim of the interviews was to provide rich descriptions as precise and as close to the participants' experiences as possible. Data were collected using the "Experience Interview" technique (33), a semi-structured participant-centered, strategic conversation format developed from communication theory (34).

All the interviews were conducted by the first author (BS). Each interview lasted between 90 and 120 min and was audiotaped and transcribed verbatim by the same author. Altogether, providing the introductory information, conducting the interviews, and administrating the EDE-Q and EDE took two and a half hours over the two meetings, a total of 5 h for each participant. All the procedures were conducted in accordance with the Helsinki Declaration, and the study was approved by the Norwegian Regional Committee for Medical Research Ethics.

2.3 Data analyses

We used guidelines from grounded theory to develop an empirical model of trajectories based on the data collection and analyses of the women's experiences (35). To analyze the interviews, NVivo 12 was used to organize the data (36). Subsequently, summaries and notes from the transcription process were analyzed. The analytical process was not carried out in isolation; rather, it was based on immersion in the data and repeated sortings, codings, and comparisons as per grounded theory (37). Ensuring a continuity of descriptions and interpretations was important throughout the process.

The analyses involved seven main steps. First, the first author, an experienced clinical psychologist and psychotherapist specialized in EDs, conducted the interviews; further familiarization with each narrative was achieved by listening to the audio files, transcribing the interviews verbatim, checking the accuracy of the transcripts, and reading and re-reading the transcripts. Concurrently, the second (FS) and fifth (AH) authors listened to the tape recordings and participated as co-readers of the transcripts and as discussants of possible interpretations. The first author made detailed notes from the interviews as well as observations and comments about potential significance to gain an overall impression and capture relevant and varied experiences. Throughout the process, we reflected upon potential biases and preconceived ideas that we might have brought to the analyses and that could possibly influence our interpretations.

The second step involved analyzing the interview transcripts. Each text was examined using open thematic coding (35) according to the bottom-up principle (38, 39) to reveal different themes. We examined the individual words, phrases, and sentences in each transcript and identified relevant categories. During the discussion of the interviews, the team became aware of some tendencies associated with being pregnant and a mother and the emergence of symptoms of EDs. All the text excerpts that included statements about ED symptoms through pregnancy and early motherhood as well as about being a mother were coded and labeled according to their meaning.

Third, we explored different outcomes from the transcribed interviews from the postpartum period. We then looked back on the birth and pregnancy descriptions to see how different trajectories led to different outcomes. We summarized each woman's experiences of ways in and out of eating problems during pregnancy and postpartum. Each summary was used to identify experiences and how their thoughts and practices relating to their body, weight, and food through pregnancy and early motherhood emerged.

In the fourth step, we identified possible common structural components in the women's experiences of the trajectory of their ED pathology. We systematized the experiences that showed different trajectories through open coding and validation against the original text using confirmatory and selective coding (35). This resulted in three higher order constructs: precursors, triggers, and protective factors.

Fifth, we conducted axial coding (35). While open coding refers to the deconstruction of data (i.e., breaking data apart), axial coding refers to the reconstruction of data. In this process, we explored how the different higher-order constructs were related to each other and grasped the complexity of the women's narratives. This allowed us to describe the experiences longitudinally from before pregnancy to birth and early motherhood. In this part of the analyses, experiences from the higher-order constructs were combined into five trajectory constructs, which represented the lowest number of constructs needed to describe how the participants perceived their trajectory to motherhood. The language of the participants guided the trajectories' labels. Their experiences were identified with short descriptions, which became the name of the trajectory. The five trajectory constructs were labeled "The mastering mother," "The succeeding mother," "The inadequate mother," "The depressed mother," and "The overwhelmed mother." This coding provided us with a model that accommodated the individual variations in the participants' narratives in terms of precursors, triggers, and protective factors.

Sixth, to ensure that each trajectory fitted with the original narratives, the data were analyzed a third time according to the top-down principle. Through this process, the constructed trajectories were validated by checking each pathway against the original texts to determine whether further refinements were needed to adequately represent the original data and minimize overlaps between the trajectories.

Finally, to check credibility, the analyses were regularly discussed within the research team to ensure that the themes were well represented in the data and vice versa. As a result, the themes and interpretations were continuously challenged, discussed, and reassessed.

3 Results

3.1 Participants

Background information, diagnoses, and a brief history of the participants' EDs are shown in Table 1 for both interviews. The

TABLE 1 Details of the participants.

Participant no.	Age (mean 32.8)	Earlier eating disorder diagnosis*	Years of treatment for eating disorder** (mean 7.7 years)	Re-engaged in treatment in the perinatal phase	Number of pregnancies	*In vitro* fertilization (IVF)	Gestation week at the time of the interview	Week of birth (mean 38.8)	ED diagnosis during pregnancy***	EDE-Q Global Score during pregnancy (mean 3.54)****	ED diagnosis at postpartum ***	EDE-Q Global Score at postpartum (mean 3.41) *****	Postpartum depression******	Breastfeeding
Participant 1	31	AN, restrictive type	4	Yes, not specialized	Second-time mother		32	40	OSFED, Atypical AN	4.45	OSFED, Atypical AN	4.7	Yes	No
Participant 2	39	AN, restrictive type	8	Yes, not specialized	First-time mother	IVF	19	39	OSFED, Atypical AN	2.3	OSFED, Atypical AN	2.75	Yes	Yes
Participant 3	31	AN, restrictive type	5	Yes, not specialized	First-time mother		23	39	OSFED, Atypical AN	5.5	OSFED, Atypical AN	5.5	Yes	No
Participant 4	31	EDNOS	5	Yes, not specialized	First-time mother		16	35 (cesarean section)	OSFED, Atypical AN	3.5	OSFED, Atypical AN	3.5	No	Yes
Participant 5	34	BN	9	Yes	First-time mother		12	40	OSFED, BN of low frequency	3.66	UFED	2.43	No	Yes
Participant 6	35	AN, restrictive type	15	Yes	Second-time mother		12	38 (cesarean section)	OSFED, Atypical AN	2.7	UFED	1.82	No	Yes
Participant 7	26	AN, restrictive type	8	No	First-time mother		37	38	None	1.5	UFED	2.82	No	Yes
Participant 8	30	EDNOS	9	No	Second-time mother		15	40	UFED	1.78	No diagnosis	0.25	No	Yes
Participant 9	36	BN	3	Yes	Third-time mother		14	40	Mild BN	4.4	UFED	2.59	Yes	Yes
Participant 10	37	AN, restrictive type	17	Yes, not specialized	Second-time mother	IVF	40	40	OSFED, Atypical AN	5	AN (restrictive type). Mild (BMI 17)	5.5	Yes	Yes
Participant 11	39	AN, restrictive type	3	Yes, not specialized	First-time mother	IVF	9	37	OSFED, Atypical AN	4.63	AN (restrictive type). Mild (BMI 19)	3.8	yes	Yes
Participant 12	41	AN, restrictive type	9	Yes, not specialized	Third-time mother		25	40	OSFED, Atypical AN	1.6	OSFED, Atypical AN	1.85	Yes	50/50

(Continued)

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TABLE 1 (Continued)

Participant no.	Age (mean 32.8)	Earlier eating disorder diagnosis*	Years of treatment for eating disorder** (mean 7.7 years)	Re-engaged in treatment in the perinatal phase	Number of pregnancies	*In vitro* fertilization (IVF)	Gestation week at the time of the interview	Week of birth (mean 38.8)	ED diagnosis during pregnancy***	EDE-Q Global Score during pregnancy (mean 3.54)****	ED diagnosis at postpartum ***	EDE-Q Global Score at postpartum (mean 3.41) ****	Postpartum depression*****	Breastfeeding
Participant 13	27	BN	9	Yes, not specialized	First-time mother		22	40	OSFED, Atypical AN	4.73	AN (restrictive type). Mild (BMI 17)	3.48	Yes	Yes
Participant 14	30	BN	6	Yes	First-time mother		16	39	OSFED, Atypical AN	3.16	No diagnosis	1.8	No	Yes
Participant 15	31	AN, restrictive type	7	Yes	Second-time mother		23	39 (cesarean section)	OSFED, Atypical AN	3	No diagnosis	1.8	No	Yes
Participant 16	34	AN, restrictive type	11	Yes, not specialized	Second-time mother		25	37	OSFED, BN of low frequency	2.44	UFED	1.52	No	Yes
Participant 17	37	BN	3	Yes, not specialized	Second-time mother		26	40	Severe BN	5	AN (restrictive type). Mild (BMI 19)	5.5	Yes	Yes
Participant 18	30	BN	16	Yes	First-time mother	IVF	17	38	OSFED, Atypical AN	5.1	Extreme BN	5.5	Yes	Yes
Participant 19	42	AN, binging type	3	Yes, not specialized	Second-time mother	IVF	16	41	UFED	5.1	AN (restrictive type). Mild (BMI 18)	4.58	Yes	Yes
Participant 20	28	AN, restrictive type	9	Yes	First-time mother		37	38	OSFED, Atypical AN	3.66	UFED	1.9	No	Yes
Participant 21	28	BN	7	Yes, not specialized	First-time mother		32	38	OSFED, Atypical AN	2.93	AN (restrictive type). Mild (BMI 18)	4.35	Yes	Yes
Participant 22	32	AN, restrictive type	6	Yes, not specialized	First-time mother	IVF	17	40 (cesarean section)	OSFED, Atypical AN	3.17	AN (restrictive type). Mild (BMI 18.5)	4.7	Yes	No
Participant 23	26	AN, restrictive type	2	Yes	First-time mother	IVF	27	38	OSFED, Atypical AN	4.4	AN (restrictive type). Mild (BMI 18.5)	4.7	No	Yes
Participant 24	31	BN	10	Yes	Second-time mother		26	38	OSFED, BN of low frequency	5.6	Moderate BN	4.7	Yes	Yes

*Earlier diagnosis is self-reported based on the DSM-IV diagnosis. **Years of treatment are self-reported by mail after the interview. ***Diagnosis based on the DSM-5 criteria. ****Self-report of symptoms using the EDE-Q. *****Diagnosed by a GP, self-reported by the participants to the interviewer. AN, Anorexia nervosa; BN, Bulimia nervosa; EDNOS, eating disorder not otherwise specified; OSFED, Other specified feeding or eating disorder; UFED, Unspecified feeding or eating disorder.

10.3389/fpsyt.2023.1323779

participating women were between 26 and 42 years of age (mean 32.8 years). The average age of first-time mothers in Norway is 30.6 years (2021). All the participants reported having been in treatment for a diagnosed ED within the preceding 10 years, with a duration of treatment for their ED ranging between 2 and 17 years (mean 7.7 years). None were in specialized treatment for their ED when they became pregnant.

A total of 22 of the 24 women said that they had needed treatment again during pregnancy. Nine of the participants restarted specialized treatment for EDs while they were pregnant, 13 reported that they had asked for treatment for their eating problems during pregnancy at the birth controls but did not receive specialized treatment, and two did not need specialized treatment during pregnancy. There were 13 first-time mothers, nine second-time mothers, and two third-time mothers. Seven of the participants became pregnant through *in vitro* fertilization (IVF). Gestation week at the time of the interview ranged from week 9 to week 40. Week of birth ranged from week 35 to week 40 (mean week 38.8). Four of the participants gave birth through cesarean section.

Altogether, 23 of the 24 participants received an EDE-assessed DSM-5 diagnosis of an ED at the time of the first interview, while 21 received an EDE-assessed DSM-5 diagnosis of an ED at the time of the second interview (Table 1). During pregnancy, three were shown to have BN, two were shown to have an unspecified feeding or eating disorder (UFED), and 18 were shown to have a type of other specified feeding or eating disorder (OSFED). At postpartum, two were shown to have BN, six were shown to have an UFED, and five were shown to have an OSFED (Table 1). Few women met the full DSM-5 criteria for an ED diagnosis due to their pregnancy weight. Table 1 also shows that the symptom pressure measured by the EDE-Q Global Score was generally high. The mean EDE-Q Global Score for the 24 participants was 3.54 during pregnancy and 3.41 at postpartum. Finally, postpartum depression was diagnosed by the medical general practitioner in 14 of the 24 women. Breastfeeding was performed by 20 of the 24 women.

3.2 Structural components

The comprehensive analyses of the 24 women identified three common structural components: precursors, triggers, and protective factors. The three components were all addressed in all of the 24 women's narratives.

Precursors comprised conditions such as ED history, number of births, personal characteristics, family history, body image, family transmission, and/or attitude toward pregnancy. These experiences were present before the women became pregnant and were regarded by the participants as important to their way of dealing with pregnancy and early motherhood.

Triggers were distinctive events that the participants linked to relapse or worsening of their EDs during their pregnancy, birth, or early motherhood, such as an unplanned pregnancy, ambivalence to pregnancy, IVF, change in appearance, body image, negative comments about their body, and/or lack of support.

Protective factors were experiences and events the participants linked to positive ways of dealing with pregnancy and early motherhood and that they associated with improvements in their ED pathology, such as positive body experiences, small body changes, a sense of achievement, a sense of mastery, and/or relationship satisfaction/support.

3.3 ED trajectories

On the basis of the combinations of the various content themes within the common structural components described above, we constructed five trajectories of perceived relapse, worsening, improvement, and/or recovery of the ED pathology during pregnancy and early motherhood (Table 2). In the subsections below, each trajectory is illustrated by condensed quotations from one or more participants that led to the inference of that particular path. Each trajectory is based on the mother's own statements about the experiences of the ED pathology during pregnancy and at postpartum. Information that could reveal a participant's identity has been removed.

3.3.1 The mastering mother: recovering through pregnancy and early motherhood

This trajectory is based on three of the participants. For the mastering mother, the role of being a mother is an important turning point in the trajectory of an ED. The narratives behind this trajectory are characterized by a woman experiencing being a mother as a clear task filled with mastery and a new meaning.

Precursors: Lower body mass index before pregnancy. Strong awareness of food intake and exercise were present in all the women, along with descriptions that were performance oriented and related to having a strong will. "*I have always been a person who sets goals and is obsessed about reaching them. I got obsessed with getting pregnant.*"

Women who followed this trajectory had a history of AN. They wanted to become pregnant. They planned their pregnancy, became pregnant quickly, and experienced having become pregnant as a great achievement. "*I became pregnant very quickly, and being pregnant is something I manage.*" They were also determined that their own relation to food, body, and weight should not affect their baby. This was a strong motivation for improvement.

Triggers: The narratives of these mothers contained hardly any references to distinct events that could be considered triggers for the ED pathology.

Protective factors: The women in the mastering mother category reported several protective factors. They experienced small body changes during pregnancy. "*I really enjoyed my small stomach during pregnancy. I was proud of it!*" They experienced good support and the

TABLE 2 Five trajectories of EDs through pregnancy and early motherhood.

1. "The mastering mother": ED pathology seems to be absent through pregnancy and early motherhood.
2. "The succeeding mother": ED worsens during pregnancy but reduces in early motherhood.
3. "The inadequate mother": ED worsens before pregnancy, through pregnancy, and early motherhood.
4. "The depressed mother": ED pathology is put on hold during pregnancy but worsens in early motherhood.
5. "The overwhelmed mother": ED worsens during pregnancy and early motherhood.

pregnancy as a common project. "*This was our project. And I really enjoyed my husband touching my belly*."

The protective factors continued through to delivery. The women delivered close to their delivery date. This gave them a feeling of safety. Most procedures and activities went as planned, and the mothers experienced a normal delivery. They also reported a sense of control over their body. "*I had a normal birth, and for the first time felt in control of my own body. It was stronger than I thought*." "*Being able to feel pain and at the same time have a sense of control was important to me*."

As mothers, they were obsessed with doing everything right, an obsession that functioned as a trigger, as in the trajectories of the succeeding mother and the depressed mother. Instead, they experienced mastery by being in good shape; this sense of mastery made them less stressed about thoughts about their body and food. "*Being a mother gives me a bit of a break from all these thoughts about food and exercise, and now this exercise and awareness of what I can eat finally makes sense. After all, now I have to keep myself healthy and fit for another person*."

The feeling of mastery and achievement persisted. "*I lost weight right away, and that gave me a boost*." They mastered breastfeeding, with the baby responding well and calming down easily. The women reported bonding well with the baby. "*I love his smile when he sees and hears me. It makes me forget everything else*." "*This pregnancy and being a mother have meant I do not need the ED anymore. I am mastering something else now*."

3.3.2 The succeeding mother: improvement after birth

This trajectory is based on four of the participants. The ED became worse during pregnancy but subsided when the participants became mothers. Birth and early motherhood are important turning points for the trajectory of the ED in the succeeding mother. The narratives of this trajectory are characterized by how these mothers struggled during early pregnancy but experienced birth and being a mother as something that gave them a feeling of being someone. They grew into the role of being a mother.

Precursors: Before becoming pregnant, these mothers had a history of AN with a combination of low self-esteem, feeling not being good enough, and perfectionism. Their ED had been a way of giving them a sense of succeeding at something. "*I have never been satisfied with something halfway, and I wanted to be the perfect pregnant and the perfect mom. I think I mean thin and healthy*." To these women, pregnancy became difficult to deal with alongside their precursors of rigidity and inflexibility. "*I have always been a person who had plans and rules for everything. Just like I planned my pregnancy*."

Triggers: The ED triggers of the succeeding mother kicked in at the first trimester if they had become pregnant earlier than planned, had strong fears about becoming a mother, and had concerns about the changes to their body beyond their control. "*I need to have control over everything I do, but when I got pregnant nothing went as I had planned*." Women following this trajectory seek to ensure a thin pregnancy, with strict rules and fixed regimes. This focus makes it difficult to connect to the baby during the first two trimesters.

Protective factors: Protective factors in the succeeders arose if they had a small stomach and gained less weight than they had feared. The worsening of their ED pathology eased and even declined when these mothers were able to connect to their baby through its activity and movements. The mothers enjoyed sharing these moments with their partner. In the last trimester, these women even allowed themselves to dream of becoming a good mother.

The mothers in this trajectory may experience protective factors through delivery if the birth is planned by cesarean section. This makes the delivery predictable and gives the women more of a sense of control. In our study, all four succeeding women experienced a good sense of control over their delivery.

This feeling of control continued through early motherhood. After delivery and in early motherhood, in this trajectory the triggers became less dominant, which led to improvements in the ED pathology that had worsened during pregnancy. Being a mother was something that succeeders managed and that gave them a feeling of self-confidence. "*The role of being a mother gave me a focus and a clear role*." "*In a way, I avoided walking around feeling inept, as I had done in all other areas*." This led to less fear about not being good enough. Through the baby, the women obtained a sense of being "good enough." Their lack of self-confidence weakened when the contact with the baby was good. "*I am experiencing a mutual beneficial interaction and think I am valuable*."

Those in the succeeding mother category felt good when they lost weight and when their bodyweight was back after a few weeks to what it was before pregnancy. Hence, one protective factor seems to be a feeling of contentment with their own bodies.

The mothers following this trajectory mainly experienced breastfeeding as unproblematic. Breastfeeding also seemed to contribute to healthier eating patterns. "*As long as I breastfeed, it is easier to eat regularly and be more flexible*." In addition, a good collaborative relationship with their partner contributed to the positive development in this trajectory. "*My husband has been very supportive to me and gave me a lot of positive comments on me being a good mother*." So, too, did simply being with the baby. "*My daughter makes me feel good. She makes me feel needed. It is like I no longer need the ED to feel special*."

3.3.3 The inadequate mother: inadequacies throughout pregnancy and early motherhood

This trajectory is based on seven of the participants. The women in the inadequate mother category reported that their ED pathology re-emerged or intensified before they became pregnant and continued to intensify through pregnancy and early motherhood. They interpreted their ED as something to hold onto when everything else was unpredictable. Throughout the trajectory, a feeling of insecurity dominated and intensified as the pregnancy developed to the time around delivery and beyond.

Precursors: All seven women in this trajectory had a history of severe AN. Several of them had suffered from anxiety in their childhood. "*I was always described as a very worried type through my childhood. Now, worrying about another person is making this worse*." These women came to pregnancy with a general feeling of insecurity and a high level of anxiety. Even before becoming pregnant, they were scared of doing something wrong that could harm the baby in the future. Most of them were therefore ambivalent about becoming pregnant, and when they became pregnant, the pregnancy was difficult to deal with.

Triggers: Six of the seven inadequate mothers became pregnant through IVF. For all of them, the inability to become pregnant and difficulties in becoming pregnant through IVF were a trigger for their

ED, which developed further into pregnancy. They experienced their inability to become pregnant naturally as a loss of control. "*In the past, the ED was a lot about mastery and control. I have set myself goals and managed to reach them. When I wasn't able to get pregnant, I had no control*."

All the women in this trajectory experienced pregnancy as extremely overwhelming and as something that triggered feelings of guilt and self-contempt. "*I've ruined myself all these years with my ED. It's my fault. And now I cannot focus on the baby, but only myself. What kind of a mother will I be?*" Throughout pregnancy, these mothers set high expectations for themselves and how they might appear as mothers. "*I have always been concerned about what others think of me. What did other people think of me, knowing about my history with EDs? This was something I was obsessed about during pregnancy and as a mother*." Together with the continued fear of doing something wrong that could harm the baby, these expectations seemed to nourish the ED pathology.

All the brooding and rumination over doing things right led to the mothers feeling detached from their body and their baby. They were not sensitive to the baby's movements and were afraid that they would not notice if something was wrong. During pregnancy, they had a strong focus on excessive exercise and made detailed plans to "*get the body back*" after birth. The IVF process also triggered disgust toward their own body that lasted throughout the pregnancy and after birth. "*My body is bulky and disgusting. I do not recognize it*."

The feeling of inadequacy during pregnancy continued into feeling inadequate as a mother. Excessive exercise continued to take their attention away from their baby. They hoped that by focusing on their body shape, appearance, and weight, they would feel better about themselves. This focus helped them obtain a sense of mastery but reduced their attention on their baby. Their parenting thus became inconsistent and unpredictable. "*I cannot focus on the child right after eating. I become completely distant*."

At the same time, they were afraid that they would no longer enjoy time with their baby. "*It takes up too much of my time, and there is none left to focus on the child*." Overconcern for how others might think of them as a mother led these mothers to retain their strict ED regimes. They did not dare prioritize activities other than the baby and exercise. These mothers admitted that they found it difficult to differentiate between their own needs and their baby's.

The women in the inadequate mother category felt that the quality of their motherhood was being judged. "*When I go to the controls with my baby, I feel like I am going to take an exam each time. It feels uncomfortable to put the baby on the weighing scales*."

Feeding their baby poses a challenge for those with EDs. The baby's appetite and hunger are difficult to deal with. "*I do not know whether she is hungry or just in need of comfort. I always offer breastfeeding first*." Breastfeeding also became a way of losing weight or being able to eat "normal" amounts of food. "*Breastfeeding gives me permission to eat more than I normally can*." Transitioning to solid food is difficult, and the fear of stopping breastfeeding is seen as a trigger. "*I then have to change routines, and that's scary*."

Those in the inadequate mother category struggle with feelings of not being a good enough mother. "*That someone else is completely dependent on me scares the crap out of me*." Often, the mothers in the study did not feel enough support from their parents, husband, or friends. They felt a fear of being judged by others and were oversensitive to being negatively evaluated. "*I need to know I am doing things right. I need to hear it from both my partner and the health center*."

Their ED pathology was something that the inadequate mothers held onto; strict routines and rules created a feeling of safety. "*The focus on the ED made me feel safer. I had something concrete to hold onto when everything else was unpredictable*."

Protective factors: The narratives behind this trajectory contain only modest references to distinct events that could be considered factors protective against EDs.

3.3.4 The depressed mother: EDs worsening after birth

This trajectory is based on ten of the participants. All were second- or third-time mothers. All these of the participants were diagnosed with postpartum depression after birth by a medical general practitioner. During pregnancy, the women in the depressed mother group put their ED pathology on hold by planning how to deal with body, weight, and shape changes after birth. The ED pathology intensified into early motherhood when nothing went as planned.

Precursors: These women noted that their body was changing in ways that differed from the first time they became pregnant. In our study, these women all had a history of BN. The depressed mothers referred to their ED pathology as involving the desire to hold onto still being identified as "*the thin girl*." They often grew up with a mother who binged and purged and talked about how they gained weight through their pregnancies.

Triggers: During pregnancy, the women in this trajectory tended to experience rapid body changes. Detachment from their body and pregnant stomach triggered a fear of reawakening their ED pathology. These women made a rule for themselves that their ED behavior would not be something to fall back into, and they put all such behavior on hold during their pregnancy.

Among the depressed mother group, the delivery became a further trigger for their ED pathology. Nothing went as planned. In our study, all the women in this trajectory experienced complications. "*It all became very acute. Nothing went as planned, and it was so chaotic. I was supposed to have a normal birth, but then suddenly the situation went out of control. A lot of doctors and nurses were around me, my partner was gone, and everything happened very fast*."

Several things worsened in the postpartum period. All the women in the depressed mother group were diagnosed with postpartum depression. They were not able to fulfill their plans about exercise and healthy dieting. This made them feel like a failure. "*I am nothing. I wasn't able to complete anything. I got restless and exhausted*." They had trouble soothing their baby. "*If he cried, nothing I did calmed him down. He was struggling with a lot of stomach difficulties and cried a lot*." Breastfeeding was complicated and they could not manage it. "*I gave up. I was useless*." Being the mother of two could be challenging. "*The ED was a way of not dealing with the challenges and my secret escape from all that I cannot deal with*."

Protective factors: The women had managed to get their body back after the previous birth and the plan for how to achieve it this time protected them from ED behavior during pregnancy. This trajectory does not contain references to distinct events that could be considered protective factors against EDs after birth.

3.3.5 The overwhelmed mother: chaos, shame, and guilt throughout pregnancy and early motherhood

This trajectory is based on six of the participants. The narratives behind this trajectory were characterized by using the ED pathology

to deal with the chaos during pregnancy and early motherhood, as well as a kind of self-affirmation of "me as a bad person." An ED pathology while being a mother increases self-blame and provokes shame and guilt.

Precursors: The women in this trajectory typically had a history of intense self-hatred that they linked to traumas in early childhood. These women regarded the ED as a way of dealing with chaos earlier in life. All the women in this trajectory had a history of BN and descriptions of impulsivity. "*I have always been described as impatient and as making decisions without thinking. That's how this 'pregnancy' thing was seen too*." They said that thanks to their treatment history, they had managed to bring more stability into their lives with routines and exercises. In this way, they had managed their impulsivity and BN in recent years.

Triggers: These mothers typically experienced pregnancy as a threat to their sense of control over their lives. They lost all their routines. "*It's all so chaotic. Nothing works. I have lost my own way of living*." Anger and self-hatred were other triggers. "*I feel so angry at this 'thing' inside me, which destroys my body and forces me to eat. And at the same time, I feel like a terrible person for feeling this way*."

Difficulties in dealing with being pregnant triggered a worsening of the ED pathology. Through the ED pathology, they tried to disconnect from being pregnant. "*I cannot deal with the baby inside me. I cannot do it because it makes me feel guilty and like a terrible person for still doing all these harmful things to my body*."

The worsening of the ED involved a vicious circle of purging and overeating. "*I need something that I can hold onto and help me to forget everything else. I cannot control anything right now. Planning my overeating helps me*." The vicious circle continued into early motherhood. The ED became a protection for dealing with shame and guilt. "*Binging and purging allow me to detach from everything. It's like a protection for me*." "*I am afraid of disclosing this to the health care professionals. I am not able to stop, and I am afraid they will think I am a terrible mother*."

In early motherhood, they expressed a fear of harming their child. These mothers were typically worried about transferring their problems to their babies. "*I am terrified that I am going to ruin my baby with my eating problems*."

Three of these mothers delivered later than expected, resulting in a bigger body. They experienced a loss of control during the birth and found it difficult. This resulted in a feeling of being overwhelmed and an alien self. "*I lost all control during birth. My body was huge, and I did not recognize myself at all*."

The hatred of their bodies triggered a further ED pathology. "*My body feels like an alien. I can still feel anger toward the baby for having destroyed my body*." During pregnancy, they felt stuck in a body they hated. Because of the baby, they had lost control over their body. "*I hate this. I am stuck. No freedom*." Members of the overwhelmed mother group typically expressed frustration with their maternal body as well. "*As a pregnant woman, I am like a container that needs to be burst so that the contents can come out. When you have sacrificed your body by giving birth, you must sacrifice it again by being bound to it 24/7. I simply hate it*."

The disgust with themselves was very strong, making it difficult to form a relationship with their baby. "*I get terrified if she looks like me. I heard she had inherited my thighs. That made me feel really bad for her. Poor girl. I am hurting her*." They experienced a sense of ambivalence toward their baby and a fear about connecting to the child. "*In one moment, I can feel intense love for him, but then I start to panic and search for reasons why I cannot allow myself this love. I cannot allow myself to think of myself as a mother and for her to feel love for me. Who do I think I am then?*" Some saw themselves in the baby and consequently could not find the baby lovable. That scared them.

For these mothers, breastfeeding became overwhelming. In the narratives, these women described breastfeeding as something "*suffocating*" and regarded their "*own milk as dirt*." "*Despite the pain, I breastfeed 24/7. And I think I have to in order to be a good mother. I have no other way of calming the baby down*." After some months, they decided to start with a bottle, and their partners took responsibility for the feeding. All of the women in this trajectory stopped breastfeeding.

Protective factors: Good support from the partner was identified as an important protective factor in early motherhood.

4 Discussion

In this study, we explored the experiences that women with a history of EDs go through from pregnancy to early motherhood. We aimed to describe this process from the women's perspectives. On the basis of analyses of the women's descriptions, we identified different trajectories of the ED pathologies during pregnancy, birth, and postpartum. To the best of our knowledge, this is the first study to examine these processes and trajectories among this highly vulnerable group of mothers.

It is widely accepted that pregnancy and postpartum are particularly vulnerable times for women's mental wellbeing (40–42). However, in-depth descriptions of how women with a history of EDs experience the trajectory of their eating problems through these phases of life are lacking. Such descriptions are important because they can increase health care providers' sensitivity to and understanding of differences in psychological dynamics between women with similar symptoms.

The results revealed great variations in the ED trajectories and in the experience of becoming a mother among these women. Some seemed to improve or recover from their ED pathology, whereas others relapsed or saw their ED intensify.

We identified five distinct trajectories into motherhood: the mastering mother, the succeeding mother, the inadequate mother, the depressed mother, and the overwhelmed mother. These five trajectories reflect the complexity of the ED pathologies during pregnancy and early motherhood. They show how women link combinations and varying degrees and qualities of precursors, triggers, and protective factors to improvement, worsening, or relapse through these phases of life.

In three of the trajectories, we found triggers for worsening or relapse during pregnancy that continued into early motherhood. In the depressed mother trajectory, the women seemed to put their ED pathology on hold during pregnancy, but it intensified after birth and into early motherhood. During those periods, they were unable to complete their plans and experienced failure as a mother. In the inadequate mother trajectory, the women seemed to be overwhelmed by anxiety and unpredictability that worsened their ED pathology

before pregnancy when they failed to become pregnant. In the overwhelmed mother trajectory, it seemed to be the actual pregnancy that triggered the reappearance of the symptoms. In this trajectory, the women deviated significantly from those in the other trajectories. This trajectory included precursors of self-hatred directed toward themself as a whole, their body, and/or their baby.

These findings agree well with previous findings that pregnancy and early motherhood may be vulnerable periods for women's mental wellbeing (41, 43) and can be an extremely challenging time for women with an ED (3, 26, 27, 29, 44, 45). They are also consistent with previous findings that women who experience anxiety, depression, and high body dissatisfaction during pregnancy are more likely to develop postpartum depression (46, 47).

In two of the trajectories we identified, the mastering mother and the succeeding mother, the process of becoming a mother seemed to lead to improvement and recovery. Underlying mechanisms seemed to be a sense of mastery, a new meaning in life, and a feeling of self-worth. Even though the women in both the mastering mother and the succeeding mother trajectories recovered in the postpartum phase, these trajectories appeared to differ during pregnancy. In the succeeding mother trajectory, the women experienced a relapse during pregnancy followed by improvement in early motherhood. These women experienced motherhood as something that gave them a feeling of being someone. This is consistent with previous findings that being a mother can change women's sense of self-identity in a positive way and thereby reduce their ED pathology (14, 15, 17, 19). However, in the mastering mother trajectory, the improvement occurred during pregnancy and early motherhood, whereas in the succeeding mother trajectory, it occurred only in early motherhood. We also found that precursors such as perfectionism, rigidity, and high achievement may be protective factors associated with improvement. It is well known that being pregnant and becoming a mother affects a woman's self-identity (42). This study suggests that in women with a history of EDs, becoming a mother is a determinant of relapse, worsening, or recovery from EDs.

We did not investigate the clinical implications directly, but we can assume that women in the mastering mother trajectory would profit from support that strengthens the positive focus on the role of being a mother. Women in the succeeding mother trajectory might need comfort, predictability, and help in making good routines for themselves and their baby. Women in the inadequate mother trajectory would need support to feel good enough, to be reassured that the baby is doing well, and to cope with emotional experiences. Women in the depressed mother trajectory may need help establishing routines to which they are able to stick. Women in the overwhelmed mother trajectory would most likely profit from help that emphasizes building self-compassion and reducing shame.

It should also be borne in mind that these five trajectories are not mutually exclusive. Despite the different combinations of structural components, the narratives of the participating women had several themes in common. These included low self-esteem, feelings of shame, and problems with emotional regulation. To translate the findings of this study into health care service procedures and treatment strategies, further research is needed. Most importantly, however, this study points to the need to take the patient's experience into consideration when a woman with a history of EDs becomes pregnant or plans to become a mother.

4.1 Strengths and limitations

Many patients do not disclose their eating problems to health care providers. The strengths of this study are the relatively large number comprising the non-clinical sample of women with a history of severe EDs, the high-quality in-depth interviews, and the longitudinal design, with data collections during pregnancy and 4–6 months postpartum, including retrospective data from the delivery. The use of standard diagnostic interviews both during pregnancy and at postpartum strengthened the diagnostic validity of the study. Another strength is the inclusion of the categories of AN, BN, OSFED, and UFED in both data collections; most studies are limited to AN and BN at only one time point. By including OSFEDs and UFEDs, one might capture cases that still have an ED (48), but who do not fulfill all the criteria for a specific ED. Both OSFEDs and UFEDs might be more suitable to select pregnant women whose clinical characteristics can be temporarily masked during pregnancy. Studies show that OSFEDs and UFEDs may be as severe and longstanding as a specific ED (49).

This study has several limitations. All the participants had received some kind of psychotherapy for their ED. This may have increased their understanding of their condition that would not otherwise have been there. We did not know how representative the participants are of women with a history of EDs. Even though the recruitment setting was non-clinical, we cannot exclude the possibility that the recruitment process facilitated the recruitment of women with the most salient eating problems. Although the participants were diagnosed as having an ED, we did not know how many or who had recovered before they became pregnant. Past history of the ED and its severity were self-reported; the participants' health records were not verified. Consequently, we could not differentiate between those women who had an ED diagnosis when they fell pregnant and then worsened and those who had recovered and then relapsed. Additionally, having the same person conduct the semi-structured interviews and EDE might have influenced the responses in the interviews and the outcomes of the diagnosis. The interview time point during pregnancy varied between week 9 and week 40 and at postpartum between 4 and 6 months after delivery. Finally, we did not include the participants' partners. They might have provided us with comparative information.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Regional Committees for Medical and Health Research Ethics (REC) 20th of May 2020, Reference 92665. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

BS: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Validation, Writing – original draft, Writing – review & editing. FS: Formal analysis, Methodology, Project administration, Supervision, Validation, Writing – review & editing. IK: Project administration, Validation, Writing – review & editing. KG: Methodology, Project administration, Supervision, Validation, Writing – review & editing. AH: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Supervision, Validation, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. The research was supported financially by the Norwegian Women's Public Health Association through a grant for the project "Mummy bodies, eating disorders, pregnancy and postpartum" (Grant: 40404).

Acknowledgments

We are immensely grateful to the women who shared their intimate thoughts with us. We would like to thank Editage (www.editage.com) for English language editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Psychiatry

TYPE Perspective
PUBLISHED 18 January 2024
DOI 10.3389/fpsyt.2023.1321265

OPEN ACCESS

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RECEIVED 13 October 2023
ACCEPTED 27 December 2023
PUBLISHED 18 January 2024

CITATION
Turchioe MR, Hermann A and Benda NC (2024) Recentering responsible and explainable artificial intelligence research on patients: implications in perinatal psychiatry.
Front. Psychiatry 14:1321265.
doi: 10.3389/fpsyt.2023.1321265

Recentering responsible and explainable artificial intelligence research on patients: implications in perinatal psychiatry

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In the setting of underdiagnosed and undertreated perinatal depression (PD), Artificial intelligence (AI) solutions are poised to help predict and treat PD. In the near future, perinatal patients may interact with AI during clinical decision-making, in their patient portals, or through AI-powered chatbots delivering psychotherapy. The increase in potential AI applications has led to discussions regarding responsible AI and explainable AI (XAI). Current discussions of RAI, however, are limited in their consideration of the patient as an active participant with AI. Therefore, we propose a patient-centered, rather than a patient-adjacent, approach to RAI and XAI, that identifies autonomy, beneficence, justice, trust, privacy, and transparency as core concepts to uphold for health professionals and patients. We present empirical evidence that these principles are strongly valued by patients. We further suggest possible design solutions that uphold these principles and acknowledge the pressing need for further research about practical applications to uphold these principles.

KEYWORDS

artificial intelligence (AI), explainable AI, bioethics, perinatal psychiatry, patient centered care

1 Introduction

An estimated one in five women in the United States experience depression between conception and 6 months postpartum (1). For this reason, the United States Preventive Services Task Force recommends routine perinatal depression (PD) screening (2). Other studies have estimated perinatal anxiety may be more prevalent, but there are not yet widely used, perinatal-specific screening tools such as the Edinburgh Postnatal Depression Scale (3). Clinician time constraints, resource availability, validity of screening tools across the perinatal period, and patient willingness to report mental health symptoms present challenges to identification (4, 5). Many also face barriers to treatment including limited access to perinatal psychiatrists and financial constraints (6, 7). As a result, therapeutic interventions are initiated late after symptoms develop (e.g., *secondary prevention*) (5), and as many as 75% of women who experience symptoms of perinatal mood and anxiety disorders (PMADs) go untreated altogether (8). Left untreated, PMADs can lead to poor maternal and infant outcomes, including pre-eclampsia (9), prematurity (10), low birth weight (11, 12), and behavioral dysregulation (13–15), lower vagal tone, decreased immunity, and adverse neurodevelopmental

outcomes in the child (16). Suicide and overdoses are leading causes death in the first year postpartum (17–19).

In the setting of underdiagnosed and undertreated PMADs, novel strategies are needed. Artificial intelligence (AI) is poised to help address these barriers to PMADs diagnosis and treatment. AI involves the development of computer systems that are able to perform tasks that normally require human intelligence such as classifying and predicting disease, recommending treatments, and producing interactive chatbots that leverage large language models to generate humanlike responses (20). For example, AI models can accurately identify women with an elevated risk for PD, enabling primary prevention, before the onset of severe symptoms (4–6). Primary prevention is significantly more effective than secondary prevention for at-risk women (21). Numerous studies have reported on predictive models that can predict PD with high accuracy using a range of datasets (22–24). Specifically, researchers have used electronic health records (EHRs) (25), administrative claims data (26), actively and passively collected data from smartphones (27), social media data (27), and patient-reported outcomes (27, 28), to predict PD, and, in one study, postpartum psychiatric admission. AI-powered chatbots have also become increasingly researched in mental health generally for their potential to deliver psychotherapy (29, 30), and may soon be tailored to the unique needs of perinatal individuals (31, 32).

Artificial intelligence for perinatal psychiatry is now in the early, proof-of-concept stages, but researchers, health systems, and companies are planning for implementation (32). The American College of Obstetrics and Gynecology (ACOG) has also issued guidelines highlighting the potential for AI and other technologies to enhance pregnancy-related care (33). Now is the time to ensure that patient perspectives are understood and integrated into care delivery that uses AI; failure to do so may undermine the very trust in clinicians that is so fundamental in mental healthcare. Research on the bioethical implications of AI in healthcare has raised many important patient safety and quality considerations (34). These conversations have generated popular terms such as *responsible AI (RAI)*, which calls for AI that is ethical, transparent, and accountable while also aligning with stakeholder expectations (35, 36). Similarly, there has been significant interest in *explainable AI (XAI),* which is a set of techniques ensuring that a person can understand how or why an AI system came up with a certain output (37). XAI can be considered a subdomain of RAI because transparency and explainability help identify biases and support autonomous decision-making.

However, RAI and XAI work has primarily assumed that AI was *patient-adjacent:* that patients are recipients of AI-propagated benefits or harms, but that they do not interact directly with it. Rather, we argue that there is a need to equally consider *patient-centered AI*, in which the patient interacts directly with AI during the course of their care. There are many envisioned use cases of patient-centered AI in perinatal psychiatry. Patient engagement and shared decision-making continue to rise in importance in healthcare, making it likely that AI-generated risk predictions will be discussed or presented to patients in clinical care as part of the decision-making process (38). Additionally, new United States policies prohibiting "information blocking" have also led to a deluge of information being returned to patients through patient portals (39), and this information may soon include AI-generated risk predictions that are integrated into EHRs. Finally, AI-powered chatbots delivering psychotherapy represent another example of patients directly interacting with AI (40). Considering patient-centered AI calls for understanding how to responsibly implement AI in a manner that further fosters, rather than undermines, trust. Therefore, in this perspective, we will describe RAI and XAI research, relate it to patient-centered AI, articulate important bioethical concepts in patient-centered RAI and XAI, and describe why these concepts are of particular importance for perinatal psychiatry. We argue that patient-centered AI must consider bioethical constructs while also factoring in important elements of context including type of data being used to develop AI, persons with whom AI or data are shared, what tasks AI supports, and intended time period of use (i.e., preconception, pregnancy, or postpartum).

2 The current landscape of RAI and XAI

Many ethical concerns have been raised about the uses of AI in healthcare. From a legal and regulatory standpoint, the European Union (EU) has issued seven key requirements for trustworthy AI, which relate to human agency and oversight, technical safety and rigor, privacy, transparency, fairness, societal and environmental well-being, and algorithm accountability (21). The EU also has strict regulations, the General Data Protection Regulation (GDPR), regarding data sharing and secondary uses of personal data, which relate to AI algorithm development (41). Such guidance and regulations are lacking, however, in the United States and many other nations worldwide, though the White House has proposed the AI Bill of Rights, containing many elements similar to the GDPR (42).

Responsible AI encompasses the conceptual and empirical work investigating responsible uses of AI (36). Four key ethical principles of beneficence, non-maleficence, autonomy, and justice have been adapted to the AI use case, with new acknowledgments of the interplay between these principles and the external agencies, patients, and the complex technical and clinical environments with which AI is used (43). Research has shown that deliberately communicating information about plans to enact these principles when implementing AI in healthcare is associated with favorable attitudes, satisfaction, and high usage intentions among clinicians (36). Some have proposed practical guidelines to operationalize these principles when AI is implemented in clinical practice, including checklists, governance processes, and training for clinicians (44). We have identified that communicating the purpose (why the AI was developed and what it does), process (how it operates), and performance (how well it functions) of an AI system helps users form greater trust (45). In general, however, the majority of RAI work has been highly theoretical, and more practical guidance is needed (46). This research has also primarily considered clinicians to be the end users, while patients are passive participants in the AI–they are considered recipients of the benefits and harms of AI, but not agents interacting directly with it (47–49).

A fifth bioethical principle, explainability, has been proposed as relating to, and upholding, the other four principles previously mentioned (36, 50). Explainability, or XAI, is the idea that humans should have insight into how an AI system works. In the literature, it is an often-used yet poorly defined term. Some have defined it as broadly as technological transparency in general, while others argue it has specific requirements including the ability of a human operator to reconstruct how an AI system uses data, moves through a

decision-making process, and arrives at a conclusion (37, 51). XAI has been described as a necessary component of RAI because without explainability, it is difficult for clinicians to exercise their independent clinical judgment (i.e., act autonomously), or for them to ensure that AI is helping, not harming, all of their patients–not just a select few (i.e., upholding beneficence, non-maleficence, and justice) (36). XAI is necessary because of the "black box" problem; for many types of models, particularly those that use deep learning (a type of machine learning), the internal workings of the algorithm are unknown to the developers or end users. Explainability measures attempt to "shine a light" into the black box by using additional algorithms to understand how and why an AI model is producing certain output (52, 53). For example, XAI may tell a clinician which variables included in a model are most contributing to a specific patient's risk of developing PMADs. To further enhance clinical utility, researchers have also explored visualizations of these explainability measures (54). However, as with RAI research in general, nearly all of the research into XAI techniques considers clinicians to be the primary end users (38). Therefore, the unique information needs and bioethical concerns of patients who may be directly interacting with AI in the course of their care have not been fully considered.

Concepts of RAI and XAI are also complex as perspectives may vary based on context. For example, a recent survey of 610 United States-based adults (sampled to reflect racial, sex, and age demographics of the United States) found that willingness to share health information varied by the type of data (sexual health information, imaging data, genetic data, or mental health information) and persons with whom the information would be shared (e.g., health technology companies, doctors and nurses, and chosen friends and family members). Of note for perinatal psychiatry, participants were least comfortable sharing sexual and mental health information, respectively (55).

3 RAI and XAI matter to perinatal psychiatry patients

Trust in AI is one of the biggest challenges in clinical practice and one of the goals of AI implementation has been to foster appropriate trust. Much of the AI implementation research to date has focused on presenting model output and fostering trust in AI among clinicians (45). Maintaining the trust of patients who may be directly interacting with AI is of equal importance, as trust is a fundamental requirement of patient-centered perinatal psychiatry.

Perinatal psychiatry presents a complex bioethical case because of the sensitivity of both pregnancy and mental health data, and the multiple layers of autonomy. In pregnancy, the autonomy, harms, and benefits afforded to the pregnant person, newborn or fetus, and partner must be weighed simultaneously (56, 57). Mental health issues in the perinatal person can negatively impact the newborn or fetus, and partners play an important supportive role in caring for both the perinatal patient experiencing PMADs and the newborn. There is also a layered network of care providers that may at different points in time include, obstetrics, midwifery, doulas, mental health professionals, primary care providers, and pediatricians. Although, the perinatal person may have different levels of comfort disclosing PMADS symptoms to different roles, for example their own obstetrician vs. their child's pediatrician. Furthermore, perinatal persons may be reticent to accept AI solutions that can predict or treat PMADs. Some concerns relate to the way their personal health data is being used. Numerous research studies have noted that integrating multiple datasets including EHRs, claims data, patient-reported outcomes, and data collected from smartphones and social media improves prediction accuracy (26–28). Perinatal people may be alarmed to discover their EHRs are being repurposed and used for AI-based risk prediction, and may first learn about it when encountering an AI-based risk prediction with their clinicians. Similarly, perinatal persons may have unique concerns about wearable data being hacked or inappropriately shared (e.g., disclosing their location and movements in ways that may be dangerous). For example, many have shed light on the privacy violations and monetization of data collected from period tracking applications (58, 59). These issues are often compounded by the broader concerns about revealing a mental health diagnosis during the perinatal period, such as fear of stigma or loss of custody of one's baby (22, 60). Moreover, ethical considerations and factors needed to build trust differ by demographic variables, such as race and/or ethnicity, due to well-documented issues of algorithmic bias (61). Therefore, it is imperative that approaches to patient-centered AI for perinatal applications inclusively represent different patient groups, taking special care to ensure minoritized groups may equitably reap benefits and not be disproportionately exposed to harms of AI.

Although in its nascent stages, research on perinatal patients' attitudes toward AI confirms their strong desire to be involved and informed about how AI is being used in their care. For example, one survey examined the perspectives of 258 English-speaking United States persons registered with an online survey-sampling platform regarding their attitudes toward AI use in mental healthcare. The sample was reflective of the United States population based on race. While the study involved persons with inadequate health literacy (24%), those with less than a Bachelor's degree (47%), and persons reporting Hispanic/Latino ethnicity (6.5%), these numbers are generally lower than national averages. The authors found most participants reported it was "very important" for them to understand AI output, that participants with a history of pregnancy were significantly more likely to feel this transparency was important, many participants were concerned about medical harm resulting from AI, inappropriate data sharing, and that AI may lead to their mental health provider not knowing them as well (62). Similarly, another study surveyed 150 pregnant persons in Spain from a single hospital. The respondents had somewhat higher rates of tertiary education than the Spanish public (41% in the study vs. 33% nationally). They found that participants strongly endorsed the need for AI to be responsible, trustworthy, useful, and safe, many have privacy concerns, and, importantly, XAI would increase the trust and confidence of participants who were averse to AI being used in their care (63). Importantly, in both studies, participants reported generally high levels of openness to AI being used in one's healthcare, but all wanted their clinical care team to play a role in ensuring the safe, responsible use of AI (62, 63). These issues should be further evaluated in a sample that is better representative of those that have lower literacy, less education, and a greater proportion of those with Hispanic/Latino ethnicity.

The United States-based study described also, found differences in participants' comfort with AI based on the task the AI performed. Participants were least comfortable with diagnosis delivery tasks (i.e.,

AI telling someone they have a mental health condition) and recommending medication. Participants were relatively more comfortable with non-pharmacological treatment recommendations and AI performing mental health assessments (62).

4 How can we uphold patient-centered RAI and XAI in perinatal psychiatry?

A practical understanding of patient-centered RAI in perinatal psychiatry is critically needed to support patients in seeking care, receiving care, and maintaining a positive therapeutic alliance with mental health professionals when AI may be involved. As a first step, it is important to identify the bioethical issues of importance to patients that may be operationalized in practice in the future. Previously, our team has synthesized research on RAI generally (64), as well as the ethics of using consumer-generated data (65), AI in psychiatry (20), and maternal health (66, 67) to identify core ethical concepts to be considered in the perinatal psychiatry space.

We propose six bioethical constructs for upholding patient-centered RAI, including *autonomy, privacy, beneficence, justice, transparency, and trust* (also shown in Figure 1). *Autonomy* calls for patient self-determination regarding how their data are used by those developing AI, and provide informed consent in ways that are specific to the data type, recipient, and use case. We assert that this autonomy lies with the birthing person involving informal support (e.g., partners, family members) as desired, or in rare circumstance where medical proxies may be required. Relatedly, *privacy* calls for the appropriate and confidential uses of personal health data to train AI, and for data use to be deferential to patient wishes as described in a consent process. Communication of privacy-related practices is even more crucial from a reproductive health perspective given the sensitivity of the data that may be involved. When data involve the infant, privacy from the perspective of the non-birthing partner may also become a consideration. *Beneficence* calls for AI to demonstrably improve patient outcomes and, as an implied partner to this, that risks and harms from AI are minimized (i.e., non-maleficence). In perinatal settings, beneficence must not only consider the birthing person but also ensuring potential harms to the child are minimized while prioritizing the autonomy and wellbeing of the birthing person. *Justice* calls for the equal and fair access of the benefits of AI to be evenly distributed among all patients. As part of this, it is important to consider the diversity of patients affected by AI, which includes considering potential sources of algorithmic bias as well as differing information needs and preferences based on different levels of health literacy, numeracy, and experiences of implicit bias in healthcare interactions. Given United States-based disparities in perinatal health

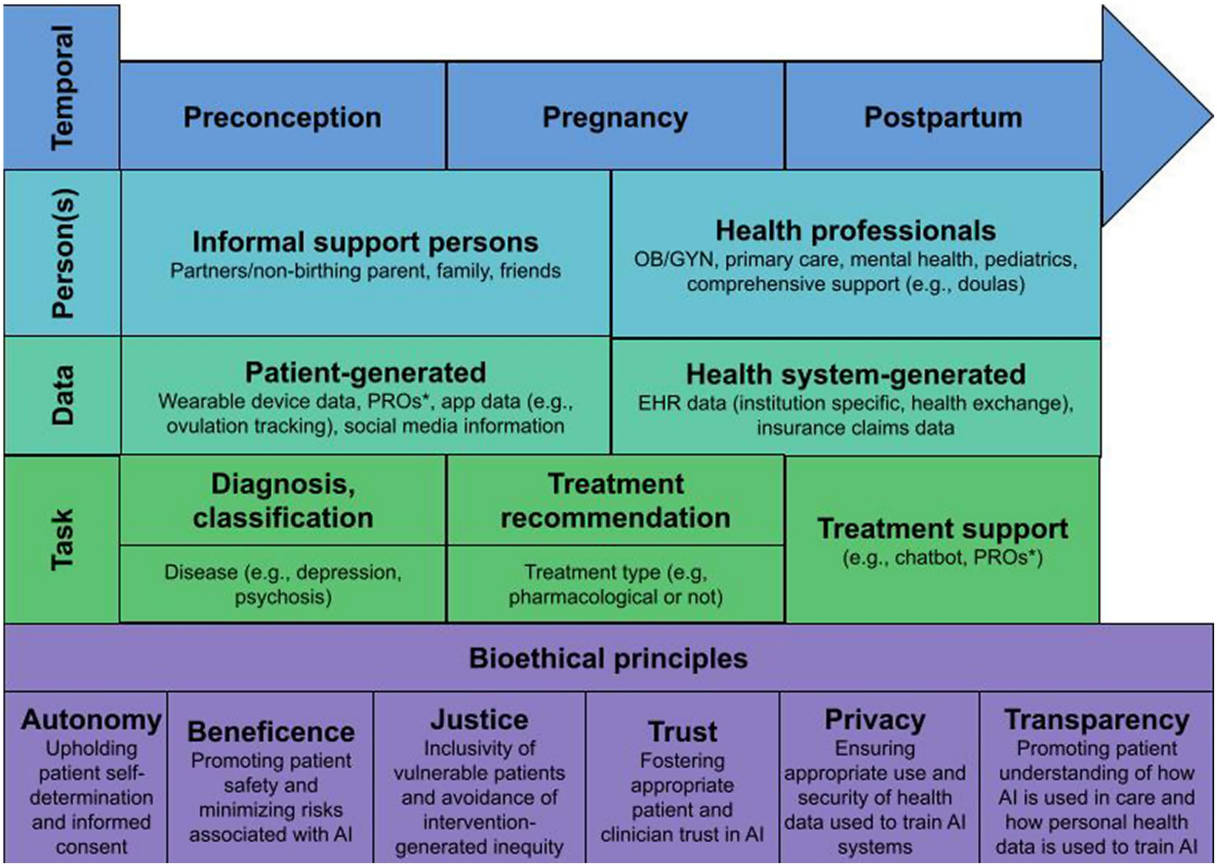

FIGURE 1
Temporal, person, data, and task-based elements that must be considered in the context of bioethical principles to support RAI and XAI for perinatal psychiatry. * Patient reported outcomes.

outcomes, the disproportionate share of adverse perinatal outcomes occurring in low-and-middle-income countries, and the lack of mental health support for minoritized groups, justice holds particular importance in perinatal psychiatry. *Transparency* calls for XAI that considers the patient as the end user, and ensures that patients can understand how AI is used in their care, how their personal health data was used for that AI, and, crucially, how AI arrived at a specific conclusion relating to their health or healthcare. This principle may be the most different from the general discussions of XAI and RAI as communicating AI output to patients has not previously been explored. Finally, underlying each of these principles is *Trust*—the need to ensure that trust between patients, clinicians, and AI is not undermined. Because AI research both within and beyond perinatal psychiatry has demonstrated that clinicians' perceptions of AI play a significant role in patients' attitudes toward it (62, 63, 68, 69), we must consider the interplay of trust between patient, clinician, and AI.

Our empirical research with 258 pregnancy-capable (female sex at birth) United States-based survey respondents (also described above) showed that these concepts resonated with participant groups relevant to perinatal psychiatry. The majority of participants surveyed about the potential use case of AI for mental health endorsed that it was "very important" that they could understand which of their individual risk factors for depression are used by AI (85%), AI will decrease the chance of negative outcomes (77%), they were aware of how their personal data was being used for AI (75%), they were able to make up their own mind about their risk for depression based on AI output (71%), they can understand how likely it is that they develop depression within the next year according to AI (71%), and AI will improve depression and/or depressive symptoms (62%) (62).

The endorsed importance of the six bioethical constructs among survey participants suggests they may serve as a future research agenda for those studying the ethical implications of patients interacting with AI in mental healthcare. However, given the sensitivities and complexities related to perinatal psychiatry, there are also data, person, task, and temporal factors that must be considered. Figure 1 outlines important elements to consider as it pertains to each of these factors in the context of perinatal psychiatry. First, patients may have different needs or perspectives, or there may be different persons to involve based on *temporal* factors, specifically whether they are preconception, currently pregnant, or postpartum. This also considers that patient perspectives and needs are fluid within and outside of these time frames. Second, there are numerous *persons* who may influence data used for AI or may have access to AI-related information, including both informal support persons and health professionals. Which persons are involved and patient perspectives regarding their involvement will likely be individually dependent. Third, AI may be informed using various different kinds of patient and health-system generated *data* elements, some of which have been described. While these elements may not differ much for perinatal persons, the information may have increased sensitivity which should be considered, for example, app-related data that track ovulation or pregnancy, or mental health reported outcomes. Fourth, AI may be used to support diagnosis/classification, treatment recommendation, or treatment support related tasks. Needs and opinions on diagnosis and classification tasks may vary based on perceived severity of disease (e.g., psychosis vs. moderate depression) or other factors. Based on our previous work, patient comfort with treatment recommendation tasks may vary based on whether or not the treatment involves pharmacotherapy, and these perceptions may also differ throughout the preconceptions, pregnancy, and postpartum life-cycle. Fourth, treatment support may come in many different forms with varied levels of autonomy, such as using patient-reported outcomes (PROs) to support health-professional led care to having a nearly-autonomous chatbot leading therapy. Last, these factors must continue to be weighed with the foundation of bioethical principles described above. There are likely more questions than answers related to AI use for perinatal psychiatry in these nascent stages, but we advocate that a research agenda should consider these bioethical constructs and contextual factors in order to ensure AI in perinatal psychiatry may be safe, inclusive, and patient-centered.

It may be possible to design patient education materials, or features in the AI-integrated technology itself, to uphold bioethical principles in practice while still considering important contextual factors. For example, computational interpretability methods that explain important predictors in AI-generated risk prediction [e.g., SHapley Additive exPlanations, or SHAP (70)] may improve patient and clinician trust in the AI and foster its appropriate, safe use. Because visualizations objectively improve comprehension (71, 72), these methods should include visualizations that are comprehended by patients, not just clinicians. Additionally, patient educational materials or "InfoButtons" embedded directly in AI-enhanced technologies can explain an AI's purpose, its use of personal health data, and its performance, which may support autonomy and transparency. Communication of this information should also follow inclusive design principles to uphold distributive justice (73). Based on described shortcomings in the samples included in previous relevant research (62, 63), it is also important that further empirical studies be conducted with samples that reflect the ethnicity, literacy, and educational backgrounds of diverse perinatal populations. This may be accomplished scientifically by instituting sampling quotas or over-sampling typically under-represented groups. Practically, it will be important to work with community-based organizations to support: recruitment, use of appropriate language, and fostering trust with groups that have a history of facing discrimination in a healthcare setting.

In the near future, perinatal patients may interact with AI during clinical decision-making (38), in their patient portals (39), or through AI-powered chatbots delivering psychotherapy (40). Current discussions of RAI are limited in their consideration of the patient as an active participant with AI. Therefore, we propose a patient-centered, rather than a patient-adjacent, approach to RAI and XAI, that identifies autonomy, beneficence, justice, trust, privacy, and transparency as core concepts to uphold. Although we suggest possible design solutions, research about practical applications to uphold these principles is needed as a next step.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

MT: Conceptualization, Writing – original draft. AH: Writing – review & editing. NB: Conceptualization, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the National Institute of Mental Health (R41MH124581-S1; PI—Pathak). MT is supported by the National Institute of Nursing Research (R00NR019124; PI—MT), and NB is supported by the National Institute on Minority Health and Health Disparities (R00MD015781; PI—NB).

Conflict of interest

MT and AH are co-founders and have equity in Iris OB Health, New York.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Psychiatry

TYPE Original Research
PUBLISHED 22 January 2024
DOI 10.3389/fpsyt.2024.1295988

OPEN ACCESS

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RECEIVED 17 September 2023
ACCEPTED 02 January 2024
PUBLISHED 22 January 2024

CITATION
Matsunaga M, Okajima J, Furutani K, Kusakabe N and Nakamura-Taira N (2024) Associations of rumination, behavioral activation, and perceived reward with mothers' postpartum depression during the COVID-19 pandemic: a cross-sectional study.
Front. Psychiatry 15:1295988.
doi: 10.3389/fpsyt.2024.1295988

Associations of rumination, behavioral activation, and perceived reward with mothers' postpartum depression during the COVID-19 pandemic: a cross-sectional study

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Introduction: The COVID-19 pandemic has led to increased social isolation for mothers, and rumination exacerbates postpartum depression in mothers with poor social support. Although behavioral activation can help to decrease their depressive symptoms, the mechanism by which behavioral activation reduces postpartum depression remains unclear.

Methods: We examined the effects of rumination and behavioral activation on depression in postpartum women by examining a model mediated by subjective reward perception. A questionnaire was administered to 475 postpartum women (Age: *Mean* = 30.74 years, *SD* = 5.02) within 1 year of childbirth using an Internet survey. The measurements included perinatal depression, rumination, and behavioral activation, and we assessed environmental reward. To control for confounding variables, we assessed psychiatric history, social support, parenting perfectionism, and COVID-19 avoidance.

Results: Eighty-four (17.68%) mothers had possible postpartum depression. The covariance structure analysis showed that not only was there a direct positive path from rumination to postnatal depression but also a negative path via reward perception.

Discussion: This finding indicated that the COVID-19 pandemic could have increased depression in many of the mothers. Rumination not only directly relates to postpartum depression, but it could also indirectly relate to postpartum depression by decreasing exposure to positive reinforcers. In addition, having a history of psychiatric illness increases the effect of rumination

10.3389/fpsyt.2024.1295988

on postpartum depression. These findings suggest that psychological interventions are needed to reduce rumination and increase contact with positive reinforcements to reduce postpartum depression, especially for high-risk groups.

KEYWORDS

postpartum depression, rumination, behavioral activation, reward perception, perfectionism, COVID-19

1 Introduction

Postpartum depression refers to depressive episodes that are prevalent following childbirth (1). Postpartum depression has major implications for the mother's functioning, interpersonal relationships, parenting behaviors, and her offspring's health and developmental outcomes (2, 3). A meta-analysis review showed a 12% incident rate of postpartum depression [95% confidence interval; CI: 0.04–0.20] among mothers (4), with a previous study in Japan showing a prevalence rate of 10%–15% (5). The spread of COVID-19 has led to increased social isolation during pregnancy and postpartum periods, with women avoiding interactions with others or not going out to prevent contracting the COVID-19 infection (6). Rates of perinatal depression and anxiety have thus increased during the COVID-19 pandemic (6–8).

However, the COVID-19 pandemic situation in Japan differed from that in other countries. Specifically, instead of implementing a lockdown of cities by law, the government requested self-restraint to reduce social interaction, along with hand hygiene and mask-wearing (9). Consequently, the traditional support system for perinatal women in Japan, "delivery at hometown," was also restricted. This limitation left mothers vulnerable to the loss of social support and an increased burden of housework and childcare (10). Furthermore, as reported by Tsuno et al. (11), home visits by healthcare professionals and infant checkups or vaccinations were canceled. The deprivation of support during pregnancy or after delivery was also associated with postnatal depression.

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (12), perinatal depression involves a major depressive episode that occurs during pregnancy or within 4 weeks following delivery. Although the biological factors influencing mood during the early postpartum period may be less relevant subsequently, the first year after delivery is replete with many unique psychological stressors (13). In other clinical practice and research, postpartum depression is defined as occurring anytime within the first 12 months after childbirth (13, 14).

Ando and Muto (15) conducted a longitudinal study from the onset of pregnancy to 1 year postpartum. Factors influencing depression could differ depending on the time and physiological factors; for example, low estrogen levels could contribute to depression in the early postpartum period. Furthermore, from 6 months postpartum, the tendency to persist in self-directed emotions and attention, such as self-preoccupation, contributes to high depression levels. Maladaptive emotion regulation strategies (e.g., rumination, self-blame, and catastrophizing) have a significant negative effect on perinatal depression (16).

Regarding the relationship between rumination and postpartum depression, Raes et al. (17) reported that the level of rumination compared to negative affect did not predict depressive symptoms at 12 and 24 weeks postpartum when baseline symptoms and history of major depressive episodes were controlled. This result suggests that a history of major depression when pregnant or earlier is an important predictor of postpartum depression.

Additionally, O'Mahen et al. (18) found that women who were low in social functioning showed a higher correlation between rumination during pregnancy and postpartum depression. This suggests that social functioning moderates the impact of rumination on postpartum depression. In a later study, the researchers (19) also examined the impact of rumination on parental problem-solving effectiveness in postnatal mothers. They found that dysphoric ruminating mothers exhibited poorer problem-solving skills and less confidence regarding their problem-solving abilities compared to dysphoric distracting, non-dysphoric distracting, and non-dysphoric ruminating mothers.

As described above, rumination is associated with postpartum depression and it decreases postpartum mothers' confidence in their ability to solve problems. Further, rumination exacerbates postpartum depression in mothers with a history of depression during or prior to pregnancy, and in those with poor social support.

Rumination is classified as an avoidance behavior, and it primarily involves cognitive avoidance coping. The behavioral theory posits that certain environmental changes and avoidant behaviors inhibit individuals from experiencing environmental rewards and reinforcement, subsequently leading to the development and maintenance of depressive symptoms.

Ferster (20) noted that the most obvious characteristic of a depressed person is the loss of interest in certain kinds of activities coupled with an increase in avoidance and escape activities such as complaints, crying, and remaining in bed all day. Such behaviors also reduce the frequency of behaviors that result from positive reinforcers. Additionally, owing to depressive symptoms, many of the depressed person's behaviors do not receive sufficient reinforcement. As such, they have a high frequency of avoidance, escape from aversive stimuli, and have a reduced frequency of positively reinforced behavior. Consequently, they do not develop a repertoire of positive behaviors (problem-solving, goal achievement, etc.).

Carvalho and Hopko (21) examined the relationship between avoidance and depression using self-report and behavioral indices of environmental reward as proxy measures for

positive reinforcement. They reported that both indices of environmental reward significantly mediated the relationship between avoidance and depression.

Thus, based on this behavioral model of depression, rumination is used as a means of coping with depressive mood and providing temporary mood relief, while maintaining and exacerbating the depressive mood in the long term because of reduced rewards.

Further, behavioral activation, such as increasing activity to increase exposure to rewards, is useful during depression. Increasing goal- and value-based activity levels reduces depression (22).

Regarding the postpartum (perinatal) period, women who received a 12-session guided Internet behavioral activation intervention showed a large effect size on depression at 6 months post-intervention compared with those in the treatment as usual group (23). Another study conducted behavioral activation for 8 weeks on postpartum mothers who were prone to isolation during the COVID-19 pandemic, using an online videoconferencing application [e.g., Zoom; (24)]. Participants reported that behavioral activation helped with support and social connection, creative problem-solving, and attending to pandemic-related symptoms.

Although evidence has shown that behavioral activation is effective for perinatal depression, the detailed mechanisms through which behavioral activation reduces postpartum depression via reward perception are unclear. Further, several risk factors for postpartum depression have been noted, in addition to behavioral factors such as rumination and behavioral activation. For example, the greatest predictor of postpartum depression was the assessment of psychiatric disorders both prior to and during pregnancy (25). Additionally, the strongest postpartum depression risk predictors among psychosocial factors were severe life events, some forms of chronic strain, relationship quality, and support from partners and mothers (26).

Perfectionism plays a critical role in anxiety disorders and depression (27). Definitions of perfectionism center on the pursuit of high standards and self-criticism over not meeting these standards. A meta-analysis showed that perfectionism was also associated with symptoms of maternal perinatal depression and anxiety (28). Parental perfectionism was positively correlated with parental burnout, and perfectionistic concerns were associated with increased tendencies to ruminate about the past (29).

We examined the effects of rumination and behavioral activation on depression in women within 1 year after childbirth by testing a model in which subjective reward perception acts as a mediator (**Figure 1**). We hypothesized that rumination would directly predict postpartum depression, which is predicted indirectly via reward perception. We expected that behavioral activation would directly reduce postpartum depression and indirectly reduce postpartum depression via reward perception. Additionally, we expected that avoiding closed and crowded situations to prevent COVID-19 infection and parenting perfectionism would affect postpartum depression via rumination, behavioral activation, and reward perception. We also tested whether the hypothesized model differs depending on risk factors for postpartum depression, such as a history of mental illness and support from partners or mothers, and clarify the exacerbating factors for postpartum depression in the high-risk group.

2 Materials and methods

2.1 Participant and procedures

We administered a survey registered with a web-based research firm, in January 2022, to 500 mothers. The inclusion criteria were mothers aged 18 years or older with a child under the age of 1. The exclusion criteria were women who were over 50 years old and could not read Japanese. Data from 475 mothers (valid response rate of 95%) were included in the analysis. However, data for mothers with more than one-third non-responses to all items (n = 13, 2.6%), with no children (n = 7, 1.4%), and with children older than 13 months (n = 5, 1.0%) were excluded. The mean age of the mothers was 30.74 years (SD = 5.02); most mothers were married (449, 94.53%) and on parental leave (279, 58.74%; **Table 1**).

Most children were from first-time mothers (268, 56.42%), and children's mean age was 6.04 months (SD = 3.46). Children's sex included 251 (52.84%) boys and 220 (46.32%) girls, while 4 (0.84%) mothers did not provide an answer.

The Research Ethics Committee of the Faculty of Contemporary Psychology at XXX University approved this study (no. ZZZ) [blinded for review]. Informed consent for use of data collected via questionnaires was obtained from participants following the protocol approved by the university's research ethics committee.

2.2 Measures

The Edinburgh Postnatal Depression Scale (EPDS; (30)) was developed to screen for postpartum depression. Okano (31) developed the Japanese version of the EPDS that was used in this study. Participants were requested to respond to 10 questions about their feelings over the past 7 days based on a four-point scale (0–3). The total scores range from 0 to 30, with higher scores indicating a higher likelihood of postpartum depression. For the Japanese version, a score of nine or higher is regarded as indicative of probable depression. The sensitivity was 0.75, and the specificity was 0.93 in the study by Okano (31).

The cutoff point of nine for the Japanese version of the EPDS has been validated in other previous studies (32–34). The sensitivity and specificity of the Japanese version of the EPDS for identifying major depressive episodes both exceed 80%. The factor analysis of the Japanese version of EPDS has not been fully elucidated. First, a confirmatory factor analysis was conducted assuming a one-factor structure. However, the variables of goodness of fit were not sufficient (adjusted goodness of fit index; AGFI = 0.766, comparative fit index; CFI = 0.782, root mean square error of approximation; RMSEA = 0.165). Kubota et al. (35) reported that the result of exploratory factor analysis indicated a three-factor model consisting of anxiety, depression, and anhedonia. Therefore, a confirmatory factor analysis of three factors was conducted, and the goodness of fit was better than that of a one-factor structure; the statistical values were sufficient (AGFI = 0.952, CFI = 0.932,

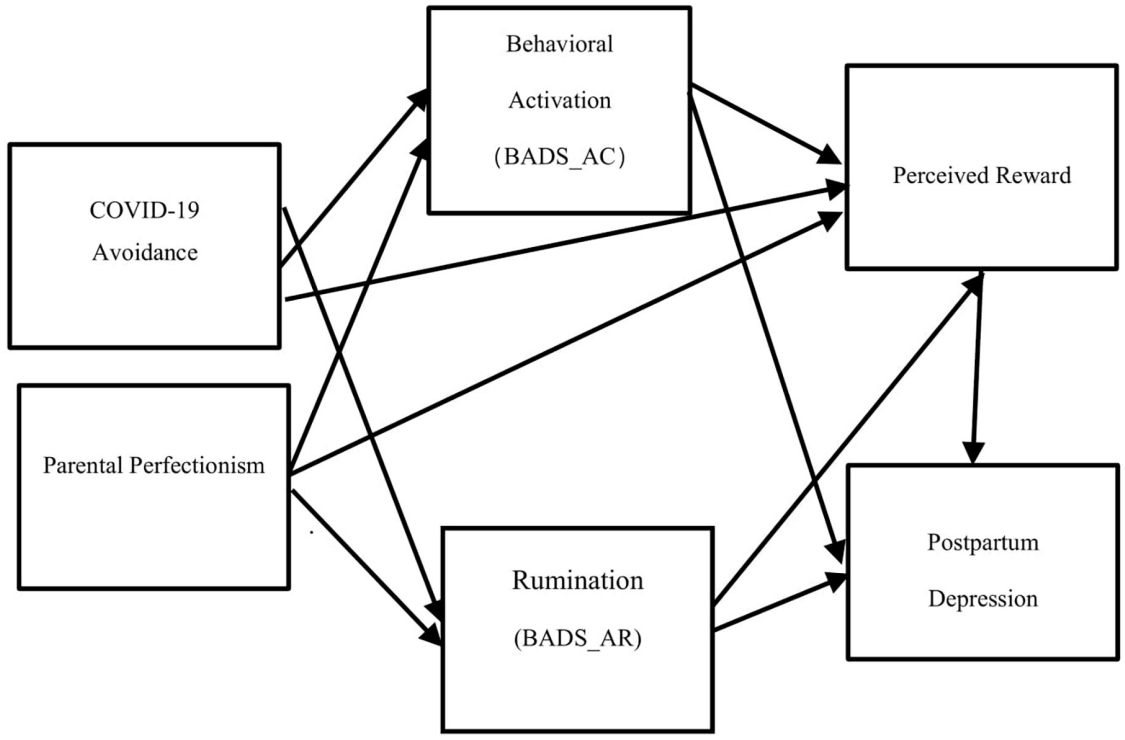

FIGURE 1
The hypothesized model. BADS, behavioral activation for depression scale; AC, activation factor; AR, avoidance/rumination factor; EROS, environmental reward observation scale; EPDS, Edinburgh postnatal depression scale.

RMSEA = 0.080). These results supported the validity of the EPDS in this study. In addition, the EPDS was analyzed using the total score in accordance with previous studies (17–19). In this study, Cronbach's alpha was 0.85.

The Japanese version of the Behavioral Activation for Depression Scale [BADS; (36)] measures the activation or avoidance of behavior and resulting impairment of social functioning. This scale comprises 25 items and four factors: Activation (BADS-AC), Avoidance/Rumination (BADS-AR), Work/School Impairment, and Social Impairment. The original version of the BADS was developed by Kanter et al. (37) who reported a good factor structure, Cronbach's $\alpha = 0.87$, and test–retest reliability coefficient of $r = 0.74$. The Japanese version has also demonstrated a good factor structure (RMSEA = 0.77), good internal consistency ($\alpha = 0.78$), and good construct reliability. In the current study, the confirmatory factor analysis for the four-factor structure revealed that the goodness of fit was sufficient (AGFI = 0.779; CFI = 0.822, RMSEA = 0.090), and Cronbach's alpha in this sample was 0.88, In this study, only the BADS-AC and AR subscales were used in the analysis to examine the relationship between behavioral activation and rumination, and postpartum depression. BADS-AC consists of seven items that assess not only one's engagement in more pleasurable activities but rather in those that help them achieve their specific goals (37). BADS-AR consists of eight items that measure one's avoidance of aversive thoughts and feelings. Kanter et al. (37) reported that the correlation between BADS-AR and the rumination subscale of the Response Styles Questionnaire was high ($r = 0.64$, $p < 0.01$). There was also a high correlation between BADS-AR and BDI ($r = 0.63$, $p < 0.01$). Previous studies have suggested that rumination predicts the onset, length, and severity of depressive episodes (38–40). In addition, Kanter et al. (37) proposed that rumination represents a dysfunctional attempt to avoid a depressive affect. In this study, participants rated each item on a seven-point scale ranging from 0 (*not at all*) to 6 (*completely applicable*), and scores were calculated for each factor. Higher scores indicate stronger characteristics for each factor.

The Japanese version of the Environmental Reward Observation Scale [EROS; (41)] comprises 10 items regarding the subjective evaluation of the level to which positive reinforcers (rewards) accompany one's behavior. Four responses were requested (from 1 = *strongly disagree* to 4 = *strongly agree*). Five items were reverse scored. The higher the score, the higher the perceived reward associated with the behavior. Kunisato et al. (41) reported a good factor structure (AGFI = 0.90, CFI = 0.89, RMSEA = 0.08), good internal consistency ($\alpha = 0.78$), and good test–retest reliability ($r = 0.75$) of the scale. In this study, a confirmatory factor analysis also showed that the goodness of fit was acceptable (AGFI = 0.772, CFI = 0.788, RMSEA = 0.133). In addition, Cronbach's alpha was 0.79.

Avoidance of Cs from the classification of coping behaviors for COVID-19 was used (42). The World Health Organization proposed the three Cs based on English acronyms meaning "crowded places," "close-contact settings," and "confined and enclosed space" to prevent the spread of COVID-19. The re-spread of COVID-19 during this survey period (January 2022) was assumed to affect the avoidance of the Cs. Therefore, the three items of "avoidance of the three Cs" from Koiwa et al. (42) were used for

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TABLE 1 Participants' characteristics.

Characteristic	Number of Women (*N* = 475)
Age (years)	30.74 (SD = 5.02)
Marital status	
Single	26 (5.47%)
Married	449 (94.53%)
Number of children	
1 (first pregnancy)	268 (56.42%)
2	144 (30.32%)
3	50 (10.53%)
4 or more	13 (2.74%)
Age of child (months)	6.04 (SD = 3.46)
Sex of child	
Boy	251 (52.84%)
Girl	220 (46.32%)
No answer	4 (0.84%)
Work status	
Not working	144 (30.32%)
Working	50 (10.53%)
Maternity leave	279 (58.74%)
History of mental illness	
Yes	65 (13.68%)
No	410 (86.32%)
Support from partner	
Yes	374 (78.74%)
No	92 (19.37%)
No partner	9 (1.89%)
Support from own mother	
Yes	332 (69.89%)
No	118 (24.84%)
No own mother	25 (5.26%)

Means are presented for continuous variables (with standard deviations in parentheses). Frequencies are presented for categorical variables.

nurses' coping behaviors related to the COVID-19 infection. This scale assesses the degree of avoidance of the three Cs using a six-point scale (from 1 = *not at all* to 6 = *very applicable*). The coefficient was α = 0.85, indicating high consistency (42). Cronbach's alpha in our sample was 0.86.

Parental perfectionism was evaluated (29). Participants were requested to respond to four questions about their tendency toward perfectionism in parenting based on a six-point scale ranging from 1 (*not at all*) to 6 (*very much*). Higher scores indicate a higher tendency toward perfectionism in parenting. A high reliability of this scale (α = 0.92) was reported (29). Cronbach's alpha in our sample was 0.84.

The Childcare Support Checklist was used (43). Of the nine items, seven were used to assess childcare environmental factors, such as a history of mental illness, life events, housing and financial situation, support from one's husband and own mother, and intimate interpersonal relationships. Two items concerned situations in which the mother was stuck in actual childcare situations and the feelings she had. Participants were requested to respond "yes" or "no" to each item.

2.3 Statistical analysis

The age and marital status of each participant were provided by an Internet research firm. The number of children, children's age and gender, and employment status were asked in a sociodemographic questionnaire. Mental illness history, partner support, and support from the biological mother were asked through a parenting support checklist (43). Statistical analyses were conducted using SPSS 25.0 and AMOS 25.0 (IBM, Armonk, NY, USA). Descriptive statistics were computed for the demographic characteristics. The reliability of the measures was calculated using Cronbach's alpha. In addition, we conducted a confirmatory factor analysis of the EPDS, BADS, and EROS using all items of the scales to examine their validity for the study population.

To test the basic relationships between variables, including sociodemographic variables, we computed Pearson's correlations. Subsequently, a structural analysis of covariance was conducted to test the hypothesis that daily exposure to rewards (EROS) mediates the effect of behavioral activation (BADS_AC) and rumination (BADS_AR) on postpartum depression (as measured by the EPDS). To control for confounding variables, we assessed psychiatric history, social support, parenting perfectionism, and COVID-19 avoidance. This model also included the variables of avoidance of crowding and closeness because of the COVID-19 pandemic (avoidance of three Cs) and parental perfectionism. Further, we conducted a simultaneous multi-population analysis of the same model, dividing the groups according to whether they had a history of mental illness and the degree of perceived support from their partners and mothers, as measured using the Childcare Support Checklist (43).

3 Results

We calculated the means and standard deviations of the total scores for each variable and alpha coefficients. The alpha coefficients ranged from 0.76 to 0.85, confirming a high degree of internal consistency (**Supplementary Appendix 1**).

For the EPDS, 169 (35.58%) participants scored above the cutoff of nine points on the Japanese version.

Regarding Pearson's correlation coefficients among sociodemographic assessment items and scales, there was no significant correlation between the EPDS scores and mother's and children's age. In addition, child's sex, number of children, and work status had no significant correlation; however, there was a negative correlation between marital status and the EPDS ($r = -0.081$, $p < 0.10$), BADS-AR ($r = -0.109$, $p < 0.05$), perfectionism ($r = -0.131$, $p < 0.01$). These scores among unmarried mothers was higher (**Supplementary Appendix 2**).

The Pearson's correlation coefficients among the measures indicated that all variables except for the three Cs related to COVID-19 avoidance significantly correlated with the EPDS.

Higher levels of postpartum depression moderately correlated with higher levels of avoidance/rumination (r = 0.535), parental perfectionism (r = 0.378), and lower levels of perceived rewards (r = −0.560). Behavioral activation weakly correlated with postpartum depression (r = −0.243). Further, the correlation between perceived reward and behavioral activation was moderately positive (r = 0.478), and the correlation between perceived award and avoidance/rumination was weakly negative (r = −0.342). The association between parental perfectionism and avoidance/rumination was moderately positive (r = 0.460), and the association between parental perfectionism and perceived rewards was negatively associated (r = −0.391; all ps < 0.01).

3.1 Testing the hypothesized model

We conducted a covariance structure analysis to test whether behavioral activation (BAD_AC) and avoidance/rumination (BADS_AR) affected postpartum depression directly, or whether this relationship was mediated by reward perception (EROS). We also hypothesized that the paths of BADS_AC, BADS_AR, and EROS are related between parenting perfectionism and coping behaviors of COVID-19 infection. However, the model did not fit the data [$\chi^2(3)$ = 29.547, p < 0.001, GFI = 0.980, AGFI = 0.861, CFI = 0.964, and RMSEA = 0.137].

Next, based on the correlation analysis results, we tested the modified version of the hypothesized model by adding a path of covariance between BADS_AC and BADS_AR and removing non-significant paths from the three Cs for COVID-19 avoidance and parenting perfectionism. The modified model had an excellent fit to the data [$\chi^2(5)$ = 2.842, ns., GFI = 0.998. AGFI = 0.992, CFI = 1.000, and RMSEA = 0.000], and we referred to it as the final model.

The following paths were observed in the final model (Figure 2): a negative path (β = −0.19) from behavioral activation (BADS_AC) to postpartum depression (EPDS) and a positive path directly to reward perception (EROS; β = 0.54). In addition, a positive path (β = 0.47) directly from avoidance/rumination (BADS_AR) to postpartum depression (EPDS) and a negative path to reward perception (EROS; β = −0.35) were observed. The negative path from reward perceptions to postpartum depression (β = −31) and behavior activation and avoidance/rumination could affect postpartum depression mediated by reward perception. A positive path from parenting perfectionism to avoidance/rumination (β = 0.46) and a negative path to reward perception (β = −0.22) were observed. A positive path from the coping behavior of COVID-19 to behavior activation was also observed (β = 0.13).

3.2 Simultaneous multi-population analysis

We conducted a simultaneous multi-population analysis of risk factors for postpartum depression, such as mental illness history and support from partners and biological mothers.

The simultaneous multi-population analysis results showed that the GFI without equality restrictions was more appropriate regardless of the presence or absence of a history of mental illness (Table 2). Comparing the path coefficients for the two groups, the path from avoidance/rumination to reward perception was not significant for mothers with a history of mental illness and only the path directly affecting depression was significant. Conversely, the direct path from behavioral activation to depression was not significant; only the path affecting depression via reward perception was significant. Among mothers with no history of mental illness, the positive path from the three Cs for COVID-19 avoidance to behavior activation was significant, whereas this path was not significant for those mothers with a history of mental illness.

We also conducted simultaneous multi-population analyses for support from partners (yes/no) and biological mothers (yes/no). In both analyses, the GFI without equality restrictions was more appropriate than that with equality restrictions. Regarding the presence of partners' support, there was a significant group difference in the value of the path from the three Cs for COVID-19 avoidance to behavior activation. In the group that did not expect support from their partners, there was no significant association between avoidance of crowding and closeness because of the COVID-19 pandemic and behavior activation (Table 3).

Regarding biological mothers' support, there were significant group differences in the values of the paths from parenting perfectionism to avoidance/rumination (p < 0.01), behavior activation to reward perception (p < 0.01), and avoidance of crowding and closeness for the prevention of COVID-19 to behavior activation (p < 0.05). In the group that did not expect support from their biological mothers, there was no significant association between avoidance of crowding and closeness because of the COVID-19 pandemic and behavior activation (Table 4).

4 Discussion

This study examined the associations between avoidance/rumination and postpartum depression, and between behavioral activation and postpartum depression, among women within 1 year of childbirth during the COVID-19 pandemic. Further, we examined whether these behavioral patterns affect postpartum depression via reward perception and whether risk factors for postpartum depression, such as a history of mental illness and partner and biological mother's support, differed in the hypothesized model. Additionally, we clarified the factors that were associated with postpartum depression in the high-risk group.

This study's results revealed the following:

A tendency toward postnatal depression was observed in approximately 35% of the participants. This finding indicates that the COVID-19 pandemic could have increased loneliness and depression in many mothers.

Rumination was directly related to postpartum depression and could have increased it by decreasing exposure to positive reinforcers.

Parenting perfectionism could be related to rumination and associated postpartum depression by decreasing the perception of and contact with positive reinforcers.

For mothers with a history of mental illness, emotion regulation had a greater impact on postpartum depression compared to those mothers without a history of mental illness. Additionally,

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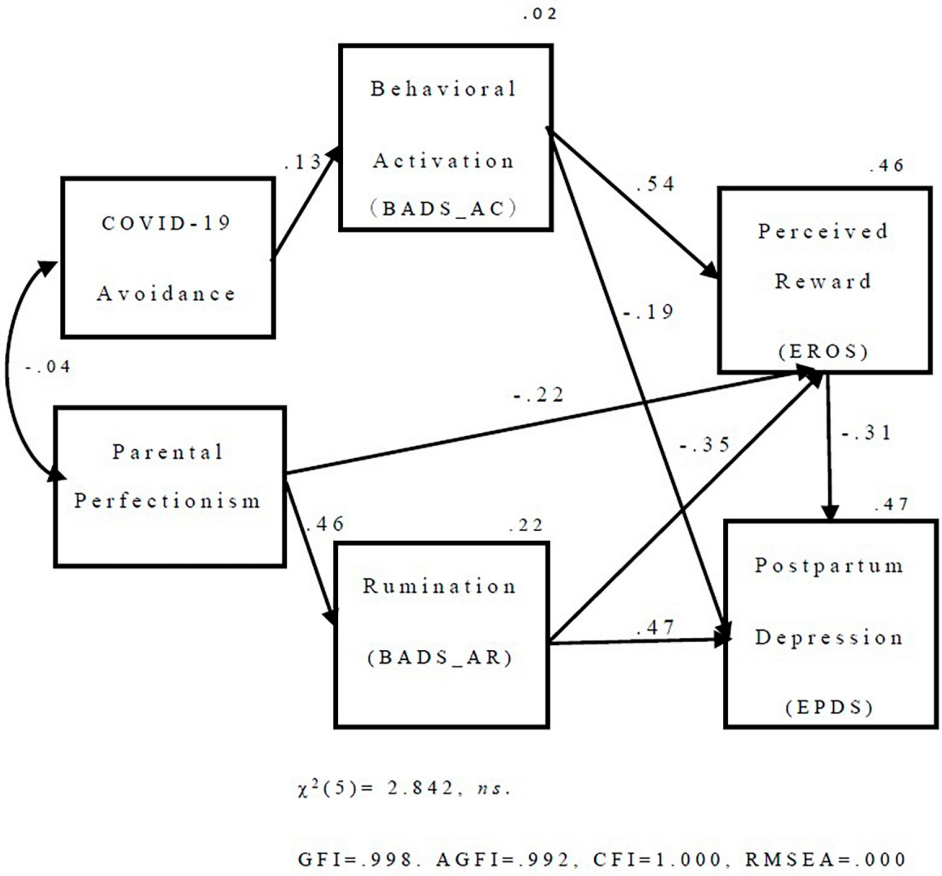

FIGURE 2
The results of covariance structure analysis. BADS, behavioral activation for depression scale; AC, activation factor; AR, avoidance/rumination factor; EROS, environmental reward observation scale; EPDS, Edinburgh postnatal depression scale.

TABLE 2 Goodness-of-fit and internal assessment of the simultaneous multi-population analysis model in mothers with or without a history of mental illness.

Goodness-of fit indexes GFI = 0.993, AGFI = 0.977, CFI = 1.000, RMSEA = 0.000, AIC = 69.706				
Variable	Mothers without a history of mental illness (*n* = 410)		Mothers with a history of mental illness (*n* = 65)	
	Standardized estimates	*p*	Standardized estimates	*p*
COVID-19 Avoidance→BADS_AC	0.163	<0.001	−0.102	0.396
Parental Perfectionism→BADS_AR	0.418	<0.001	0.542	<0.001
Parental Perfectionism→EROS	0.193	<0.001	−0.378	0.002
BADS_AC→EROS	0.576	<0.001	0.405	<0.001
BADS_AR→EROS	−0.345	<0.001	−0.152	0.211
EROS→EPDS	−0.287	<0.001	−0.243	0.018
BADS_AC→EPDS	−0.213	<0.001	−0.165	0.101
BADS_AR→EPDS	0.425	<0.001	0.590	<0.001

BADS, behavioral activation for depression scale; AC, activation factor; AR, avoidance/rumination factor; EROS, environmental reward observation scale; EPDS, Edinburgh postnatal depression scale.

the approach to prevent COVID-19 infection by avoiding the three Cs led to behavioral inactivity in mothers with a history of mental illness.

Although previous researchers have reported that rumination is significantly associated with postpartum depression, this is the first study to indicate that rumination is related to postpartum depression via a decrease in positive reinforcers.

Recent laboratory studies on rumination and reward perception showed that rumination disrupted reinforcement learning (adjusting behavior after error to behavior), thereby

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TABLE 3 Goodness-of-fit and internal assessment of the simultaneous multi-population analysis model in mothers with or without their partner's support.

Goodness-of fit indexes GFI = 0.987, AGFI = 0.955, CFI = 0.988, RMSEA = 038, AIC = 80.296				
Variable	Mothers with their partner's support (n = 374)		Mothers without their partner's support (n = 101)	
	Standardized estimates	p	Standardized estimates	p
COVID-19 Avoidance→BADS_AC	0.171	< 0.001	−0.026	0.788
Parental Perfectionism→BADS_AR	0.406	< 0.001	0.538	< 0.001
Parental Perfectionism→EROS	−0.212	< 0.001	−0.251	0.001
BADS_AC→EROS	0.518	< 0.001	0.638	< 0.001
BADS_AR→EROS	−0.339	< 0.001	−0.313	< 0.001
EROS→EPDS	−0.286	< 0.001	−0.288	0.006
BADS_AC→EPDS	−0.196	< 0.001	−0.190	0.059
BADS_AR→EPDS	0.456	< 0.001	0.500	< 0.001

BADS, behavioral activation for depression scale; AC, activation factor; AR, avoidance/rumination factor; EROS, environmental reward observation scale; EPDS, Edinburgh postnatal depression scale.

TABLE 4 Goodness-of-fit and internal assessment of the simultaneous multi-population analysis model in mothers with or without their own mother's support.

Goodness-of fit indexes GFI = 0.991, AGFI = 0.968, CFI = 0.998, RMSEA = 0.014, AIC = 73.080				
Variable	Mothers with their own mother's support (n = 332)		Mothers without their own mother's support (n = 143)	
	Standardized estimates	p	Standardized estimates	p
COVID-19 Avoidance→BADS_AC	0.200	< 0.001	−0.017	0.839
Parental Perfectionism→BADS_AR	0.381	< 0.001	0.569	< 0.001
Parental Perfectionism→EROS	−0.221	< 0.001	−0.227	< 0.001
BADS_AC→EROS	0.500	< 0.001	0.622	< 0.001
BADS_AR→EROS	−0.326	< 0.001	−0.379	< 0.001
EROS→EPDS	−0.302	< 0.001	−0.318	< 0.001
BADS_AC→EPDS	−0.168	< 0.001	−0.231	0.004
BADS_AR→EPDS	0.469	< 0.001	0.475	< 0.001

BADS, behavioral activation for depression scale; AC, activation factor; AR, avoidance/rumination factor; EROS, environmental reward observation scale; EPDS, Edinburgh postnatal depression scale.

impairing learning adaptive behavior and promoting stress-generating behavior; however, participants were not in their perinatal period (44).

Rumination might impair concentration and contingency attention associated with adaptive behavior, suggesting that rumination reduces sensitivity to contextual details (45). Further, a study on experimental rumination manipulations with postpartum mothers reported that maternal sensitivity toward infants significantly decreased after induction of the rumination task (46).

In summary, excessive rumination by postpartum mothers about their mood and consequences of their behaviors could further impair adaptive behaviors by making it difficult for them to focus on adaptive behaviors and reducing maternal sensitivity to their infants. For example, excessive ruminative thoughts could reduce their focus on successful parenting or lead to a decrease in opportunities to be in-touch with positive reinforcers because of the inability to respond to their infants' cries and actions.

Conversely, behavioral activation might indirectly reduce postpartum depression through the perception of positive reinforcers. This result indicates that both being active and increasing exposure to positive reinforcers are necessary to prevent postpartum depression. Particularly among mothers with a history of mental illness, the direct path from behavioral activation to postpartum depression was not significant, whereas the indirect path via reward perception was significant. This suggests the importance of increasing activities that match their values in life and increase opportunities to perceive positive reinforcement through parenting behaviors rather than simply extending their activities. Further, the difference in the values of the paths from behavioral activation to perceived reward was significantly higher for mothers who did not expect support from their own mothers compared to those who had their mothers' support. This finding suggests that an increased exposure to positive reinforcement through their behavior could reduce postpartum depression in mothers who do not expect support from their own mothers.

This survey was conducted during the COVID-19 pandemic, and approximately 36% of the total population had an EPDS score of 9 or higher, as the cutoff score for the Japanese version

of the EPDS. The rate is higher than the positive screening rate of 14% (47) or 29% for postpartum depression (11) in Japan during the pandemic. However, other studies did not report this difference, and whether there was any difference in the prevalence of postnatal depressive symptoms between the pre- and current COVID-19 periods could not be confirmed. The reason this cannot be confirmed is because of the variation in each country's state of emergency. The unclear classification of pre-COVID-19 and COVID-19 cohorts could have led to ambiguous findings and could not provide an accurate point of comparison, compared to a pooled prevalence reported in previously published reviews. Although a state of emergency was declared in the Tokyo metropolitan area and other urban areas during this study period, determining whether the spread of COVID-19 increased the rate of postpartum depression more than usual was difficult to determine. This is because this study included mothers from areas in which emergency declarations had not been issued and more than 1 year had passed since the COVID-19 pandemic began.

The tendency to avoid the three Cs because of the COVID-19 pandemic had a positive effect on the activation of usual behavior. This result indicates that the behavior of coping with the fear of COVID-19 infection could not necessarily be predictive of postpartum depression, as mothers are usually goal-oriented in their behavior. However, for mothers with a history of mental illness and those who could not expect support from their partners or their own mothers, the path from avoidance behavior of COVID-19 infection to usual behavioral activation was negative but not significant. Nevertheless, the possibility that these behavioral restrictions caused by the COVID-19 pandemic could increase postpartum depression cannot be completely ruled out.

Regarding the relationship between perfectionism and rumination, the results indicated that mothers who had a strong tendency toward perfectionism in parenting were more likely to ruminate and less likely to perceive rewards in their daily lives. A longitudinal study of the relationship between perfectionism and repetitive negative thinking (RNT) in antenatal and postnatal mothers found that antenatal perfectionism predicted antenatal RNT and RNT was associated with antenatal depression (48) Additionally, this longitudinal study revealed that antenatal perfectionism affects postpartum depression via RNT and antenatal depression.

Although antenatal conditions were not examined, the results are consistent with the findings of Egan et al. (48)—that parenting perfectionism affects postpartum depression via rumination. A meta-analysis on perfectionism and postpartum depression also indicates that the strength of the relationship between perfectionism and postpartum depression could increase with the length of the postpartum period (49). Shafran et al. (50) suggested that individuals with perfectionism are self-critical and evaluate themselves negatively after failing to meet their standards. Although their standards were achievable, they might have considered them as insufficiently demanding.

Based on the above information, we assume that mothers with strong parenting perfectionism might compulsively be perfect in caring for their infants and ruminate when they fail to meet their demanding standards. Even when they meet their demanding standards, they tend to discount the consequences of their behavior and could experience fewer reinforcers or have a reduced sense of positive reinforcers accompanying their behaviors. Supporting mothers with strong parenting perfectionism in adjusting their parenting goals appropriately could prove useful. This would change their cognition and behaviors: avoid blaming themselves for their mistakes or failures, realize that no mother can do everything from the beginning, and accept that becoming a mother entails learning through trial and error.

4.1 Limitations

The current results indicate that rumination was not only directly associated with postpartum depression but also indirectly linked with it via perceived reward. However, several issues remain to be addressed in future studies. First, the relationship between rumination, behavior activation, and postpartum depression before the COVID-19 pandemic should be reexamined. Regarding behavior, COVID-19 infection reduced opportunities for interpersonal interactions and going outdoors. This study considered this by including the use of measurements that assess the avoidance of crowded places, confined and enclosed spaces, and close-contact settings as variables in the analysis; however, other coping behaviors toward COVID-19 were not assessed. Further, the activity level itself could have decreased during this period, which might have also influenced the current results. In addition, we did not measure the presence or absence of previous infection with COVID-19, hospitalization, or vaccination status during pregnancy in this study. Owing to the reduction in the activity level, the rate of COVID-19 infection among pregnant women in Japan was reportedly significantly lower at 0.6% (51) than in other countries. For instance, in the US, the rate of positive test results for SARS-CoV-2 among pregnant women was 6.6% (52). Based on this observation, we hypothesized that coping behaviors aimed at preventing infection (COVID-19 avoidance), such as limiting social interactions, were more influential in causing postpartum depression than the presence of COVID-19 infection.

Second, factors related to the children were not measured. Leigh and Milgrom (53) identified that risk factors, including low self-esteem, low social support, negative cognitive attributional style, concomitant high anxiety in pregnancy, and major life events such as low income and a history of childhood sexual abuse mostly predict three outcomes: antenatal depression, postnatal depression, and parenting stress—as well as the relationship between them. Fredriksen et al. (54) also reported that parenting stress mediates the relationship between parental depressive symptoms and child developmental outcomes. Therefore, future studies should consider factors related to children and parenting stress to clarify the relationship between rumination, reward perception, and postpartum depression. Finally, the design of this study was cross-sectional; thus, it was not possible to draw conclusions about the causal relationship and true mediation of each variable. Furthermore, all variables were measured by self-report from the same informant. It was easier to find associations between variables reported by the same participant, inflating the effect size. For EPDS, the proportion of mothers with possible depression may have been overestimated because self-report measures were used to assess depressive symptoms and a structured diagnostic interview with a clinician was not performed (55) In addition, depressed individuals were negatively biased in their reports of internal status and past events.

5 Conclusion

Rumination and behavior activation not only affected postpartum depression directly but also indirectly through perceived rewards among postpartum women who gave birth during the COVID-19 pandemic. The hypothesized model also differed according to risk factors for postpartum depression, such as the presence or absence of a history of mental illness and support from partners and mothers. From a clinical perspective, these findings suggest that as with general depression, it could be useful to use behavioral activation to reduce preoccupation with rumination and increase contact with and perception of positive reinforcers to reduce postpartum depression. Especially for groups at high risk of postpartum depression, it is necessary to provide support and praise for what has been done so that they can perceive positive reinforcement.

In addition, for parenting perfectionism, it is possible to change high demanding standards to appropriate ones through cognitive behavioral strategies, such as cognitive restructuring and behavioral experiments, and decrease self-blame for mistakes and failures to reduce postpartum depression.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Research Ethics Committee of the Faculty of Contemporary Psychology at Rikkyo University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin because it was an unnamed survey using a web-based survey company.

Author contributions

MM: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review and editing. JO: Conceptualization, Data curation, Investigation, Methodology, Visualization, Writing – original draft, Writing – review and editing. KF: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review and editing. NK: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review and editing. NN-T: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review and editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was funded by Rikkyo University grant (SFR) by Prof. Dr. MM. The funder had no role in the study design, data collection and analyses, data interpretation, decision to publish, or preparation of the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1295988/full#supplementary-material

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frontiers | Frontiers in Psychiatry

TYPE Original Research
PUBLISHED 29 January 2024
DOI 10.3389/fpsyt.2024.1284090

OPEN ACCESS

EDITED BY
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RECEIVED 27 August 2023
ACCEPTED 08 January 2024
PUBLISHED 29 January 2024

CITATION
Bonanni G, Longo VL, Airoldi C, Meli F, Familiari A, Romanzi F, Pellegrino M, Visconti D, Serio A, Lanzone A and Bevilacqua E (2024) Is the mental health of couples with twins more at risk? Results from an Italian cohort study. *Front. Psychiatry* 15:1284090. doi: 10.3389/fpsyt.2024.1284090

Is the mental health of couples with twins more at risk? Results from an Italian cohort study

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Introduction: Our retrospective study aimed to investigate whether parents of twins encounter heightened psychological and emotional distress one year after childbirth, in comparison to parents of singletons within an Italian cohort.

Methods: Exclusion criteria included multiparity, preterm birth, congenital anomalies, stillbirth, >2 fetus pregnancies, and pre-existing maternal mental health disorders. Out of the 300 couples (600 parents) invited to participate, 286 parents (158 mothers, 128 fathers) successfully completed a self-administered survey. We analyzed three scores separately for mothers and fathers, differentiating between singleton and twin pregnancies: the Edinburgh Postnatal Depression Scale (EPDS) score, the State and Trait Anxiety Inventory (STAI)-Y1 score, and the STAI-Y2 score.

Results: Logistic models were used to assess the influence of age, BMI, marital status, education, and employment on the three binary scores (EPDS, STAI-Y1, and STAI-Y2), revealing no significant differences in absolute scores between parents of singletons and twins. Paired analysis revealed significantly higher EPDS (mean increase: 3.8, SD: 6.5), STAI-Y1 (mean increase: 5.4, SD: 12.5), and STAI-Y2 (mean increase: 4.5, SD: 12.4) scores for mothers ($p < 0.0001$). Approximately 10% of women and 8% of men reported suicidal thoughts.

Discussion: Contrary to expectations, no substantial psychological differences emerged between parents of twins and singletons. Adjusting for confounders through univariate analysis maintained nonsignificant trends. Nevertheless, caution in interpretation is warranted due to strict inclusion criteria favoring twin pregnancies with better outcomes. Unintended bias could have resulted from routine psychological support offered to mothers of twins in our clinic. This presents an important framework for future research, including randomized controlled trials comparing parents of multiples with psychological support to those without.Finally, the elevated prevalence of depression symptoms and suicidal thoughts in our cohort underscores the importance of mental health

10.3389/fpsyt.2024.1284090

during pregnancy and early parenting. We advocate for the screening of parents for postpartum depression and various psychological conditions, encompassing a spectrum of anxiety disorders. Those at elevated risk of mental distress should be proactively offered appropriate support.

KEYWORDS

twin pregnancies, multiples, twins, postpartum depression, maternal mental health, postnatal psychological distress, parenting stress

1 Introduction

The last decades have witnessed a significant increase in multiple pregnancy rates (1). The widespread of Assisted Reproduction Techniques (ART) and the rising maternal age at conception have been the major contributors to a roughly 70% increase in these pregnancies over the last fifty years (2). The heightened incidence of adverse outcomes, such as stillbirths (3, 4), neonatal deaths (5), and cerebral palsy (6), has fueled extensive research and clinical interest in multiple pregnancies. Notably, a significant proportion of twins (25%), triplets (75%), and quadruplets (100%) necessitate admission to a neonatal intensive care unit (7). While existing studies predominantly focus on neonatal and maternal risks linked with multiple pregnancies, the realm of perinatal mental health in parents of twins remains an underexplored facet in contemporary research. Recognizing this gap, the Global Twins and Multiples Priority Setting Partnership recently identified it as a top priority in the health research landscape for multiples (8).

Understanding the prevalence of anxiety and depression during the antenatal and postnatal periods is crucial for addressing the complexities of perinatal mental health. In a comprehensive 2017 meta-analysis, Falah-Hassani et al. (9) synthesized data from 66 studies encompassing 162,120 women across 30 countries. The findings disclosed a prevalence of 9.5% for self-reported antenatal anxiety symptoms and mild to severe depressive symptoms. Moreover, co-morbid anxiety symptoms alongside moderate to severe depressive symptoms were observed in 6.3% of cases. Concerning fathers, the prevalence of paternal postpartum depression was reported to be around 4%–25% globally (10). A recent systematic review and meta-analysis by Smythe et al. (11) delved into 23 studies involving 29,286 couples. The investigation revealed that up to 3.18% of parental dyads, comprising both mothers and fathers, experienced perinatal depression. Notably, the prevalence was higher during the late postnatal period (3-12 months) (11).

When families receive the news of expecting multiple pregnancies, it becomes imperative to consider their mental well-being alongside conventional concerns. Beyond the typical challenges tied to pregnancy and newborn care, parents of multiples face added stress like increased caregiving demands, lack of sleep, financial strain, and social isolation, leading to higher risks of depression and anxiety (12). Recognizing and addressing the mental health of parents of twins is essential. Existing research that compares the mental health of parents with multiples to those with singletons has yielded mixed results, partly attributable to variations in outcome measurement. A study by Choi et al. (13) revealed that mothers of multiples had a 43% higher likelihood of experiencing moderate/severe depressive symptoms at 9 months postpartum compared to mothers of singletons (13). The first 3 months of postpartum are widely recognized as the most challenging for parents of multiples (14), marked by stress, overwhelm, and sleep deprivation (15). However, our clinical experience during follow-ups led us to hypothesize that parents of multiples face unique stressors extending beyond the initial postpartum phase, including ongoing sleep deprivation, financial burdens, and social isolation related to pregnancy-related factors.

The primary aim of our study was to establish whether parents of twins demonstrate a heightened likelihood of experiencing psychological and emotional distress, specifically anxiety and depression, one year after birth, in comparison to parents of singletons within an Italian cohort. Additionally, as a secondary aim, we aimed to assess the difference between mothers and fathers within the couple in terms of psychological and emotional distress. Furthermore, we analyzed the association between elevated probabilities of depression and anxiety and potential sociodemographic and obstetric risk factors (16), including maternal age, Body Mass Index (BMI), educational level, and marital status.

2 Materials and methods

2.1 Study design and data collection

A retrospective cohort study was performed at the Department of Women and Child Health, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome, Italy, a tertiary university hospital with an annual delivery rate of approximately 4000. Inclusion criteria were primigravid women, maternal age > 18 years, and gestational age at delivery > 36 weeks (in case of twins) or > 37 weeks (in case of singletons). Exclusion criteria included congenital

anomalies, stillbirth, multiple pregnancies with more than two fetuses, and maternal pre-existing mental health disorders. Over a 12-month period (November 2018 to November 2019), we randomly selected three hundred couples who delivered at our institution. The appropriate sample size was established by first conducting a comprehensive literature review to identify analogous studies, leveraging their sample sizes as an initial reference. Subsequently, we approximated the sample size required for a 95% confidence interval, employing a standard Z-score of 1.96, which aligns with a 5% margin of error. Employing a simple random sampling method based on unique patient identifiers routinely assigned by the hospital, we enrolled 300 participants. The study adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Catholic University of the Sacred Heart (protocol code DIPUSVSP-16-11-2091).

The original population was balanced between singleton (n=150) and twin pregnancies (n=150). All women included in the study were contacted by phone at 1 year postpartum to be informed about the purpose and the characteristics of the study. During phone calls, women who accepted to participate and agreed to the informed consent received an email containing a link to the questionnaire. The same link was also sent to their partners. Socio-demographic and obstetric data (including maternal age, BMI, nationality, educational level, employment, and marital status) were extracted from a pre-existing perinatal database where data from all women who delivered at our Institution are prospectively included; then, we codified these data on an electronic file. All records were reviewed for the purpose of the study by a single reviewer (VLL). An Excel file was created matching pre-existing information (including maternal age, BMI, nationality, educational level, employment, and marital status) with results obtained from three questionnaires (Supplementary Materials): the EDPS (Edinburgh Postnatal Depression Scale), STAI-Y1 (State and Trait Anxiety Inventory), and STAI-Y2 scales.

2.2 Definition of variables and outcomes

Psychological and emotional distress were evaluated utilizing a pair of self-report questionnaires. The questionnaires yielded three distinct scores that served as the primary outcome measures: the EPDS score (17), the STAI-Y1 score, and the STAI-Y2 score (18).

2.1.1 EPDS – Edinburgh Postnatal Depression Scale

The EPDS, a widely utilized tool internationally, is employed for the screening of Post-Partum Depression (PPD), aiming to identify the onset of major depressive disorder within one year after childbirth. Comprising 10 questions, each statement presents four potential responses, scored from 0 to 3. Higher scores indicate more pronounced depressive symptoms, with a maximum score of 30. We categorized scores into four groups: Group I (≤ 8), suggesting unlikely depression; Group II (9-11), indicative of possible depression; Group III (12-13), signaling a fairly high likelihood of depression; and Group IV (≥ 14), signifying probable depression.

In addition, we conducted a separate analysis considering a positive score on question 10 ("The thought of harming myself has occurred") as a secondary outcome, identifying individuals with potential suicidal risk (17, 19). Further, we dichotomized scores using a cutoff of 11 or higher, implying the possibility of PPD warranting additional clinical investigation, such as a psychological assessment or an interview with a social worker. According to a meta-analysis on pregnant and postpartum women by Levis et al. (20), the EPDS cutoff value of 11 or higher maximizes combined sensitivity and specificity in women (20). Regarding the suggested cutoff for fathers, a recent systematic review and meta-analysis validated EPDS for detecting paternal postpartum depression, with lower cutoff scores ranging from 7 to 10 (21).

2.1.2 STAI – State and Trait Anxiety Inventory

The State-Trait Anxiety Inventory (STAI) is a widely utilized tool for measuring trait and state anxiety, with clinical applications in diagnosing anxiety disorders and distinguishing between anxiety and depressive syndromes. The STAI most popular version (Y) consists of 20 items assessing trait anxiety and 20 items assessing state anxiety. State anxiety items include descriptors such as "I am tense; I am worried" and "I feel calm; I feel secure," while trait anxiety items encompass statements like "I worry too much over something that really doesn't matter" and "I am content; I am a steady person." Responses are rated on a 4-point scale (e.g., from "Almost Never" to "Almost Always"), with higher scores indicating an elevated risk of anxiety (18). Scores for version Y of the STAI range from a minimum of 20 to a maximum of 80. STAI scores are often classified as follows: "no or low anxiety" (20-37), "moderate anxiety" (38-44), and "high anxiety" (45-80) (22). Alternatively, scores of 42 or higher (for STAI-Y1) and 43 or higher (for STAI-Y2) have been proposed to detect clinically significant symptoms and differentiate between healthy adults and those with anxiety disorders (18, 23). The internal consistency coefficient was previously reported as the same for mothers and fathers (24).

2.3 Statistical analysis

A comprehensive descriptive statistical analysis was conducted on both the entire sample and distinctively for singleton and twin pregnancies. For categorical variables, absolute and relative frequencies were presented, while numerical variables were summarized using either means and standard deviations or medians and interquartile ranges, as appropriate. The correlation between psychological scores was evaluated by calculating the Pearson correlation coefficient and presenting the scatter plots. In this manner, no distinction was made between mothers and fathers.

In order to discern disparities in psychological and emotional distress, a comparative analysis of psychological scores was undertaken between the two groups (singleton vs. twin pregnancies), independently for mothers and fathers. These scores were evaluated in both categorical and continuous manners. The applicable statistical tests, namely Chi-square/Fisher test and t-test/Mann-Whitney, were employed for these comparisons.

Additionally, paired analysis tests were conducted to assess score differences between mothers and fathers within the same family.

Furthermore, the influence of potential risk factors on psychological and emotional distress was examined using logistic univariate models. Three such models were estimated, utilizing dichotomous scores (EPDS, STAI-Y1, and STAI-Y2) as outcomes and incorporating all available covariates (age, BMI, marital status, education, employment) as controls. Adjustment was made for singleton and twin pregnancies, and odds ratios with corresponding 95% confidence intervals were provided.

To explore the interrelation between psychological scores, the Pearson correlation coefficient was computed, accompanied by scatter plots to visually represent the relationships.

No correction for multiple comparisons was undertaken as all analyses were pre-specified in the protocol. The significance threshold was set at 0.05 (two-tailed), and all analyses were executed using SAS 9.4 software.

3 Results

Three hundred couples were invited to participate (Figure 1). Out of these, 159 (53.00%) provided informed consent and responded to the questionnaire. The responses included those from only the mother (n=31), only the father (n=1), or both the mother and the father (n=127). The response rate was consistent between singleton and twin pregnancies, at 77 (51.33%) and 82 (54.67%) respectively. In total, the number of mothers who responded to the questionnaire was 158 (57 + 19 + 70 + 12), while the number of fathers was 128 (57 + 1 + 70).

The baseline sociodemographic characteristics of the entire cohort are summarized in Table 1, both for singletons and twins. All responding parents were different-sex couples. The mean maternal age at the time of delivery was 34.0 years (SD 4.9), ranging from 21 to 48 years. The median maternal weight and BMI at delivery were 62.0 kg [IQR 56.0-70.0] and 22.8 kg/m2 [IQR 20.5-25.7], respectively. White ethnicity was the most prevalent (n=154, 97.5%). Approximately 80% (n=142) of the women were married, and around 73.1% (n=106) were employed during pregnancy. Nearly all women who participated in the study had received secondary education or higher (147; 96.1%), and they delivered using the NHS (132; 95.7%).

The men included in the analysis were slightly older, with a mean father age at delivery of 37.1 years (SD 5.8). Almost all fathers were of white ethnicity (n=126; 97.7%). Most men participating in the study were married (n=126; 97.7%), stably employed (n=113; 88.3%), and had received a secondary education or higher (n=113; 87.6%). As shown in Table 1, no significant differences were observed between singletons and twins, except for post-partum weight (0.007) and BMI (0.006) in mothers. As expected, these measures were higher in mothers with twin pregnancies compared to mothers of singletons.

Psychological and emotional distress were assessed using EPDS, STAI-Y1, and STAI-Y2 scores. A high positive correlation (r^2 > 0.700) was observed among these scores, indicating a strong association between post-partum depression and state and trait anxiety. Further details are provided in Supplementary Figure 1.

The psychological scores collected are summarized in Table 2 and visualized in Figure 2. Overall, 36 (22.8%) women and 5 (3.9%) men exhibited a higher likelihood of depression based on EPDS scores, with 15 (9.5%) mothers and 10 (7.8%) fathers showing signs of suicidal risk. The mean EPDS score was 9.1 (SD 5.7) for women and 5.4 (SD 3.9) for men. Among the sampled participants, 24.0% of mothers experienced trait anxiety, and 19.6% experienced state anxiety, compared to 10.2% and 6.3%, respectively, among fathers. Specifically, the mean STAI-Y1 and STAI-Y2 scores exceeded 35 for women and 31 for men. No statistically significant differences were observed in EPDS and STAI-Y1/2 scores between parents of singletons and twins, regardless of whether the variables were considered categorically or continuously. Upon closer examination of categorized scores, a slight, albeit nonsignificant, higher prevalence of depressive

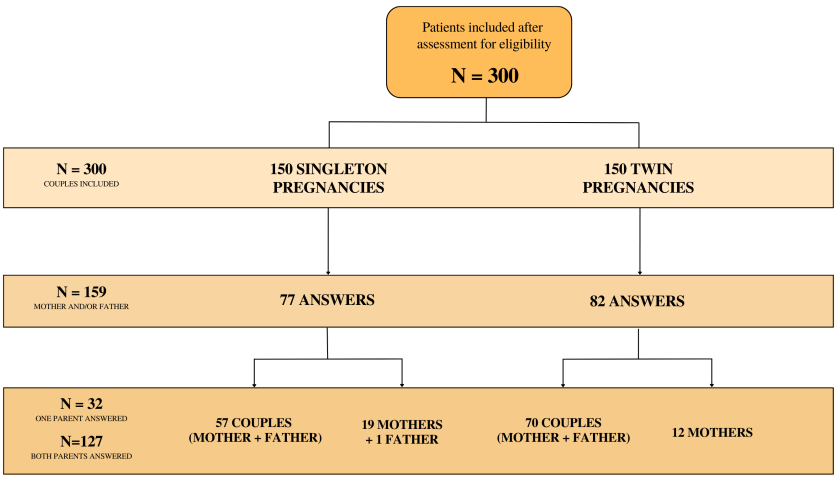

FIGURE 1
Design and flow of participants through the study.

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TABLE 1 Baseline characteristics of both the maternal and paternal cohorts are presented, along with separate analyses for singleton and twin pregnancies.

Characteristic	Mother		
	All (n=158)	Singleton (n=76)	Twin (n=82)
Age, years, mean (SD)	33.99 (4.85)	33.84 (4.23)	34.13 (5.39)
Height, cm, mean (SD)	166.36 (5.35)	166.33 (5.86)	166.39 (5.23)
Weight, kg, median [IQR]	62.00 [56.00; 70.00]	60.00 [56.00; 67.50]	65.00 [56.00; 76.00]
Post-partum BMI, kg/m^2, median [IQR]	22.83 [20.52; 25.71]	21.84 [20.18; 24.42]	24.02 [20.70; 26.99]
White, n (%)	154 (97.47)	74 (97.37)	80 (97.56)
Italian, n (%)	142 (89.87)	69 (90.79)	73 (89.02)
Married, n (%)	123 (80.39)	55 (77.46)	68 (82.93)
Secondary or higher education, n (%)	147 (96.08)	70 (98.59)	77 (93.90)
Employed, n (%)	106 (73.10)	51 (80.95)	55 (67.07)
NHS delivery, n (%)	132 (95.65)	73 (9.33)	59 (93.65)
	Father		
	All (n=128)	Singleton (n=58)	Twin (n=70)
Age, years, mean (SD)	37.05 (5.78)	36.55 (4.94)	37.45 (6.39)
Height, cm, mean (SD)	177.95 (6.35)	177.81 (6.36)	178.06 (6.39)
Weight, kg, median [IQR]	80.00 [72.00; 87.00]	80.00 [72.00; 86.00]	79.00 [72.00; 88.00]
Post-partum BMI, kg/m^2, median [IQR]	24.84 [23.15; 27.44]	25.40 [23.18; 27.70]	24.69 [23.15; 27.14]
White, n (%)	126 (97.67)	55 (94.83)	71 (100.00)
Italian, n (%), missing=50	75 (94.94)	8 (100.00)	67 (94.37)
Married, n (%)	126 (97.67)	58 (100.00)	68 (95.77)
Secondary or higher education, n (%)	113 (87.60)	56 (96.55)	57 (80.28)
Employed, n (%)	113 (88.28)	46 (79.31)	67 (95.71)

Categorical variables are expressed as absolute and relative frequencies, while numerical variables are represented using means and standard deviations (SD), or medians and interquartile ranges (IQR) where applicable. BMI, Body Mass Index; NHS, National Health System.

symptoms and a greater probability of trait and state anxiety were observed in the twin groups compared to singletons, except for STAI-Y2 in women. Approximately 10% of women and 8% of men exhibited suspected suicidal thoughts; although risk appeared somewhat higher among mothers of twins at the 10% level (p= 0.07), this difference did not reach statistical significance at the 5% level.

When focusing solely on pregnancies with both partners participating (n=127), paired comparisons of scores between mothers and fathers were conducted. Mothers exhibited significantly higher scores with an increase of 3.8 (SD 6.5) for EPDS; 5.4 (SD 12.5) for STAI-Y1 and 4.5 (SD 12.4) for STAI-Y2. These differences were statistically different from 0 (p<0.0001). These discrepancies were slightly more pronounced in singleton pregnancies, both in continuous and categorical ways. More details are reported in Supplementary Table 1.

Subsequently, we conducted a series of univariate and multivariable logistic regression models, employing higher EPDS (≥11), STAI-Y1 (≥42), and STAI-Y2 (≥43) scores in a dichotomous way as the focal outcomes. Particularly, high-risk depression was observed for 52 (32.9%) women and 13 (10.2%) men, a high level of trait anxiety for 49 (31.0%) mothers and 21 (16.4%) fathers and a high level of state anxiety for 36 (22.8%) and 13 (10.2%), respectively. More details on this categorization are reported in Supplementary Table 2. None of the univariate analyses yielded statistically significant findings, thus emphasizing the absence of conclusive associations.

Importantly, upon comprehensive adjustment for potential confounders (including age, BMI, marital status, education, and employment) through univariate analysis, the overall direction and the statistical significance of the results remained consistently non-significant except for mother civil status on STAI-Y1 and father age in EPDS: married women had lower risk of suffered from state anxiety [OR 0.38, 95% CI 0.17; 0.87] and increasing the father ages decrease the risk of depression [OR 0.89; 95% CI 0.79; 0.99]. No significant differences were observed among twins and singletons (Table 3).

4 Discussion

In this study, contrary to our initial expectations, we did not observe a significant difference in psychological and emotional distress between parents of twins and parents of singletons. However, when examining partners within the study cohort, mothers consistently displayed significantly higher median scores for Postpartum Depression (PPD), trait anxiety, and state anxiety compared to fathers (all p<0.001). Notably, this trend was more pronounced in singleton pregnancies. Despite thorough adjustments for potential confounders, including age, BMI, marital status, education, and employment, the inherent association between twin pregnancies and elevated EPDS scores in both partners persisted.

The greater disparity in mental health symptoms between mothers of singletons and their partners compared to mothers of twins and their partners could be attributed to different underlying factors. The heightened level of paternal involvement in parenting among fathers of twins (25, 26), as opposed to fathers of singletons, might contribute to a more balanced distribution of parenting-related stressors and responsibilities. This increased paternal involvement could potentially lead to fathers of twins experiencing mental health outcomes more closely resembling those of mothers. Additionally, other factors may come into play, including the unique challenges faced by parents of twins, fostering a shared understanding, and potentially cultivating greater mutual

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TABLE 2 EPDS, STAI-Y1, and STAI-Y2 scores by parent and pregnancy type.

	Mothers			
	All (n=158)	Singleton (n=76)	Twin (n=82)	*p-value*
EPDS				
Suicidal risk, n (%)	15 (9.49)	4 (5.19)	11 (13.58)	0.3073
EPDS				
Depression not likely, n (%)	81 (51.27)	38 (50.00)	43 (52.44)	0.3685
Depression possible, n (%)	30 (18.99)	18 (23.68)	12 (14.63)	
Fairly high possibility of depression, n (%)	11 (6.96)	6 (7.89)	5 (6.10)	
Higher probable depression, n (%)	36 (22.78)	14 (18.42)	22 (26.83)	
***EPDS total**, Mean (SD)*	9.09 (5.70)	9.14 (4.85)	9.05 (6.41)	0.9161
STAI-Y1				
No or low anxiety, n (%)	86 (54.43)	38 (50.00)	48 (58.54)	0.3496
Moderate anxiety, n (%)	34 (21.52)	20 (26.32)	14 (17.07)	
High anxiety, n (%)	38 (24.05)	18 (23.68)	20 (24.39)	
***STAI-Y1 total,** Mean (SD)*	38.34 (10.26)	39.62 (10.60)	37.15 (9.85)	0.1307
STAI-Y2				
No or low anxiety, n (%)	95 (60.13)	42 (55.26)	53 (64.63)	0.4538
Moderate anxiety, n (%)	32 (20.25)	18 (23.68)	14 (17.07)	
High anxiety, n (%)	31 (19.62)	16 (21.05)	15 (18.29)	
***STAI-Y2 total,** Mean (SD)*	35.97 (9.94)	37.17 (9.93)	34.87 (9.89)	0.1460
	Fathers			
	All (n=128)	Singleton (n=58)	Twin (n=70)	*p-value*
EPDS				
Suicidal risk, n (%)	10 (7.81)	5 (7.14)	5 (8.62)	0.2664
EPDS				
Depression not likely, n (%)	103 (80.47)	50 (86.21)	53 (75.71)	0.4257
Depression possible, n (%)	16 (12.50)	6 (10.34)	10 (14.29)	
Fairly high possibility of depression, n (%)	4 (3.13)	1 (1.72)	3 (4.29)	
Higher probable depression, n (%)	5 (3.91)	1 (1.72)	4 (5.71)	
***EPDS total**, Mean (SD)*	5.41 (3.88)	4.72 (3.44)	5.97 (4.15)	0.0700
STAI-Y1				
No or low anxiety, n (%)	96 (75.00)	43 (74.14)	53 (75.71)	0.7162
Moderate anxiety, n (%)	19 (14.84)	10 (17.24)	9 (12.86)	
High anxiety, n (%)	13 (10.16)	5 (8.62)	8 (11.43)	
***STAI-Y1 total,** Mean (SD)*	33.41 (7.77)	33.79 (7.17)	33.09 (8.27)	0.6101
STAI-Y2				
No or low anxiety, n (%)	104 (81.25)	48 (82.76)	56 (80.00)	0.8858
Moderate anxiety, n (%)	16 (12.50)	7 (12.07)	9 (12.86)	

(Continued)

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TABLE 2 Continued

	Fathers			
	All (n=128)	Singleton (n=58)	Twin (n=70)	*p-value*
High anxiety, n (%)	8 (6.25)	3 (5.17)	5 (7.14)	
***STAI-Y2 total,** Mean (SD)*	31.95 (7.57)	32.00 (7.26)	31.90 (7.86)	0.9410

Scoring categories for EPDS, STAI-Y1, and STAI-Y2 are presented, separately for mothers and fathers, based on singleton and twin pregnancies. Absolute/relative frequencies and means/SDs, along with p-values from Chi-square/Fisher tests (categorical) and t-student tests (numerical) are included for inter-group comparisons. EPDS, Edinburgh Postnatal Depression Scale; STAI, State and Trait Anxiety Inventory.

support between partners. Future investigations on this topic are warranted to delve deeper into these dynamics and provide a more comprehensive understanding of the implications for parental mental health.

In the context of existing literature comparing parents of twins to parents of singletons, our findings contrast with specific earlier studies (13, 27–32), yet align with the consistency demonstrated in numerous other investigations (33–39). The observed variability in scientific literature could be attributed to various factors. Primarily, the presence of high levels of heterogeneity in outcome measures assessing the risk of depression and anxiety often poses challenges in making comparisons and achieving result standardization. For instance, studies that failed to identify inter-group disparities in PPD predominantly utilized the EPDS (12). Furthermore, discrepancies can arise from differences in inclusion criteria across these studies. Notably, our research benefits from a robust framework with well-defined inclusion criteria, rigorously excluding instances of preterm births, fetal anomalies, and severe maternal comorbidities. However, it is important to acknowledge a limitation of our study, namely the absence of *In Vitro* Fertilization (IVF) data, which hindered our ability to control for a factor more frequently associated with a heightened risk of psychological impairment.

While this study sheds light on various dimensions, certain limitations warrant consideration. The relatively small sample size necessitates cautious interpretation of the results, as the statistical power may be limited. The low response rate of 53% may have introduced non-response bias, potentially skewing the sample toward a representation of individuals more inclined to participate due to milder distress levels. Additionally, the retrospective design of the study posed challenges in administering questionnaires and restricted participant inclusion. While excluding preterm birth or congenital anomalies allowed for a focused examination of unique psychological aspects associated with multiple pregnancies, without the confounding influence of adverse medical outcomes, we acknowledge that it may have inadvertently selected a group of twin pregnancies with better outcomes. This could indeed be a limitation, as our study population may not be fully representative of the broader spectrum of twin pregnancies, often characterized by higher medical complexities.

Our established practice at the multiple pregnancy specialty program, where we offer complimentary psychological support to mothers of twins at no cost, may have inadvertently introduced bias. The presence of a multidisciplinary staff, including a specialized nurse and a psychologist, could have influenced our results and mitigated the previously observed differences in anxiety and depression levels between mothers of twins and mothers of singletons. This distinctive approach, in contrast to the predominantly medicalized perspective on twin pregnancies observed in certain healthcare systems, likely played a pivotal role in the comparable mental health outcomes between parents of twins and parents of singletons. We highlight this care model as a potential explanation for our findings, proposing it as a noteworthy consideration for future research.

It is important to contextualize our study within the societal framework of Italy, where new parents, including those with twins, benefit from income-based economic support through the 'Baby Bonus.' This support increases for the second child, as is the case with twins, yet it remains a modest contribution (ranging from EUR 80/month to EUR 160/month). Maternal and paternal leave is

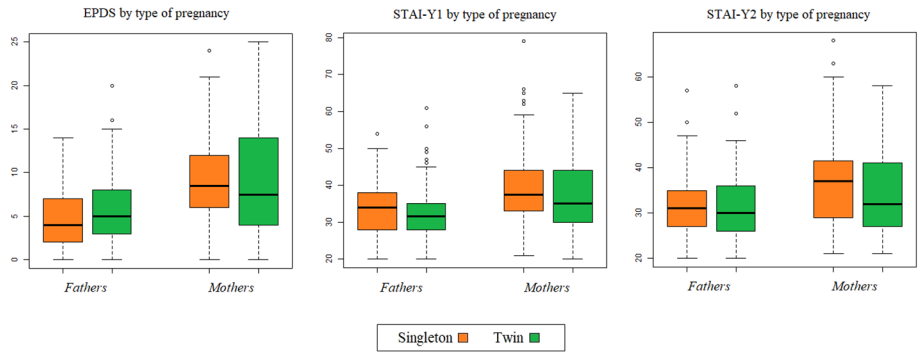

FIGURE 2
Boxplot of type of pregnancy and psychological scores, separated for fathers and mothers.

TABLE 3 Univariate logistic regression models, employing higher EPDS (≥11), STAI-Y1 (≥42), and STAI-Y2 (≥43) scores in a dichotomous way as the focal outcomes.

Mother	EPDS	STAI-Y1	STAI-Y2
	OR [95% CI]	*OR [95% CI]*	*OR [95% CI]*
Twin vs singleton	1.42 [0.73; 2.77]	0.95 [0.48; 1.87]	0.91 [0.43; 1.91]
Age, years	1.01 [0.94; 1.08]	1.00 [0.93; 1.07]	0.97 [0.90; 1.05]
BMI, kg/m²	1.05 [0.97; 1.13]	1.02 [0.94; 1.10]	1.04 [0.95; 1.13]
Married vs single	0.51 [0.23; 1.15]	**0.38 [0.17; 0.87]**	0.54 [0.22; 1.28]
Secondary or higher vs low education	0.50 [0.10; 2.57]	0.91 [0.16; 5.15]	0.56 [0.10; 3.18]
Employed vs unemployed	1.03 [0.47; 2.24]	1.02 [0.46; 2.25]	0.63 [0.27; 1.46]
Father	EPDS	STAI-Y1	STAI-Y2
	OR [95% CI]	*OR [95% CI]*	*OR [95% CI]*
Twin vs singleton	1.99 [0.58; 6.84]	1.43 [0.55; 3.72]	1.37 [0.42; 4.43]
Age, years	**0.89 [0.79; 0.99]**	0.94 [0.86; 1.03]	0.90 [0.81; 1.01]
BMI, kg/m²	1.00 [0.87; 1.15]	**0.83 [0.70; 0.98]**	0.94 [0.80; 1.11]
Married vs single	–	–	–
Secondary or higher vs low education	0.76 [0.15; 3.80]	0.83 [0.21; 3.21]	0.76 [0.15; 3.80]
Employed vs unemployed	–	3.01 [0.37; 24.21]	1.66 [0.20; 13.79]

Bolded values indicate confidence intervals that do not include 1, indicating statistical significance.
-, missing values for some variables are due to instability in the estimation of odds ratios and confidence intervals, making them unavailable or unreliable.

consistent for singletons and twins, fully compensated for 5 months and partially compensated for an additional 6 months.

It is important to acknowledge the unintentional absence of same-sex couples and the predominantly white composition (98%) in our sample. The experiences and psychosocial factors of same-sex couples may differ, limiting the generalizability of our findings to these populations. Additionally, our study did not comprehensively address cultural and racial factors due to the predominantly white sample, potentially impacting the broader applicability of our results. A noteworthy aspect is that most participants were married, suggesting stronger social support and healthier relationships with their domestic partners. This, coupled with the psychological assistance provided, could have influenced our findings. These considerations provide a foundational context for future studies, underlining the need for diverse samples and exploring the impact of psychological support on parents of multiples, particularly within various cultural and relational contexts.

A notable strength of our study is the inclusion of fathers in the investigation, an area that has been understudied in the past. The higher prevalences of EPDS scores among fathers of twins compared to fathers of singletons in our cohort may signify potential disparities in support. This highlights an important avenue for future research to delve deeper into understanding the unique challenges fathers face in coping with twin pregnancies.

In conclusion, our study reveals no significant overall distress differences between parents of twins and singletons at one year postpartum, yet highlights a consistent trend of higher postpartum depression and anxiety scores among mothers when compared to fathers, particularly in singleton pregnancies. Our results also emphasize the critical need to prioritize mental health in prenatal care. When pregnancies are diagnosed, the mental health of families should be placed on an equal footing with other concerns. The observed high prevalence of depression symptoms and suicidal thoughts, notably among mothers of twins, underscores the urgency of integrating mental health screenings for both singleton and twin pregnancies. Identifying and offering targeted support for postpartum depression and anxiety are deemed crucial. Moreover, active involvement of fathers can aid couples in coping with the stress of twin pregnancies. Our routine practice at the multiple pregnancy specialty program, offering no-cost psychological assistance to mothers of twins, may have influenced results, possibly reducing the previously observed difference in anxiety and depression levels between mothers of twins and singletons. While this care model offers a potential explanation for our findings, it underscores the need for future research, including a randomized controlled trial comparing parents of multiples receiving psychological support with those who do not receive such assistance, with the aim of further elucidating the impact of integrated psychological care on the well-being of parents navigating the challenges of multiple pregnancies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics Committee of Catholic University of the Sacred Heart (protocol code DIPUSVSP-16-11-2091). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

GB: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing. VL: Conceptualization, Investigation, Methodology, Writing – original draft, Writing –

review & editing. CA: Formal analysis, Writing – original draft, Writing – review & editing. FM: Investigation, Resources, Writing – review & editing. AF: Investigation, Resources, Writing – review & editing. FR: Investigation, Resources, Writing – review & editing. MP: Investigation, Resources, Writing – review & editing. DV: Investigation, Resources, Writing – review & editing. AS: Investigation, Resources, Writing – review & editing. AL: Supervision, Writing – review & editing. EB: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We thank the Ministry of Health of Italy: current research year 2023.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1284090/full#supplementary-material

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frontiers | Frontiers in Psychiatry

TYPE Original Research
PUBLISHED 29 February 2024
DOI 10.3389/fpsyt.2024.1272513

OPEN ACCESS

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RECEIVED 04 August 2023
ACCEPTED 05 February 2024
PUBLISHED 29 February 2024

CITATION
Quiray J, Richards E, Navarro-Aguirre Y, Glazer D, Adachi J, Trujillo E, Perera D, Garcia EP and Bhat A (2024) The role of doulas in supporting perinatal mental health – a qualitative study.
Front. Psychiatry 15:1272513.
doi: 10.3389/fpsyt.2024.1272513

The role of doulas in supporting perinatal mental health – a qualitative study

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Objective: The perinatal period presents several opportunities to identify and treat perinatal mental health and substance use disorders by integrating into existing care pathways. We aimed to examine the role of birth doulas in supporting their clients' perinatal mental health.

Methods: Thematic content analysis of focus groups with doulas, and interviews with doula clients was used to characterize the doula-client relationship, investigate whether and how doulas provide mental health and substance use support, and identify barriers and recommendations for doulas to support their clients' mental health. Participants were doula clients from communities underserved due to race, income, language and culture.

Results: Doulas and clients reported positive relationships, supported by congruence in culture, language, and lived experiences. Doulas varied in their confidence in identifying perinatal mental health problems, though most agreed that doulas could support their clients' mental health to different degrees. Barriers to engaging in perinatal mental health treatments included low perceived need and socio-economic burden.

Conclusions: With adequate support and training, doulas can play an important role in supporting their client's emotional well-being.

KEYWORDS

perinatal mental health, maternal mental health, doula, screening, qualitative, needs assessment

Introduction

Perinatal (pregnancy and the first year postpartum) mental health (PMH) and substance use disorders (SUD) are the most common complications of pregnancy yet frequently go undetected and untreated, especially among historically underserved communities such as Black, Latina/o/x, Indigenous, and people of low income. Perinatal mental health conditions include depression, anxiety, obsessive compulsive disorder, post-traumatic stress disorder, bipolar disorder and psychosis. Black and Latina/o/x women are less likely to receive mental health screening (1), assessment (2, 3), or treatment (4–7) than White women. These inequities persist after adjusting for education and income (8) and have been exacerbated by the COVID-19 pandemic (9). Factors contributing to this treatment gap and inequities, include mental health workforce shortages (10), lack of culturally congruent providers (11) structural racism resulting in mistrust in the medical system (12), employment, income, transportation, insurance status and type, refugee status, and immigration status (13). Addressing subjective perceptions of need for mental health treatment is also important as low income mothers and pregnant people with psychological distress may be reluctant to engage with mental health services due to a belief that only severe mental health conditions warrant treatment (14). Social norms surrounding discussion and treatment of mental illness and stigma may vary by race and ethnicity (15), and underserved people can experience the "double stigma," of mental illness and discrimination, contributing to lower rates of treatment seeking (16). Black and Latina/o/x women may be more likely than non-Hispanic White women to report perceived stigma about depression (17), or to believe that mental health treatment will be unhelpful (18). They may be less likely to find antidepressant medication (19) and counseling (20) acceptable. Mothers with income inequity have reported that mental health treatment would do nothing to address their psychological distress, which they viewed as due entirely to external stressors such as poverty (14).

Barriers to PMH treatment access can be addressed by integrating care into community-based settings, with the support of trusted individuals such as doulas. Birth doulas are individuals from the same community as their client, who are trained to provide psychosocial, emotional, and educational support during pregnancy, childbirth, and postpartum, and act as a liaison between their client and the health care system (21). They help people navigate systemic healthcare racism and socioeconomic barriers (22–24). Including doulas in prenatal care improves pregnancy and birth outcomes (25, 26) and patient satisfaction (27), and is a promising approach to address racism and inequities in maternal health.

Doulas can potentially play a greater role in the identification and initial support of clients with PMH and SUD as they interact frequently with their clients through the perinatal period and develop longitudinal, trusting relationships. Screening, education, and support offered by doulas may be more acceptable to clients, without the barriers of stigma and mistrust of the healthcare system. Studies describe the emotional support provided by doulas during labor and delivery (28), and in the postpartum period (29), and doula's PMH training needs (30–33). Our aim in this qualitative analysis is to understand the role of doulas in perinatal mental health, from the perspective of both doulas and clients.

Materials and methods

This qualitative study includes focus groups with birth doulas (referred to as doulas here) and individual interviews with clients. We obtained Institutional Review Board (IRB) approval and collaborated with Open Arms Perinatal Services (OAPS) to recruit study participants. OAPS is a non-profit organization in King County, WA that provides services to clients living within 200% of the federal poverty level. It supports over 500 pregnant people and babies each year, 90% of whom are from underserved communities (34). We used convenience sampling to identify doulas and their clients using a combination of active(potential participants were contacted by phone and informed about the study) and passive(distributing fliers through the internal listserv) recruitment strategies. All participants provided informed consent and received $30 per hour compensation.

Conceptual model

Focus group and interview guides were developed in collaboration with OAPS, based on the potential role for non-specialty health workers to be involved in their clients' PMH care (35). In doula care, the role of doulas as culturally congruent liaisons between health care providers and clients may offset tensions arising from systemic racism and race/culture discordance between provider and patient (21). However, this pathway does not address other barriers to care that are common among populations experiencing disparities, including low perceived need for care, low awareness of services, low perceived access to care, low perceived effectiveness of care, and stigma (13). Hence, our interview and focus group questions were designed to examine the role of doulas in addressing these barriers and specifically in educating, screening, and referring clients with PMH and SUD concerns.

Data collection

To limit bias that might be seen in a single group, we planned to conduct focus groups with doulas until we reached saturation. The focus group interviews were conducted by a facilitator separate from the study team, and an observer (YN) who made field notes. Three focus groups lasting 60-90 minutes each, with one, two and six participants respectively, were conducted between June 2022 and July 2022 in a Zoom virtual meeting room. To reduce stigma and encourage self-disclosure we conducted individual interviews with doula clients between July 2022 and September 2022 until saturation was reached. Individual interviews in English and Spanish conducted by JQ and YN lasted between 30-60 minutes. Transcriptions were created from the recorded focus groups and interviews, and Spanish language interviews were translated.

Data analysis

Coding and analysis were performed by JQ, ER, YN, DG and AB. JQ is a research coordinator and identifies as a queer, second-generation Filipino American. ER is a Black female psychiatry resident physician, YN is first-generation Latina research coordinator. DG is a White female health services research coordinator. AB is a female perinatal psychiatrist and health services researcher who is a first-generation Asian immigrant. Using transcriptions as data, thematic content analysis combined with rapid team-based qualitative analysis were carried out using a process of progressive data reduction to narrow the focus and generate more specific codes from general codes (36, 37). Themes derived from interview questions were transferred to a doula and client summary template. The research team assessed and edited summary templates for agreement through coding of one identical doula and client transcript, then independently coded different transcripts. Themes and codes were revised through an iterative process in team meetings until consensus was reached. Results were presented to doula participants for feedback at a team meeting.

Results

Doula and client participant demographics are summarized in Table 1. All participating doulas owned an independent practice and/or were contracted with an organization. In total, 28 doulas were contacted, and nine doulas consented to participate. A total of 44 doula clients were contacted (18 of whom were Spanish speaking) and 10 participants consented to participate. Of the ten participants included, five were interviewed in Spanish. All clients identified as female and received care from birth doulas who primarily serve during pregnancy and birth with a few postpartum visits. Eight out of nine clients had a doula for the first time; one client had the same doula for three consecutive pregnancies. All clients were postpartum at the time of the interview.

TABLE 1A Birth doula demographics.

Focus Group	Years in practice	Race
A	9	Another Hispanic, Latino/a, or Spanish origin
B	3	Black
B	3	Another Hispanic, Latino/a, or Spanish origin
C	1	White
C	6	Black
C	6	Mexican
C	10	White
C	1	Black
C	7	Black

Table 1b Client demographics.

Participant	Interview language	Race	MH history	Pregnancy stage	Prenatal care receipt
1	English	White	Depression symptoms	7 weeks postpartum	OB/GYN
2	English	Dominican and Black	None	16 weeks postpartum	Midwife
3	English	Black	Alcohol use before pregnancy, current depression symptoms	24 weeks postpartum	OB/GYN and Midwife
4	English	Black	Depression symptoms and stress	20 weeks postpartum	OB/GYN
5	Spanish	Mexican	None	12 weeks postpartum	OB/GYN
6	Spanish	Hispanic, Mexican	None	20 weeks postpartum	Primary care
7	Spanish	Latina, Peruvian	None	24 weeks postpartum	OB/GYN
8	Spanish	Latina, Mexican	None	12 weeks postpartum	Midwife
9	Spanish	Mexican	None	20 weeks postpartum	Midwife

Themes

We examined the role of doulas in perinatal mental health through four themes, with a total of ten codes that emerged from doula and client narratives (Table 2).

1. Doula – client relationship (n=3): nature of relationship, quality of relationship, and congruence
2. Social support and PMH and SUD (n=1): PMH and SUD stigma in communities
3. Doula's response to client's PMH and SUD (n=4): education, approach to identification of PMH and SUD, variability in capacity to manage clients' PMH and SUD problems, and referrals to services and treatments
4. Barriers to PMH and SUD treatment (n=2). Low perceived need for care and low perceived access to care and client unable to access PMH care to due socio-economic burden

Doula – client relationship

Both doulas and clients reported positive relationships, supported by congruence in culture, language, and lived experiences. In addition to labor and delivery support, doulas

TABLE 2 Qualitative findings from focus groups with doulas and interviews with clients.

Theme	Code	Quote from doula	Quote from doula client
Doula – client relationship	Nature of relationship	"…it's important from my perspective to show my clients to navigate in the system, for them to know what to expect there. My advocacy is not to speak for them but to say, "You can do this. You have the power to do this, and remember that all the time…" (A) "And that was two times where Mom had postpartum depression … and I was able to help her to see what she was going through and to recognize that was not just in her head … And it had a name, and it needed medication, and it needed support. And she got it." (C)	"I was going through some difficult emotional challenges and changes in my life during the pregnancy, and she was really there to be a sounding board and to help me prepare for what my life might look like in different situations and just to have compassion and empathy … I had to have a medical appointment… – and she was able to help attend that appointment with me and help me get the kids in the stroller and do things that were physically challenging for me because I was just a few days' post C-section." (Participant 1) "She was there when I had my child and was an advocate" (Participant 4) "…she also does the translator service. So, there were things that my husband didn't understand like hospital things, health; but she helped, and, in fact, the doctors said that: "Oh, that's very good," and she said, "We have two for one", because she helped as a doula and helped as a translator." (Participant 5)
	Quality of relationship	"….you also become her counselor, her confidante, her friend, her sister, and sometimes her aunt" (C)	"I thought I was going to feel a little uncomfortable because … it was only by zoom. But no, she is nice, she was very supportive and helped me a lot" (Participant 8) "It was very friendly. Like if she was like an aunt…. who was taking care of me." (Participant 9)
	Congruence	"I feel I really can't understand my clients unless they are Latina because I am Latina. I am an immigrant, and I can know how all my community is going to be similar" (A) "A lot of my clients do identify as Black. And they want to have someone in their space that looks like them and has that in common" (B) "I decided to become a doula because I have been working in the deaf community for the last eight years. And as I became friends with more and more deaf people, I started hearing a lot of really traumatic birth stories about lack of access in their native language in birth work" (C)	"she's also Hispanic, we didn't know which country, but we know she's Hispanic. And no, the truth is that she helped a lot, she's an older person, which that gave me that trust, for me it was as if my mother was with me…" (Participant 5) "The fact that she spoke Spanish, obviously, and that she is of my same race, you could say, because she is Argentinian. So, it wasn't a person from here who speaks Spanish with that accent … So, everything flowed from the moment we had the Zoom meeting, before we met in person, and the moment when she was already there was as if we knew each other for a while. I think it was because of that why she understood perfectly what I was saying." (Participant 7) "My doula was black. I'm white, but my husband and all my children are black, and so it might not necessarily be that she connected with me culturally, but I felt like I had a connection with her because she respected my family structure. I knew she respected the interracial marriage. I know that she respected black people and the situations that they deal with that white people don't have to deal with and the situations that we might encounter being an interracial couple or having black children…" (Participant 1)
Social support and PMH/SUD	PMH and SUD stigma in communities	"You don't want to express it to anybody … those symptoms aren't really discussed because of the stigma around them" "they didn't want to accept that they have a problem…, for Hispanics, seeing a counselor, not a chance, "Oh, I am not crazy."… and that's why they don't seek that type of help and because they don't have enough information, either" There are "stigmas around Black mental health…. it's a new concept to seek outside support and being honest about what you're experiencing … There's just been a lot of secrecy when it comes to mental health stigmas" (B) "…with my community [Latino/a/x], it's really a taboo talking about mental health, and this could be really offensive for some people. So, we have to be really care about the way that we are asking or presenting something."	"…the one I've talked about those aspects with is my mom. She told me that if I felt some symptoms, to talk to my doctors. Or, in this case, also with my husband so that he could help me make some kind of decision in case something like that would happen to me or similar aspects." (Participant 6) "My family was afraid that I would get postpartum depression because … they heard me more than anything talk when I was pregnant: 'Please let it be over'…they told me: 'When you give birth you have to have willpower, you might get this, you might get that.' And I was like, "Well, I hope I don't get it because it's not something I can control." (Participant 7)
Doula's response to PMH/SUD	Education	"…everything education-based … after they've given birth, I let them know those first three days there's a big hormone influx, so you're going to feel a lot of different feelings. And then, in about two weeks, I'll check in with you again and see how you're feeling … if you're feeling these intrusive thoughts about maybe wanting to cause harm to your baby … just letting them know what those symptoms…" (B)	

(Continued)

10.3389/fpsyt.2024.1272513

TABLE 2 Continued

Theme	Code	Quote from doula	Quote from doula client
	Approach to identification of PMH/SUD	"I really like to give them a questionnaire to complete. On the questionnaire she put more things than she told me in person." (A) "I would say that having a questionnaire or paperwork for my clients is not appealing. I try to give it as a way of empowerment and for them to utilize … but I would never feel comfortable saying, "I want you to complete this PHQ9 as a way for me to gauge how you're doing." (C) "You get to know this person. And when something is not right, you would know something is not right … as for substance abuse, I did have a client… – she confided me – that she was using I got her into rehab … she got the help that she needed." (C)	
	Variability in capacity to manage clients' PMH and SUD problems	Regarding substance use, "that was the very first time that I encountered that problem". "I had to turn a client away because her level of anxiety and depression was too much for me and I just didn't know how to handle it" (B) "So, I kind of usually avoid when I see clients with substance abuse, because I was scared that I was not able to help my clients since I did not have any experience of this field" (C) "It's really hard for me because I don't feel I have the tools to help … I don't have a really good response in the middle of the night" (A) "Everybody [doulas] turned her down because nobody was prepared to deal with that amount of stress that she was going through." (B) "I did have a client … [confide in me] that she was using … So, I got her into rehab … and continue to seek counseling and continue to be monitored … I actually became kind of a big sister to that human being … I make sure that every step, I was there to support and to help her." (C) "just life experience … [knowing] people who are dealing with substance issues … it's just learning who they are, learning about their story, creating a safe space for them to feel open enough to say what's going on…" (B)	"…we also touch on mental health issues and things like that; she would ask me how I was feeling, and sometimes she would tell me that it was a bit normal to feel overwhelmed when the baby and the sibling were first born. She also shared her experiences and I believe that the fact that she also opens up with you generates more confidence to tell her my things as well." (Participant 8)
	Referrals to services and treatment	"…I really like to connect them with some particular services. I like to offer them this Perinatal Support Washington…" (C) "I want to help you. In order to help you we need to go through my organization to look for the best resources for you," (A)	"…she reached out and she spent time trying to research things and find providers and call places and give me resources." (Participant 1)
Barriers to PMH and SUD treatment.	Low perceived need for care and low perceived access to care	"In their opinions, they either are not getting the help, or they don't know that there is help … I think a lot of my clients didn't know what the symptoms are. They think it's just a part of the experience for the first-time moms, or even the second-time moms because, the nature of mood disorders looks different, and it varies per pregnancy" (B)	"I didn't actively look for a mental health therapist or anything because I felt like I needed money, like, my own money … I think I had already put it in my mind that I wasn't gonna be able to get it" (Participant 3)
	Client unable to access PMH care to due socio-economic burden	"I see that mental health can come up as something that is struggling at any point during pregnancy or postpartum, but it has to be maybe lower on the priority list than it … could be for someone who has more of their basic needs met" (C)	"…there's no psychiatrists around here that take it, so that has been a big problem why at times when I definitely felt like I needed more mental health care or was really struggling, I just couldn't get it." (Participant 1)

PMH, Perinatal Mental Health; SUD, Substance Use Disorder.

provided advocacy, translation services, decision making support and logistical support.

Participant 1 had the same doula from two previous pregnancies and appreciated that rapport during virtual care visits with their most recent pregnancy due to COVID-19 restrictions.

"…[it's]hard to make that bond, especially in a pandemic, and [to] have that connection with someone new. So, being able to have that same support person I think was really, really, really helpful for me."

Cultural and linguistic congruence between Spanish-speaking doulas and clients supported strong relationships, especially for some whose immediate families lived outside of the United States. Congruence in lived experiences was also important. A client in an interracial marriage felt respected and understood by her doula. A doula who had previously worked in the deaf community utilized their experience to provide more accessible services.

Only one client reported a negative relationship with two doulas due to inconsistent care from the first doula and disagreement during their birth with the second doula.

"Her phone[was] always messed up … she couldn't even come to the[birth] … so then I had to get the hospital doula, and my doula wasn't as holistic … when I was talking about having a placenta birth, she kind of made a face … [I was going to]say a lotus birth and she didn't understand what that was, and she was taken aback … she kept throwing little things out there to say, 'You still want to do that?" (Participant 2)

Social support and PMH and SUD

Within clients' communities, cultural norms and beliefs impacted perceptions of PMH and SUD. Several doulas also described the lack of discussion and treatment of PMH primarily in communities of color. Two Spanish-speaking clients stated their families believed PMH symptoms could be controlled through self-management.

"I did recently tell my mother: "Oh, mom … I feel bad or I feel this", she told me: "No, just sleep well, eat at your own time, be calm, don't worry…" (Participant 5)

Many clients stated that PMH and SUD were not explicitly discussed in their social networks, though they believe their families would support treatment and discourage use of substances. Two clients with self-reported PMH symptoms openly discussed their PMH within their communities more so during postpartum and were able to receive support from their families.

"So, I had that at that time [in home country], but just having my spouse there … always cheering me on, and taking me out … and also removed the stress of caring for the baby because my mom was also like, 'she can't just stay with the baby'…" (Participant 4)

Both doulas and clients agreed that it was important for clients to feel close and safe with the people they discuss PMH and SUD challenges with.

Doula's response to client's PMH and SUD

Two of three clients with PMH symptoms reported that their doulas discussed PMH with them and provided resources. The third client's doula provided emotional support but did not explicitly discuss MH. All but one of the clients who did not report symptoms would be willing to discuss their PMH with their doula if they were to experience it and would involve their doula in PMH care if given a choice. The one client who was hesitant stated it would be contingent on having a positive relationship with their doula.

One doula reported challenges with adding PMH support to her existing responsibilities *"Man, I'm trying to handle the induced labor and we were having trouble … And then, I have these other clients calling me off the hook. My phone is ringing off the hook."*(C)

Some doulas preferred to use standardized questionnaires when evaluating PMH. Others used informal screening questions:

"…are you getting enough rest? Are you sleeping well? Are you making sure you[are] letting your body heal?"(C)

One doula described their hesitancy with using standardized questionaries because they felt that utilizing questionnaires would align them more with institutions rather than serving as an advocate for the client.

Some of this variability in the capacity to manage PMH and SUD symptoms amongst the doulas was attributed to lack of experience. Doulas who felt confident in the management of PMH and SUD reported that they had a strong rapport with their clients, received additional training, and/or had lived experiences with PMH and SUD. Upon recognition or identification of PMH or SUD, most of the doulas made referrals to available services and treatments. Both doulas and clients noted additional referral support from doulas such as assistance in making phone calls, check-ins about referral completion and encouragement to continue treatment. One doula who noted a specific interest in PMH started a support group for Black clients.

Barriers to PMH and SUD treatment

Doulas reported barriers to supporting their clients' PMH included their own lack of knowledge and comfort, and dearth of appropriate referral options. Doulas found that stigma and fear of consequences can prevent clients from accessing care and further barriers include insurance, scheduling difficulties, cultural congruence with provider and client, and appointment adherence. Doulas also observed a de-prioritization of PMH symptoms among clients struggling to meet basic needs.

Clients were open to having doulas attend their PMH treatment appointments to facilitate trust and communication as needed, particularly if they had a trusting relationship with the doula *"…if she were in a very intimate moment of my life, which is like giving birth, without her being my family I gave her that confidence and she gave me her support, I feel that she would also be part of the family and I could*

ask her to accompany me to that type of appointments." (Participant 6)

Unique factors were identified related to the fact that doulas were from the same community as their clients. One doula reported being cautious about broaching the topic of PMH with their clients because of the stigma associated with it. *"So … with my community, it's really a taboo talking about mental health, and this could be really offensive for some people. So, we have to be really care(ful) about the way that we are asking or presenting something."*(C)

Discussion

In this qualitative analysis of the role of doulas in supporting their clients' PMH, we focused on participants from underserved communities. with and without a history of mental health symptoms.

Doula – client relationships were largely positive. Doulas provided support that extended well beyond labor and delivery, from instrumental support (helping clients get to their medical appointments), to emotional support (being a "sounding board", almost like a family member). Support in the postpartum period was especially appreciated and desired. Doulas extended their role to support clients facing linguistic barriers by helping with interpretation. Importantly, helping patients advocate for the healthcare they needed and wanted emerged as a key role for doulas, with an emphasis on the importance of remaining within scope of practice.

The relationship was viewed as especially supportive when there was congruence between the doula and client in one or more aspects – e.g., race, language, or lived experience of being a parent or having experienced racism. Interestingly, even with racial concordance, the doula's supportive personality was considered more important in nurturing a strong relationship. Among our participants who identified as Hispanic or Latina/o/x, despite being of different nationalities, the ability to converse with their doula in Spanish was a source of comfort. Congruence in age was viewed as beneficial by some, but for some, having a doula older than them, almost like a mother figure, was more important. Although doulas reported best being able to support clients from their own community, some doulas reported needing to be cautious in their approach and mindful of the stigma of mental health within the community. This contrasted with some participants reporting that they discussed their mental health issues with the doula but not with their family because of stigma. These findings highlight the unique benefits and challenges of receiving community based mental health support.

Although most doulas had were willing to support their client's PMH and SUD to different extents, some doulas avoided taking on clients with PMH and SUD due to feeling unprepared, highlighting the need to provide education and clear referral pathways so doulas can effectively build on their trusting relationship with clients to facilitate PMH and SUD treatment. Additionally, doulas explained the difficulties they experienced trying to manage the complexities of their clients' PMH needs while attending to their usual duties of providing labor and delivery support. When involving lay or community health workers in the mental health treatment pathway it is important to address scope of practice and burden (38). Doulas provided education and anticipatory guidance about postpartum depression and intrusive thoughts, identifying PMH and SUD concerns, and provided resources. Notably, some doulas specifically preferred not to use structured questionnaires to screen for PMH symptoms. Several agencies have recommended screening for perinatal depression using structured questionnaires such as the Patient Health Questionnaire – 9 or Edinburgh Postnatal Depression Scale (39, 40), and screening using standardized validated questionnaires is common, feasible, and effective in community-based settings (41). However, our findings suggest that there may be a need to study additional approaches to support screening for PMH and SUD in the context of doula care.

Treatment access was limited by the lack of providers accepting their insurance. Doulas helped to the extent they could by following up on their clients' PMH referrals. Barriers to PMH and SUD have been discussed extensively in the literature (42–44). In addition to commonly documented barriers, we found that perceived need for care and perceived access to care were low. Mental health was deprioritized due to socioeconomic burden, and participants felt that it was futile to look for PMH who accepted their insurance (usually Medicaid for our participants). Stigma regarding PMH was common and interfered with treatment access. In this context, the strong, congruent, familial relationship with their clients was conducive to identifying PMH and SUD, however doulas noted that they needed additional training and support to do this effectively and to liaison with the health care system.

Integrating mental health screening and intervention into community-based settings, within the context of maternal child health care is a promising approach to increasing detection and treatment of perinatal mental health conditions. This approach using task shared interventions delivered by community health workers or peers within existing maternal child health platforms is commonly used in several programs across the world (45).

Strengths of our study include the focus on underserved communities, obtaining the perspective of both doulas and clients, and the broad range of experiences reflected in our participant pool. Limitations include potential selection bias as participants who consented to the study may be more likely to have a positive attitude towards PMH and SUD, whereas the doulas who might not yet be confident with helping their clients with their mental health might not be well represented in the data. The willingness of doulas to support their clients' PMH and SUD may depend on local availability of PMH resources and trainings, and findings from this single site study may not be applicable to all settings.

Conclusions

We found that most doulas are already supporting their clients' mental health in several different ways, addressing barriers to mental health treatment that may be unique to underserved populations. However, they report unmet identified perinatal mental health training needs and concerns about scope of practice and burden. Several states have legislation pending that

would allow for Medicaid reimbursement of doula services, thus making doula services more accessible. This could be an inflection point for better coordination between healthcare and community-based systems, and an opportunity to decrease inequities in PMH and SUD treatment. With adequate support and training, doulas can play an important role in supporting their client's emotional wellbeing.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by University of Washington Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their verbal informed consent to participate in this study.

Author contributions

JQ: Methodology, Writing – original draft, Writing – review & editing, Data curation, Formal analysis, Project administration. ER: Formal analysis, Writing – original draft, Writing – review & editing. YN-A: Formal analysis, Writing – review & editing, Validation. DG: Formal analysis, Writing – review & editing. JA: Writing – review & editing, Project administration, Resources, Supervision. ET: Resources, Writing – review & editing. DP: Resources, Writing – review & editing, Supervision. EG: Resources, Writing – review & editing. AB: Resources, Writing – review & editing, Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Writing – original draft.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number UL1 TR002319.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1272513/full#supplementary-material

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frontiers | Frontiers in Public Health

TYPE Brief Research Report
PUBLISHED 07 March 2024
DOI 10.3389/fpubh.2024.1345442

OPEN ACCESS

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RECEIVED 04 December 2023
ACCEPTED 19 February 2024
PUBLISHED 07 March 2024

CITATION
Beck DC, Tabb K, Tilea A, Vance AJ, Hall S, Schroeder A and Zivin K (2024) Diagnosed behavioral health conditions during the perinatal period among a commercially insured population by race/ethnicity, 2008–2020. *Front. Public Health* 12:1345442. doi: 10.3389/fpubh.2024.1345442

Diagnosed behavioral health conditions during the perinatal period among a commercially insured population by race/ethnicity, 2008–2020

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Objective: We sought to examine trends in diagnosed behavioral health (BH) conditions [mental health (MH) disorders or substance use disorders (SUD)] among pregnant and postpartum individuals between 2008–2020. We then explored the relationship between BH conditions and race/ethnicity, acknowledging race/ethnicity as a social construct that influences health disparities.

Methods: This study included delivering individuals, aged 15–44 years, and continuously enrolled in a single commercial health insurance plan for 1 year before and 1 year following delivery between 2008–2020. We used BH conditions as our outcome based on relevant ICD 9/10 codes documented during pregnancy or the postpartum year.

Results: In adjusted analyses, white individuals experienced the highest rates of BH conditions, followed by Black, Hispanic, and Asian individuals, respectively. Asian individuals had the largest increase in BH rates, increasing 292%. White individuals had the smallest increase of 192%. The trend remained unchanged even after adjusting for age and Bateman comorbidity score, the trend remained unchanged.

Conclusions: The prevalence of diagnosed BH conditions among individuals in the perinatal and postpartum periods increased over time. As national efforts continue to work toward improving perinatal BH, solutions must incorporate the needs of diverse populations to avert preventable morbidity and mortality.

KEYWORDS

perinatal mental health, behavioral health, racial disparities, rates of mental health problems, maternal mental health, SUD

1 Introduction

Behavioral health (BH) disorders are a leading contributor to perinatal mortality in the U.S. (1). Behavioral health problems encompass a broad umbrella of conditions, such as mental health (MH) disorders, substance use disorders (SUD), and co-occurring MH and SUD (2). Ongoing, national efforts aim to improve clinical practice and health policy to support perinatal individuals with BH conditions (2). Equity-focused practice and policy level interventions require a data-driven understanding of trends in BH conditions by race/ethnicity. This knowledge may help foster solutions related to inequitable access to and use of treatment due to systemic racism (3). Few studies have used a racially and ethnically diverse national sample to describe diagnoses of BH conditions during the perinatal period (pregnancy and the postpartum year). Therefore, this study characterized BH (MH or SUD) diagnosis trends during the perinatal period among a racially and ethnically diverse, commercially insured population between 2008–2020.

2 Method

We examined trends in BH diagnoses identified during the perinatal period (pregnancy and 1 year postpartum) among individuals aged 15–44 using Optum Clinformatics Data Mart (CDM). CDM is a de-identified administrative medical claims database derived from a large claims data warehouse for members across 50 states. We identified individuals with deliveries from 2008 to 2020 and restricted the sample to those with continuous enrollment in a single employer-based health plan for at least 1 year before and 1 year after delivery. We identified delivery hospitalizations using standardized International Classification of Disease-9th and 10th Revision-Clinical Modification (ICD-9-CM and ICD-10-CM) diagnosis and procedure codes.

We defined BH diagnosis as evidence of any MH or SUD ICD-9/10 diagnosis code present in at least one inpatient claim or two outpatient claims during the year prior to the delivery or during the year after the delivery. We used Healthcare Cost and Utilization Project (HCUP) codes definitions to identify diagnoses (4).

We summarized demographic characteristics for all individuals with evidence of a BH disorder including any MH, any SUD, or both MH and SUD. We applied logistic regression to calculate the probability of BH diagnosis, adjusting for race, age, geographic region, insurance type, income, delivery mode, and clinical comorbidity as measured using the Bateman Comorbidity Index (5). We calculated the predicted probabilities of each outcome rate for each year of the study period by race/ethnicity to describe trends in BH diagnoses per race/ethnicity group. We used two-sided statistical tests with an alpha level of 0.05 for all statistical analyses. We performed all claims data management in SAS version 9.4 (SAS Institute) and statistical analyses in R (R Core Team).

This study was approved by the study site's Institutional Review Board (HUM00164685).

3 Results

We identified 736,325 deliveries from 621,148 commercially insured delivering individuals between 2008 and 2020. Of these, 202,489 (27.6%) had evidence of a BH diagnosis in either the prenatal or the postpartum year, 26.1% had evidence of any MH diagnosis, and nearly 4.0% had evidence of any SUD diagnosis (Table 1).

Figure 1 shows the unadjusted and adjusted BH rates per 10,000 deliveries grouped by race/ethnicity. All groups increased at the same rate over the study period. White individuals had the highest rates of BH diagnoses, followed by Black, Hispanic, and Asian groups, respectively. Asian individuals had the largest increase in BH rates from 2008 to 2020 with a 292% increase from 872.7 (95% CI: 787–957) per 10,000 individuals in 2008 to 2,544 (95% CI: 2,397–2,690) per 10,000 individuals in 2020 (Figure 1), while white individuals had the smallest increase in BH rates, with a 192% increase from 2,291 (95% CI: 2,250–2,333) per 10,000 in 2008 to 4,410 (95% CI: 4,355–4,465) per 10,000 in 2020 (Figure 1). After adjusting for age and comorbidity, the trend remained unchanged (Figure 2).

4 Discussion

This study found increasing rates of perinatal BH diagnoses during pregnancy and the postpartum year with the greatest increases among Asian individuals. As national efforts to address BH related perinatal morbidity and mortality continue, the needs of diverse groups must be addressed in the context of the systemic drivers of health disparities, including systemic racism (2). This study highlights the need for clinicians to be attentive to the BH symptoms and needs of minoritized groups during pregnancy and the postpartum year, particularly for Asian individuals. A limitation of this study is the use of a commercially insured population, and trends in diagnoses might be different among publicly insured (e.g., Medicaid insured) individuals.

This study supports the need for equitable screening, referral, and treatment of perinatal BH conditions during pregnancy and the postpartum year. Efforts continue toward implementation of structural-level supports to address the health impacts of systemic racism among perinatal individuals, including Medicaid expansion through the full postpartum year and paid parental leave policies (2). While recognizing and diagnosing BH conditions is essential so individuals can receive treatment and ongoing support, individual/health systems interventions must be coupled with structural-level policy change to counteract the health effects of systemic racism.

TABLE 1 Descriptive characteristics of the study cohort, for years 2008 and 2020, by different BH group (any MH, ANY SUD, MH or SUD, MH, and SUD).

Characteristic	2008				2020			
	Any MH	Any SUD	MH or SUD	MH and SUD	Any MH	Any SUD	MH or SUD	MH and SUD
	N = 12,524	*N* = 1,205	*N* = 13,007	*N* = 721	*N* = 19,879	*N* = 3,287	*N* = 20,985	*N* = 2,181
Age group								
15–18	263 (23.91%)	66 (6.00%)	278 (25.27%)	51 (4.64%)	131 (53.04%)	46 (18.62%)	142 (57.49%)	35 (14.17%)
19–26	1,985 (20.00%)	299 (3.01%)	2,085 (21.01%)	199 (2.01%)	3,017 (41.92%)	966 (13.42%)	3,341 (46.42%)	642 (8.92%)
27–34	6,428 (18.75%)	530 (1.55%)	6,668 (19.45%)	290 (0.85%)	10,343 (37.63%)	1,395 (5.07%)	10,851 (39.48%)	887 (3.23%)
35–39	2,923 (20.15%)	240 (1.65%)	3,029 (20.88%)	133 (0.92%)	5,139 (39.08%)	672 (5.11%)	5,345 (40.65%)	466 (3.54%)
40+	925 (23.70%)	70 (1.79%)	947 (24.26%)	48 (1.23%)	1,249 (39.80%)	208 (6.63%)	1,306 (41.62%)	151 (4.81%)
Race								
Unknown/missing	1,316 (18.91%)	33 (0.78%)	369 (8.73%)	12 (0.28%)	1,823 (33.12%)	75 (2.21%)	864 (25.44%)	47 (1.38%)
Asian	348 (8.23%)	124 (2.18%)	1,005 (17.64%)	68 (1.19%)	836 (24.62%)	483 (11.42%)	1,850 (43.72%)	288 (6.81%)
Black	949 (16.66%)	122 (1.53%)	1,353 (17.00%)	61 (0.77%)	1,655 (39.12%)	362 (5.58%)	2,399 (36.95%)	206 (3.17%)
Hispanic	1,292 (16.24%)	132 (1.90%)	1,372 (19.71%)	76 (1.09%)	2,243 (34.54%)	283 (5.14%)	1,936 (35.17%)	170 (3.09%)
White	8,619 (22.18%)	794 (2.04%)	8,908 (22.92%)	504 (1.30%)	13,322 (42.16%)	2,084 (6.60%)	13,936 (44.11%)	1,470 (4.65%)
Division								
Great lakes/northern plains	3,235 (21.38%)	278 (1.84%)	3,331 (22.02%)	182 (1.20%)	5,773 (40.43%)	919 (6.44%)	6,086 (42.62%)	606 (4.24%)
Mountain	1,200 (20.84%)	119 (2.07%)	1,251 (21.73%)	68 (1.18%)	2,120 (39.35%)	353 (6.55%)	2,242 (41.62%)	231 (4.29%)
Northeast	1,340 (20.75%)	112 (1.73%)	1,392 (21.55%)	60 (0.93%)	2,063 (40.48%)	306 (6.00%)	2,171 (42.60%)	198 (3.89%)
Pacific	965 (13.52%)	89 (1.25%)	1,006 (14.10%)	48 (0.67%)	1,851 (34.59%)	160 (2.99%)	1,914 (35.76%)	97 (1.81%)
Southeast	5,779 (19.81%)	607 (2.08%)	6,022 (20.64%)	363 (1.24%)	8,054 (38.39%)	1,546 (7.37%)	8,554 (40.77%)	1,046 (4.99%)
Unknown/Missing	*	*	*	*	*	*	*	*
Insurance								
EPO	2,152 (19.48%)	189 (1.71%)	2,229 (20.17%)	112 (1.01%)	2,443 (38.15%)	450 (7.03%)	2,618 (40.88%)	275 (4.29%)
HMO	1,558 (18.03%)	155 (1.79%)	1,608 (18.61%)	104 (1.20%)	2,073 (37.99%)	359 (6.58%)	2,184 (40.03%)	248 (4.55%)
IND	*	*	*	*	*	*	*	*
OTH	49 (32.03%)	10 (6.54%)	51 (33.33%)	8 (5.23%)	475 (44.06%)	89 (8.26%)	495 (45.92%)	69 (6.40%)

(Continued)

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TABLE 1 (Continued)

Characteristic	2008				2020			
	Any MH	Any SUD	MH or SUD	MH and SUD	Any MH	Any SUD	MH or SUD	MH and SUD
	$N = 12,524$	$N = 1,205$	$N = 13,007$	$N = 721$	$N = 19,879$	$N = 3,287$	$N = 20,985$	$N = 2,181$
POS	8,295 (19.84%)	805 (1.93%)	8,635 (20.65%)	465 (1.11%)	14,646 (38.91%)	2,348 (6.24%)	15,434 (41.01%)	1,560 (4.14%)
PPO	465 (22.77%)	45 (2.20%)	478 (23.41%)	32 (1.57%)	242 (37.69%)	41 (6.39%)	254 (39.56%)	29 (4.52%)
Federal poverty level								
Unknown/Missing	2,848 (19.56%)	310 (2.13%)	2,963 (20.35%)	195 (1.34%)	2,504 (32.38%)	423 (5.47%)	2,669 (34.51%)	258 (3.34%)
<250% FPL	1,476 (20.37%)	181 (2.50%)	1,540 (21.25%)	117 (1.61%)	4,877 (40.30%)	1,238 (10.23%)	5,328 (44.03%)	787 (6.50%)
250–400% FPL	2,007 (20.45%)	204 (2.08%)	2,092 (21.32%)	118 (1.20%)	5,213 (39.44%)	856 (6.48%)	5,479 (41.45%)	590 (4.46%)
Above 400% FPL	6,193 (19.30%)	510 (1.59%)	6,412 (19.98%)	291 (0.91%)	7,285 (40.10%)	770 (4.24%)	7,509 (41.33%)	546 (3.01%)
Delivery mode								
Vaginal	7,494 (18.61%)	684 (1.70%)	7,753 (19.25%)	425 (1.06%)	12,800 (37.43%)	2,001 (5.85%)	13,499 (39.48%)	1,302 (3.81%)
C-section	5,030 (21.47%)	521 (2.22%)	5,254 (22.42%)	296 (1.26%)	7,079 (41.58%)	1,286 (7.55%)	7,486 (43.97%)	879 (5.16%)
Bateman score								
Bateman (0,1)	11,401 (19.12%)	1,014 (1.70%)	11,818 (19.82%)	596 (1.00%)	15,132 (37.12%)	1,992 (4.89%)	15,859 (38.91%)	1,265 (3.10%)
Bateman 2+	1,123 (27.43%)	191 (4.67%)	1,189 (29.04%)	125 (3.05%)	4,747 (45.40%)	1,295 (12.38%)	5,126 (49.02%)	916 (8.76%)

*Cells of $N < 11$ redacted to preserve confidentiality.

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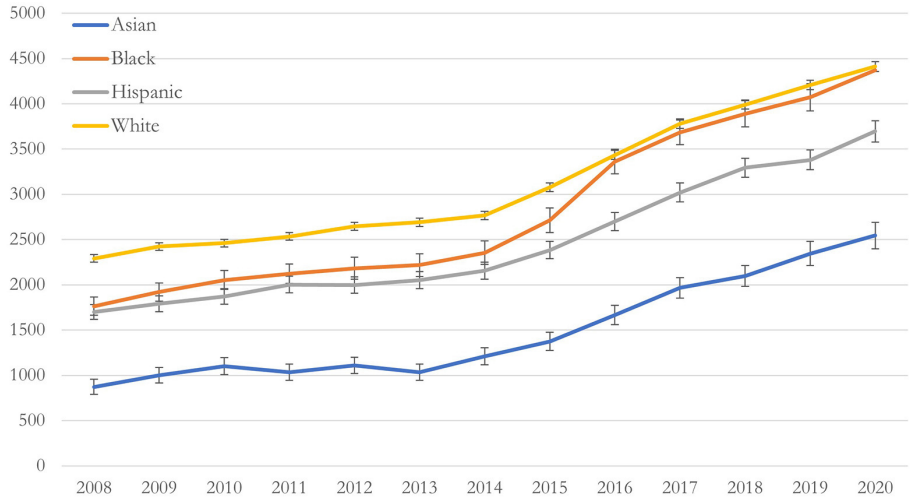

FIGURE 1
Unadjusted predicted rate of behavioral health conditions per 10,000 deliveries, by race/ethnicity, between 2008–2020 in a national commercially insured sample of perinatal individuals. Unadjusted rate of behavioral health (BH) conditions by race/ethnicity.

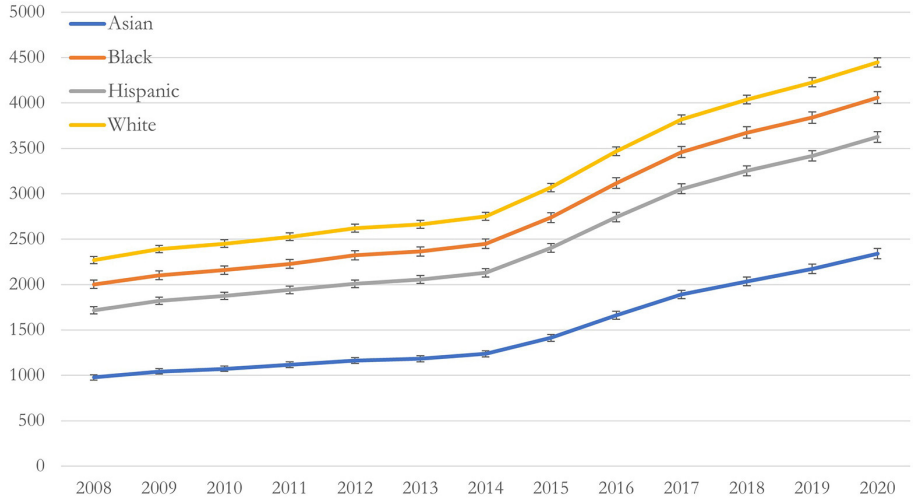

FIGURE 2
Adjusted predicted rate of behavioral health conditions per 10,000 deliveries, by race/ethnicity, between 2008–2020 in a national commercially insured sample of perinatal individuals. Adjusted rates of BH conditions by race/ethnicity adjusting for age, geographic region, insurance type, income, delivery mode, and Bateman index score.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: the data that support the findings of this study are available from Optum's de-identified Clinformatics® Data Mart Database (CDM). Restrictions apply to the availability of these data, which were used under license for this study, and thus are not publicly available. Requests to access these datasets should be directed to Optum Life Sciences, https://www.optum.com/business/life-sciences/real-world-data/claims-data.html.

Ethics statement

The studies involving humans were approved by University of Michigan Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

DB: Writing – original draft. KT: Writing – original draft, Writing – review & editing. AT: Writing – original draft, Writing – review & editing. AV: Writing – review & editing. SH: Writing – review & editing. AS: Writing – review & editing. KZ: Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. Research reported in this publication was supported by the National Institute of Mental Health (R01 MH120124) and the National Institute on Minority Health and Health Disparities (R01MD014958) of the National Institutes of Health.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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frontiers | Frontiers in Psychiatry

TYPE Original Research
PUBLISHED 08 March 2024
DOI 10.3389/fpsyt.2024.1277415

OPEN ACCESS

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RECEIVED 14 August 2023
ACCEPTED 12 February 2024
PUBLISHED 08 March 2024

CITATION
Liu Y, Wang Z, Li D and Lv B (2024) Bilirubin and postpartum depression: an observational and Mendelian randomization study.
Front. Psychiatry 15:1277415.
doi: 10.3389/fpsyt.2024.1277415

Bilirubin and postpartum depression: an observational and Mendelian randomization study

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Background: Postpartum depression (PPD) is one of the most common complications of delivery and is usually disregarded. Several risk factors of PPD have been identified, but its pathogenesis has not been completely understood. Serum bilirubin has been found to be a predictor of depression, whose relationship with PPD has not been investigated.

Methods: Observational research was performed followed by a two-sample Mendelian randomization (MR) analysis. From 2017 to 2020, the clinical data of pregnant women were retrospectively extracted. Logistic regression and random forest algorithm were employed to assess the risk factors of PPD, including the serum levels of total bilirubin and direct bilirubin. To further explore their potential causality, univariable and multivariable Mendelian randomization (MVMR) were conducted. Sensitivity analyses for MR were performed to test the robustness of causal inference.

Results: A total of 1,810 patients were included in the PPD cohort, of which 631 (34.87%) were diagnosed with PPD. Compared with the control group, PPD patients had a significantly lower level of total bilirubin (9.2 μmol/L, IQR 7.7, 11.0 in PPD; 9.7 μmol/L, IQR 8.0, 12.0 in control, $P < 0.001$) and direct bilirubin (2.0 μmol/L, IQR 1.6, 2.6 in PPD; 2.2 μmol/L, IQR 1.7, 2.9 in control, $P < 0.003$). The prediction model identified eight independent predictive factors of PPD, in which elevated total bilirubin served as a protective factor (OR = 0.94, 95% CI 0.90–0.99, $P = 0.024$). In the MR analyses, genetically predicted total bilirubin was associated with decreased risk of PPD (IVW: OR = 0.86, 95% CI 0.76–0.97, $P = 0.006$), which remained consistent after adjusting educational attainment, income, and gestational diabetes mellitus. Conversely, there is a lack of solid evidence to support the causal relationship between PPD and bilirubin.

Conclusion: Our results suggested that decreased total bilirubin was associated with the incidence of PPD. Future studies are warranted to investigate its potential mechanisms and illuminate the pathogenesis of PPD.

KEYWORDS

postpartum depression, serum bilirubin, risk factors, Mendelian randomization, oxidative stress

1 Introduction

Postpartum depression (PPD) mainly manifests as a major depressive episode combined with multiple mental and physical symptoms during the postpartum period (1). The prevalence of PPD, which has been underestimated previously, varies from 3% to 38% in different nations and is usually higher in developing countries (2, 3). Apart from the mothers, their partners and offspring may also suffer from PPD. It was estimated that the incidence of paternal depression was approximately 8% (4). For infants, retardation of weight and height was observed, as well as a decrease in cognitive and emotional development (5). The recommended multidisciplinary management of PPD includes psychosocial, psychological, pharmacological, and somatic interventions, whose effectiveness needs to be improved (6, 7). The pathogenesis of PPD has not been fully understood, and the known risk factors could be summarized into several aspects: medical history of primary mood disorders such as anxiety (8); sociodemographic characteristics such as education, age, and income (3, 9, 10); biological status during the perinatal period such as thyroid function (11); and obstetrics-related factors such as mode of delivery and preterm birth (12, 13). Given the heavy burden of the disease and the huge barrier to treatment, further studies are desperately warranted.

Bilirubin, which is the end product of heme catabolism, is cytotoxic to the central nervous system at high concentrations, while it also serves as an antioxidant at low concentrations in the serum (14). Bilirubin was found to be involved in many chronic diseases, including cardiovascular diseases, diabetes, neuropsychiatric diseases, and certain cancers (15). However, the relationship between bilirubin and depression is still controversial. It has been reported that the high level of serum total bilirubin is related to an increased risk of poststroke depression in observational studies (16, 17). In patients with diabetes, a higher level of indirect bilirubin was found in those with depression (18). On the other hand, a small-sample study confirmed a lower nocturnal bilirubin level in winter seasonal patients (19). Total bilirubin was a protective biomarker of depression in data mining from the National Health and Nutrition Examination Survey (NHANES) (20). Currently, no study has focused on the relationship between the serum bilirubin level and PPD.

The two-sample Mendelian randomization (MR) is an excellent tool for clinicians to investigate causality between exposure factors and outcomes. During the process, single nucleotide polymorphisms (SNPs) from genome-wide association studies (GWASs) are identified as instrumental variables (IVs) (21). To achieve accurate causal inference, MR analysis must satisfy the following three assumptions: 1) in univariable MR, the IVs are associated with exposure. In multivariable MR (MVMR), they are associated with at least one of the exposures; 2) IVs are independent of all potential confounders; and 3) IVs are assumed to be independent of the outcome (22). Compared with observational studies, an MR study has a better performance in controlling confounding and reverse causation (23). By applying MR analysis, researchers have tried to investigate the relationship between omega-3 fatty acids and perinatal depression (24). In another MR study, major depressive disorder was reported to be significantly associated with decreased bilirubin (25). With the continuous construction of GWAS, it is now possible to investigate PPD using the MR approach.

In the present study, we combined independent clinical analysis and two-sample MR analysis, intended to shed light on the association and causality between bilirubin and PPD for the first time and provide solid evidence of early monitoring and intervention of PPD.

2 Materials and methods

2.1 Study design and data sources

This study is composed of two major sections which are summarized in Figure 1. First, a cohort of PPD was built and important variables including total bilirubin and direct bilirubin were screened and validated to determine whether serum bilirubin level is associated with the incidence of PPD. Second, a two-sample MR analysis was performed to further investigate the causality between bilirubin and PPD with GWAS summary statistics.

For the observational study, pregnant women whose perinatal examinations and delivery were conducted at West China Second University Hospital, Sichuan University from 2017 to 2020 were selected for the present study. Participants were screened for eligibility. The inclusion criteria were as follows: a) participants who underwent regular examinations and delivered at West China Second University Hospital, Sichuan University; b) participants with a gestational age of ≥28 weeks; and c) participants who gave consent to participate and be followed up. The exclusion criteria were a) pre-existing mental illness, b) intellectual disability, and c) communication disorders.

All participants were followed up until 1 year after delivery.

2.2 Data process of the observational studies

The data of 62 variables were collected. Demographic information was collected by the electronic medical record system of West China Second University Hospital, Sichuan University. Social information was collected through questionnaires during the late stages of pregnancy (after 28 weeks until before delivery). The assessment of social support was carried out using the Social Support Rating Scale (SSRS), a well-established tool that has demonstrated high reliability and validity within the Chinese population (26). The SSRS consists of 10 items across three domains: objective support, subjective support, and utilization of social support. A score of 35 or less indicated low social support (27). Clinical characteristics were assessed and documented by eligible clinicians. Relevant laboratory indicators were extracted from the laboratory information system of West China Second University Hospital, Sichuan University during the late stages of pregnancy. Specifically, total bilirubin was measured via the vanadate oxidation method by Total Bilirubin_2 Reagents (Siemens Healthcare Diagnostics Inc., USA), with a reference

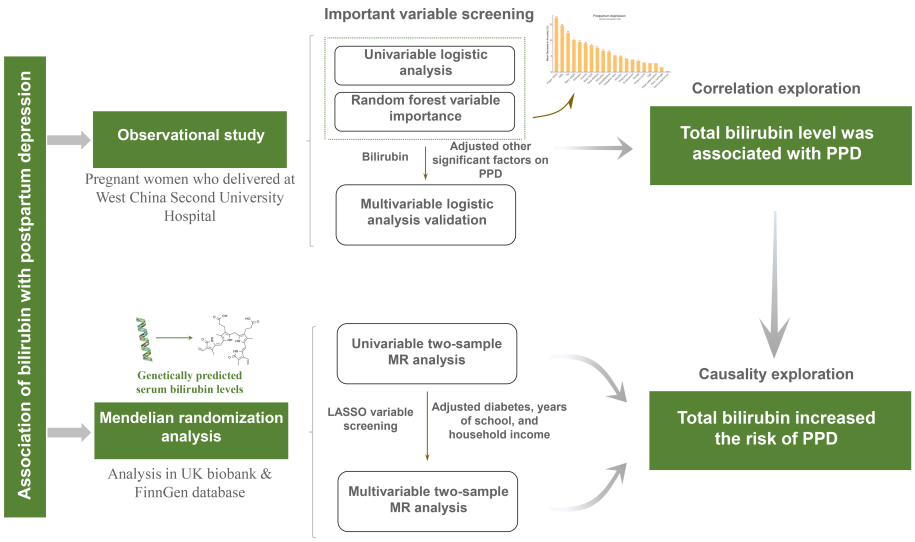

FIGURE 1
Flowchart of the study design. PPD, postpartum depression; MR, Mendelian randomization; UK, United Kingdom; LASSO, least absolute shrinkage and selection operator.

value of 5–23 μmol/L for adolescents and adults. To evaluate the depression state of each participant, the Edinburgh Postnatal Depression Scale (EPDS) was used at 3 months postpartum (28). Participants who scored 13 or more were regarded as PPD (29).

To control the quality of the questionnaires, an interview for every participant was conducted by trained investigators in separate rooms. During the interviews, the confidentiality of this investigation was declared and the authenticity of the questionnaire was emphasized. Once the questionnaires were completed, all the items were checked by the investigators.

2.3 Two-sample MR analysis

2.3.1 GWAS for bilirubin

GWASs for total circulating bilirubin (357,198 individuals) and direct bilirubin (418,830 individuals) were extracted from the UK Biobank database, with the raw data adjusted for covariates such as age, sex, sociodemographic features, and recruitment center of the participants as well as potential technical confounders including sampling time, fasting time, and sample dilution factor (30). The UK Biobank is a large-scale, long-term prospective cohort study that recruited approximately 500,000 individuals aged between 40 and 69 years from across Great Britain between 2006 and 2010 (31). Both total bilirubin and direct bilirubin were measured by a colorimetric assay (Beckman Coulter United Kingdom Ltd., Beckman Coulter AU5800 analyzer) (32).

2.3.2 GWAS for potential confounders

To avoid the interference of potential confounders, genetic instruments of education, income, and gestational diabetes mellitus were obtained from the largest available studies. SNPs for educational attainment were collected from the GWAS dataset from the Social Science Genetic Association Consortium (SSGAC) with 766,345 individuals (33). As a result of the heterogeneity of educational systems in different regions and cultures, the completed number of schooling years was used to represent educational attainment based on the 1997 International Standard Classification of Education (ISCED) of the United Nations Educational, Scientific and Cultural Organization (34).

GWAS for the average total household income before tax (397,751 individuals) from the Medical Research Council Integrative Epidemiology Unit (MRC-IEU) consortium was applied, which was derived from the UK Biobank database by PHESANT (35). The average total household income before tax measured as a grade variable was self-reported by the UK Biobank participants voluntarily.

GWAS for gestational diabetes mellitus (9,837 cases, 162,622 individuals) was obtained from the FinnGen consortium (R7 data release) (https://www.finngen.fi/en). The FinnGen study is a nationwide cohort that combined genome information with digital medical data of participants who were over 18 years of age and lived in Finland (36). Gestational diabetes mellitus was defined as O244 in the 10th edition of the International Classification of Diseases criteria. In practice, the oral glucose tolerance test was recommended during 24–28 weeks of gestation. An additional test was recommended for high-risk women between 12 and 16 weeks of pregnancy. Participants with any abnormal venous plasma glucose result (fasting plasma glucose ≥5.3 mmol/L, 1-h glucose ≥10.0 mmol/L or 2-h glucose ≥8.6 mmol/L) in a single glucose tolerance test were diagnosed as having gestational diabetes (37).

2.3.3 GWAS for postpartum depression

GWAS for PPD (13,657 cases, 236,178 individuals) was downloaded from the FinnGen consortium (R8 data release) (https://www.finngen.fi/en). The definition of PPD in FinnGen was participants with delivery history diagnosed with F32, F33, or F530 in the 10th edition of the International Classification of Diseases criteria.

2.3.4 Selection criteria of genetic instruments

All summary statistics were filtered at the minimum variant allele (MAF) frequency >0.01. SNPs were all selected at the genome-wide significance level ($P < 5E{-}8$). If there were no or less than four SNPs that met the criteria, a more lenient threshold ($P < 5E{-}6$) would be applied. Linkage disequilibrium (LD) for each trait was estimated based on the 1000 Genomes LD reference panel in European ancestry with the threshold set to r^2 >0.01 and clump window of 5,000 kb. SNPs identified as linkage disequilibrium, palindromic, or incompatible were excluded. To verify the third hypothesis of MR, SNPs significantly associated with PPD ($P < 5E{-}8$) were excluded.

2.4 Statistical analysis

2.4.1 Statistical procedure of the observational study

To assess the unadjusted association between PPD and all the other variables, categorical variables were subjected to the chi-square test, and Fisher's exact test was utilized for variables with small-sample sizes. Continuous variables were analyzed using Student's *t*-test, while the Wilcoxon–Mann–Whitney test was employed for non-normally distributed variables. To remove variables not associated with PPD, univariate logistic regression analysis was performed on all variables. The odds ratio (OR) and the corresponding 95% confidential interval (CI) were applied to determine the significance. The cutoff *P*-value for univariate logistic regression was 0.1. To further select candidate risk factors connected to PPD, the random forest algorithm on the significant variables selected by the univariate logistic regression was performed with 1,000 random permutations. After the screening process, a multivariate logistic regression analysis was performed to illustrate the independent risk factors.

2.4.2 Bidirectional Mendelian randomization analyses

We designed a bidirectional Mendelian randomization study to determine the causal relationship between bilirubin and PPD. We utilized the inverse variance-weighted (IVW) method as the primary approach for causal inference, which provides a weighted regression of IV-specific causal estimates and a stable causal inference even in the presence of heterogeneity (38). Multivariate Mendelian randomization (MVMR) analyses were performed to adjust potential confounders and explore the direct effect of each variable on the outcome (39). Least absolute shrinkage and selection operator (LASSO) regression was utilized to avoid potential bias caused by multicollinearity.

2.4.3 Sensitivity analyses for Mendelian randomization

To evaluate the reliability of the causal inference between bilirubin and PPD, sensitivity analyses were conducted, comprising weighted median, MR-Egger regression, Cochran's *Q* test, and MR-PRESSO (pleiotropy residual sum and outlier). The weighted median model can generate consistent estimates, when more than half of the analytical weights are derived from valid IVs (38). MR-Egger regression allows pleiotropy present in more than half of IVs, whereas it compromises statistical power (40). MR-PRESSO is able to detect and correct the bias caused by horizontal pleiotropic outliers (41). Causal inference can only be made when the same direction was reported in IVW estimation, weighted median method, and MR-Egger regression, and the MR-Egger regression intercept test does not detect horizontal pleiotropy. To estimate heterogeneity among SNPs for exposure and assess the consistency between assumption and MR analyses, Cochran's *Q* test was performed. To evaluate the strength of IVs for exposures in the MR analyses, *F*-statistics were calculated (42, 43). *F*-statistic >10 suggested a strong instrumental variable. All statistical analyses in the present study were performed in R 4.1.0 (https://www.R-project.org/). Logistics regressions were implemented with the R package "rms." The random forest algorithm was performed by Python 3.10, and all algorithms are available in the python library sklearn (44). The R packages "TwoSampleMR" (45) and "MRPRESSO" (41) were used to perform MR and sensitivity analyses. A two-sided significance level was set as *P*-value <0.05 for all statistical testing. In the figures, the asterisk(s) indicated the following: *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; and ****, $P < 0.0001$.

2.5 Ethics approval

This study was reviewed by the Ethics Committee of West China Second University Hospital, Sichuan University (No. 2021-186) and conducted following the principles of the Declaration of Helsinki. Informed consent was obtained from each participant. All studies included in the GWAS cited in this study were approved by a relevant review board.

3 Results

3.1 Baseline characteristics of observational studies

A total of 1,810 patients were finally enrolled in this study. As shown in Table 1, approximately one-third of the patients suffered from PPD. As for the distribution of total bilirubin level, only 22 individuals reached the high–normal total bilirubin of 23 μmol/L. Uncorrected test results indicated that there were significant differences in the levels of total bilirubin (9.2 μmol/L, IQR 7.7, 11.0 in PPD; 9.7 μmol/L, IQR 8.0, 12.0 in control, $P < 0.001$) and direct bilirubin (2.0 μmol/L, IQR 1.6, 2.6 in PPD; 2.2 μmol/L, IQR 1.7, 2.9 in control, $P < 0.003$) in the serum between PPD patients and the control group. Gestational diabetes was also found significantly different between PPD patients and the control group [155 (24.6%) in PPD; 211 (17.9%) in control, $P < 0.001$]. As for sociodemographic traits, median age (32, IQR 29, 35 in PPD; 31, IQR 29, 34 in control, $P = 0.003$), education [225 (35.7%) below bachelor's degree in PPD; 331 (28.1%) below bachelor's degree in control, $P = 0.001$], income [62 (9.8%) low income in PPD; 68 (5.8%) low income in control, $P = 0.002$], work status [615 (97.5%) employed in PPD; 1,119 (94.9%) employed in control, $P = 0.014$], and poor marriage [617 (97.8%) in PPD; 1,170 (99.2%) in control, $P = 0.016$] were statistically different.

TABLE 1 Characteristics of PPD cohort.

Characteristic	Level	Overall	Postpartum depression		P value
			Yes	No	
N (%)		1,810 (100%)	631 (34.9%)	1,179 (65.1%)	
Demographic information					
Age, median (IQR)		31 (29, 35)	32 (29, 35)	31 (29, 34)	0.003
Gain weight (kg), median (IQR)		12.5 (9.5, 15.0)	12.5 (9.5, 16.0)	12.5 (9.5, 15.0)	0.605
BMI (kg/m^2), median (IQR)		20.8 (19.34, 22.86)	20.83 (19.34, 23.05)	20.83 (19.34, 22.77)	0.482
Gestation days, median (IQR)		274 (269, 279)	274 (268, 278)	274 (269, 280)	0.022
Nationality, n (%)	Han	1,757 (97.1%)	608 (96.4%)	1,149 (97.5%)	0.239
	Others	53 (2.9%)	23 (3.6%)	30 (2.5%)	
Season, n (%)	Autumn	560 (30.9%)	197 (31.2%)	363 (30.8%)	0.953
	Spring	335 (18.5%)	118 (18.7%)	217 (18.4%)	
	Summer	465 (25.7%)	157 (24.9%)	308 (26.1%)	
	Winter	450 (24.9%)	159 (25.2%)	291 (24.7%)	
Sociological information					
Work status, n (%)	Employed	1,734 (95.8%)	615 (97.5%)	1,119 (94.9%)	0.014
	Unemployed or retired	76 (4.2%)	16 (2.5%)	60 (5.1%)	
Education, n (%)	Bachelor's degree or above	1,254 (69.3%)	406 (64.3%)	848 (71.9%)	0.001
	Below bachelor's degree	556 (30.7%)	225 (35.7%)	331 (28.1%)	
Income, n (%)	Normal level	1,680 (92.8%)	569 (90.2%)	1,111 (94.2%)	0.002
	Low income	130 (7.2%)	62 (9.8%)	68 (5.8%)	
Planning pregnancy, n (%)	No	72 (4.0%)	30 (4.8%)	42 (3.6%)	0.267
	Yes	1,738 (96.0%)	601 (95.2%)	1,137 (96.4%)	
Social support, n (%)	No	42 (2.3%)	18 (2.9%)	24 (2.0%)	0.349
	Yes	1,768 (97.7%)	613 (97.1%)	1,155 (98.0%)	
Poor marriage, n (%)	No	1,787 (98.7%)	617 (97.8%)	1,170 (99.2%)	0.016
	Yes	23 (1.3%)	14 (2.2%)	9 (0.8%)	
Clinical characteristics					
Baby weight (kg), median (IQR)		3.26 (2.92, 3.56)	3.23 (2.80, 3.54)	3.28 (2.96, 3.58)	0.004
Baby height (cm), median (IQR)		50 (48, 51)	49 (48, 51)	50 (48, 51)	0.042
Length of stay (day), median (IQR)		4 (4, 6)	4 (4, 6)	4 (4, 6)	0.654
Postpartum hemorrhage (mL), median (IQR)		400 (300, 400)	400 (300, 400)	400 (300, 400)	0.382
Fetal malformation, n (%)	No	1,724 (95.2%)	592 (93.8%)	1,132 (96.0%)	0.048
	Yes	86 (4.8%)	39 (6.2%)	47 (4.0%)	
Gestational diabetes mellitus, n (%)	No	1,444 (79.8%)	476 (75.4%)	968 (82.1%)	< 0.001
	Yes	366 (20.2%)	155 (24.6%)	211 (17.9%)	
Hypertension, n (%)	No	1,725 (95.3%)	604 (95.7%)	1,121 (95.1%)	0.619
	Yes	85 (4.7%)	27 (4.3%)	58 (4.9%)	
Hepatitis B, n (%)	No	1,708 (94.4%)	593 (94.0%)	1,115 (94.6%)	0.678
	Yes	102 (5.6%)	38 (6.0%)	64 (5.4%)	

(Continued)

TABLE 1 Continued

Characteristic	Level	Overall	Postpartum depression		P value
			Yes	No	
Clinical characteristics					
Twin pregnancies, n (%)	No	1,642 (90.7%)	561 (88.9%)	1081 (91.7%)	0.063
	Yes	168 (9.3%)	70 (11.1%)	98 (8.3%)	
Placenta previ, n (%)	No	1,715 (94.8%)	598 (94.8%)	1117 (94.7%)	1
	Yes	95 (5.2%)	33 (5.2%)	62 (5.3%)	
Uterine myoma, n (%)	No	1,635 (90.3%)	569 (90.2%)	1,066 (90.4%)	0.935
	Yes	175 (9.7%)	62 (9.8%)	113 (9.6%)	
Ovarian cyst, n (%)	No	1,800 (99.4%)	627 (99.4%)	1,173 (99.5%)	0.746
	Yes	10 (0.6%)	4 (0.6%)	6 (0.5%)	
Fetal growth restriction, n (%)	No	1,777 (98.2%)	617 (97.8%)	1,160 (98.4%)	0.462
	Yes	33 (1.8%)	14 (2.2%)	19 (1.6%)	
Preterm birth, n (%)	No	1,575 (87.0%)	522 (82.7%)	1,053 (89.3%)	< 0.001
	Yes	235 (13.0%)	109 (17.3%)	126 (10.7%)	
Delivery mode, n (%)	Cesarean section	679 (37.5%)	249 (39.5%)	430 (36.5%)	0.337
	midwifery	10 (0.6%)	2 (0.3%)	8 (0.7%)	
	Natural birth	1,121 (61.9%)	380 (60.2%)	741 (62.8%)	
Fetal gender, n (%)	Female	925 (51.1%)	321 (50.9%)	604 (51.2%)	0.924
	Male	885 (48.9%)	310 (49.1%)	575 (48.8%)	
Fetal distress, n (%)	No	1,759 (97.2%)	601 (95.2%)	1,158 (98.2%)	< 0.001
	Yes	51 (2.8%)	30 (4.8%)	21 (1.8%)	
Breastfeeding, n (%)	No	28 (1.5%)	17 (2.7%)	11 (0.9%)	0.007
	Yes	1,782 (98.5%)	614 (97.3%)	1,168 (99.1%)	
Pregnancy, n (%)	1	621 (34.3%)	186 (29.5%)	435 (36.9%)	0.014
	2	517 (28.6%)	186 (29.5%)	331 (28.1%)	
	3	358 (19.8%)	132 (20.9%)	226 (19.2%)	
	4	189 (10.4%)	73 (11.6%)	116 (9.8%)	
	>=5	125 (6.9%)	54 (8.6%)	71 (6.0%)	
Abortion, n (%)	0	834 (46.1%)	260 (41.2%)	574 (48.7%)	0.004
	1	545 (30.1%)	194 (30.7%)	351 (29.8%)	
	2	271 (15.0%)	107 (17.0%)	164 (13.9%)	
	>=3	160 (8.8%)	70 (11.1%)	90 (7.6%)	
Parity, n (%)	0	1,130 (62.4%)	388 (61.5%)	742 (62.9%)	0.484
	1	645 (35.6%)	227 (36%)	418 (35.5%)	
	2	33 (1.8%)	15 (2.4%)	18 (1.5%)	
	>=3	2 (0.1%)	1 (0.2%)	1 (0.1%)	
Apgar 10 min, n (%)	0~3	36 (2.0%)	30 (4.8%)	6 (0.5%)	< 0.001
	4~7	5 (0.3%)	3 (0.5%)	2 (0.2%)	
	8~10	1,769 (97.7%)	598 (94.8%)	1,171 (99.3%)	

(Continued)

TABLE 1 Continued

Characteristic	Level	Overall	Postpartum depression		P value
			Yes	No	
Laboratory indicators					
White blood cell (10^9/L), median (IQR)		9.2 (7.8, 11.1)	9.2 (7.9, 11.0)	9.2 (7.8, 11.1)	0.584
Platelet (10^9/L), median (IQR)		179 (145, 213)	182 (146, 218)	177 (144, 211)	0.125
Hemoglobin (g/L), median (IQR)		112 (104, 118)	111 (104, 118)	112 (104, 117)	0.885
Ferroprotein (ng/nl), median (IQR)		18.4 (12.2, 26.0)	19.0 (11.9, 26.8)	18.1 (12.4, 25.9)	0.518
Prothrombin time (s), median (IQR)		10.8 (10.3, 11.4)	10.8 (10.4, 11.4)	10.8 (10.3, 11.4)	0.817
International normalized ratio, median (IQR)		0.96 (0.92, 1.01)	0.96 (0.91, 1.01)	0.97 (0.92, 1.01)	0.233
Activated partial thromboplastin time, median (IQR)		26.1 (24.8, 27.6)	25.9 (24.8, 27.4)	26.2 (24.8, 27.7)	0.23
Fibrinogen (mg/dL), median (IQR)		416 (356, 470)	416 (355, 470)	414 (358, 470)	0.871
Thrombin time (s), median (IQR)		16.3 (15.8, 16.9)	16.3 (15.8, 16.9)	16.3 (15.8, 16.9)	0.741
Alanine aminotransferase (U/L), median (IQR)		17 (12, 28)	18 (12, 28)	17 (13, 28)	0.927
Aspartate aminotransferase (U/L), median (IQR)		21 (18, 27)	21 (17, 27)	21 (18, 27)	0.627
Total bilirubin (umol/L), median (IQR)		9.5 (7.8, 11.8)	9.2 (7.7, 11.0)	9.7 (8.0, 12.0)	< 0.001
Direct Bilirubin (umol/L), median (IQR)		2.1 (1.7, 2.8)	2.0 (1.6, 2.6)	2.2 (1.7, 2.9)	0.003
Total protein (g/L), median (IQR)		66.0 (62.8, 69.7)	65.7 (62.8, 69.5)	66.2 (62.8, 69.8)	0.244
Albumin (g/L), median (IQR)		38.7 (36.3, 41.3)	38.6 (36.3, 41.4)	38.8 (36.3, 41.2)	0.91
Globulin (g/L), median (IQR)		27.4 (25.2, 30.1)	27.2 (25.2, 29.9)	27.5 (25.4, 30.2)	0.165
Albumin/Globulin, median (IQR)		1.4 (1.3, 1.6)	1.4 (1.3, 1.6)	1.4 (1.3, 1.6)	0.234
R-glutamyltransferase (U/L), median (IQR)		15 (10, 23)	14 (10, 23)	15 (10, 23)	0.816
Lactate dehydrogenase (U/L), median (IQR)		180 (163, 202)	180 (164, 202)	179 (163, 202)	0.894
Alkaline phosphatase (U/L), median (IQR)		85 (55, 122)	87 (55, 124)	84 (55, 121)	0.624
Total bile acid (umol/L), median (IQR)		2.3 (1.6, 3.6)	2.4 (1.6, 3.6)	2.3 (1.6, 3.5)	0.521
Urea nitrogen (umol/L), median (IQR)		3.5 (3.08, 4.35)	3.48 (3.08, 4.35)	3.5 (3.08, 4.35)	0.638
Creatinine (umol/L), median (IQR)		44 (40, 48)	44 (40, 48)	44 (40, 48)	0.732
Cystatin C (mg/L), median (IQR)		0.77 (0.64, 0.98)	0.77 (0.64, 0.99)	0.77 (0.64, 0.97)	0.751
Uric acid (umol/L), median (IQR)		257 (217, 307)	254 (218, 304)	259 (217, 309)	0.265
Thyroid stimulating hormone (mIU/L), median (IQR)		1.95 (1.25, 2.86)	1.86 (1.17, 2.79)	1.97 (1.30, 2.89)	0.166
FT4 (pmol/L), median (IQR)		14.54 (13.22, 16.08)	14.53 (13.21, 15.88)	14.55 (13.27, 16.18)	0.397
Thyroid peroxidase antibody (U/ml), median (IQR)		41.2 (30.4, 56.1)	41.1 (30.7, 55.6)	41.2 (30.4, 56.2)	0.541

PPD postpartum depression, IQR interquartile range, BMI body mass index.

In contrast to prior studies, it appears that the mode of delivery was not significantly associated with PPD ($P = 0.337$), and neither was thyroid function (TSH, $P = 0.166$; FT4, $P = 0.397$).

3.2 Identification of risk factors of postpartum depression

To rule out the irrelevant variables of PPD, univariate logistic regression analysis was conducted on all 62 variables. Of these, 20 were found to be statistically significant ($P < 0.1$, Table 2). The random forest algorithm was further performed and identified 12 important variables associated with PPD (Figure 2). Next, multivariate logistic regression analysis was conducted to adjust confounding factors of PPD. Finally, as presented in Table 2, Apgar score at 10 min (OR = 0.79, 95% CI 0.71–0.88, $P < 0.001$), the serum level of total bilirubin (OR = 0.94, 95% CI 0.90–0.99, $P = 0.024$), thyroid peroxidase antibodies (TPOAbs) (OR = 1.00, 95% CI 0.99–1.00, $P = 0.002$), bachelor's degree or above (OR = 0.73, 95% CI 0.59–0.92, $P = 0.006$), and breastfeeding (OR = 0.39, 95% CI 0.17–0.86, $P = 0.02$) were identified as independent protective factors against PPD. Conversely, low income (OR = 1.54, 95% CI 1.05–2.26, $P = 0.025$), gestational diabetes mellitus (OR = 1.69, 95% CI 1.32–

TABLE 2 Univariate and multivariate logistic regression of variables of PPD.

Characteristics	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.04 (1.01, 1.06)	0.002		
Gestation days	0.99 (0.98, 0.99)	<0.001		
Baby weight	0.70 (0.60, 0.82)	<0.001	0.72 (0.51 - 1.01)	0.058
Baby height	0.94 (0.91 0.97)	<0.001	1.06 (0.98 - 1.14)	0.136
Apgar 10min	0.80 (0.73, 0.87)	<0.001	0.79 (0.71 - 0.88)	<0.001
Total bilirubin	0.94 (0.91, 0.97)	<0.001	0.94 (0.90 - 0.99)	0.024
Direct bilirubin	0.85 (0.77, 0.92)	<0.001	0.95 (0.82 - 1.08)	0.447
TPOAB	1.00 (0.99, 1.00)	0.002	1.00 (0.99 – 1.00)	0.002
Work status				
Employed	Reference			
Unemployed	0.49 (0.27, 0.83)	0.011		
Education				
Below bachelor's degree	Reference		Reference	
Bachelor's degree or above	0.70 (0.57, 0.87)	0.001	0.73 (0.59 - 0.92)	0.006
Income				
Normal level	Reference		Reference	
Low income	1.78 (1.24, 2.55)	0.002	1.54 (1.05 - 2.26)	0.025
Poor marriage				
No	Reference			
Yes	2.95 (1.29, 7.12)	0.012		
Fetal malformation				
No	Reference			
Yes	1.59 (1.02, 2.45)	0.038		
Diabetes				
No	Reference		Reference	
Yes	1.49 (1.18, 1.89)	0.001	1.69 (1.32 - 2.16)	<0.001
Twin pregnancies				
No	Reference			
Yes	1.38 (0.99, 1.90)	0.053		
Preterm birth				
No	Reference			
Yes	1.75 (1.32, 2.30)	<0.001		
Fetal distress				
No	Reference			
Yes	2.75 (1.57, 4.91)	<0.001		
Breastfeeding				
No	Reference		Reference	
Yes	0.34 (0.15, 0.72)	0.006	0.39 (0.17 - 0.86)	0.02
Number of pregnancies				
1	Reference			
2	1.31 (1.03, 1.69)	0.031		
3	1.37 (1.04, 1.80)	0.026		
4	1.47 (1.05, 2.06)	0.026		
>=5	1.78 (1.20, 2.63)	0.004		
Number of abortions				
0	Reference		Reference	
1	1.22 (0.97, 1.53)	0.088	1.20 (0.95 - 1.52)	0.128
2	1.44 (1.08, 1.91)	0.012	1.38 (1.03 - 1.86)	0.032
>=3	1.72 (1.21, 2.42)	0.002	1.72 (1.20 - 2.47)	0.003

PPD postpartum depression, OR odds ratio, CI confidence interval, TPOAB thyroid peroxidase antibody.

2.16, $P < 0.001$), and the number of abortions were associated with an increased risk of PPD.

3.3 Selection and verification of instrumental variables

For serum bilirubin, 122 and 63 independent SNPs were selected as IVs for total and direct bilirubin (Supplementary Tables 1, 2) at the genome-wide significance level ($P < 5E{-}8$), respectively. Eight palindromic SNPs for total bilirubin and six palindromic SNPs for direct bilirubin were excluded to ensure the harmonization of the

effect of IVs on the outcome and exposure. For PPD, a less stringent significance threshold (P < 5E−6) was used in IV selection (Supplementary Tables 3, 4). One palindromic SNP was deleted. All F-statistics of IVs were above 10, suggesting strong IVs.

3.4 The causal effects of bilirubin on postpartum depression

To investigate the causality of bilirubin on PPD, univariate MR analysis was performed using total and direct bilirubin as exposure, respectively. The results showed that an increased level of serum total bilirubin was significantly associated with a decreased risk of PPD (IVW: OR = 0.86, 95% CI 0.76–0.97, P = 0.006), while the causal association for direct bilirubin was not statistically significant (IVW: OR = 0.90, 95% CI 0.78–1.03, P = 0.131) (Figure 3).

Table 3 illustrates the results of the sensitivity analyses. Consistent directions of the causal estimates were observed in the weighted median and MR-Egger methods. No significant outlier was detected by the MR-PRESSO outlier test. No significant evidence of horizontal pleiotropy was observed for total (P = 0.576) and direct (P = 0.195) bilirubin. However, Cochran's Q test reported mild heterogeneity in both the SNPs of total bilirubin (P = 0.010) and direct (P = 0.026) bilirubin. To validate the direct causal effects of bilirubin on PPD, MVMR was carried out. Total bilirubin, direct bilirubin, year of schooling, average total household income before tax, and gestational diabetes mellitus were admitted as exposures. Due to potential multicollinearity between exposures, direct bilirubin was excluded from the MVMR analysis via LASSO regression variable selection. As shown in Figure 4, the result for total bilirubin remained consistent after adjusting educational attainment (years of schooling), income (average total household income before tax), and gestational diabetes mellitus. Interestingly, higher educational attainment was demonstrated to be a protective factor of PPD (OR = 0.61, 95% CI 0.51–0.72, P < 0.001), while gestational diabetes mellitus was hazardous (OR = 1.11, 95% CI 1.07–1.15, P < 0.001), which were consistent with the cohort observation and prediction model. Taken together, these results suggested a genuine causality of total bilirubin on PPD after adjusting educational attainment, income, and gestational diabetes mellitus.

3.5 Reverse causal effects of postpartum depression on bilirubin

To investigate the directionality of the causal relationship between bilirubin and PPD, we further conducted reverse MR analyses. The results demonstrated that PPD showed statistically significant causal effects on both total and direct bilirubin (IVW: Beta = -0.03, 95% CI -0.04, -0.01, P = 0.014 and IVW: Beta = -0.02, 95% CI -0.04, -0.01, P = 0.022 respectively) as shown in Figure 5. However, MR-Egger regression described an opposite direction (total bilirubin Beta = 0.052, 95% CI -0.030, 0.131, P = 0.230, P = 0.23; direct bilirubin Beta = 0.024, 95% CI -0.062, 0.113, P = 0.593) (Figure 5). No evidence of horizontal pleiotropy or heterogeneity was detected. The MR-PRESSO outlier test did not identify any significant outliers (Table 3). Collectively, there is a lack of concrete results to support the causal inference from PPD on neither total bilirubin nor direct bilirubin.

4 Discussion

As a common psychological disease, PPD has a severe influence on the family and society and requires appropriate management (6). The pathology of PPD is not yet clear, although dozens of socioeconomic,

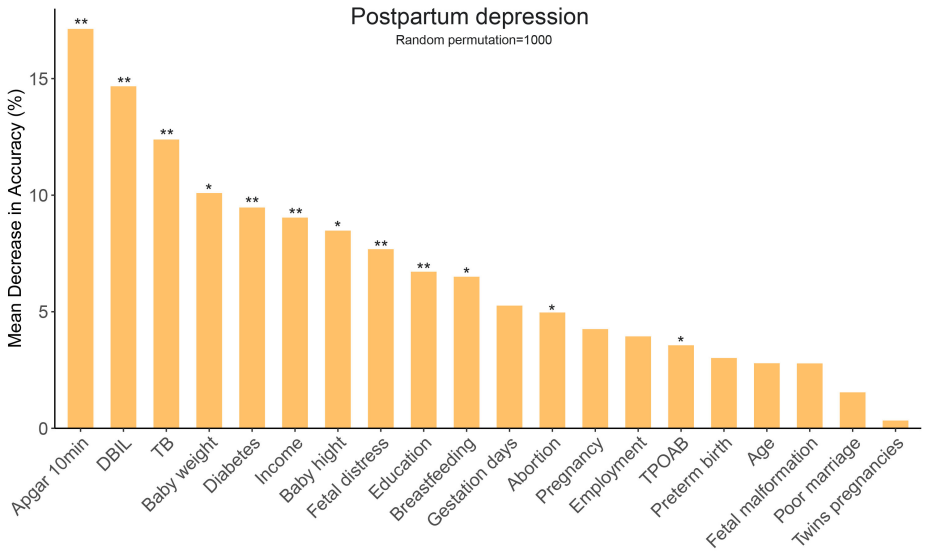

FIGURE 2
Random forest algorithm for selecting important variables related to PPD. PPD, postpartum depression; TB, total bilirubin; DBIL, direct bilirubin; TPOAB, thyroid peroxidase antibody. *, P < 0.05; **, P < 0.01.

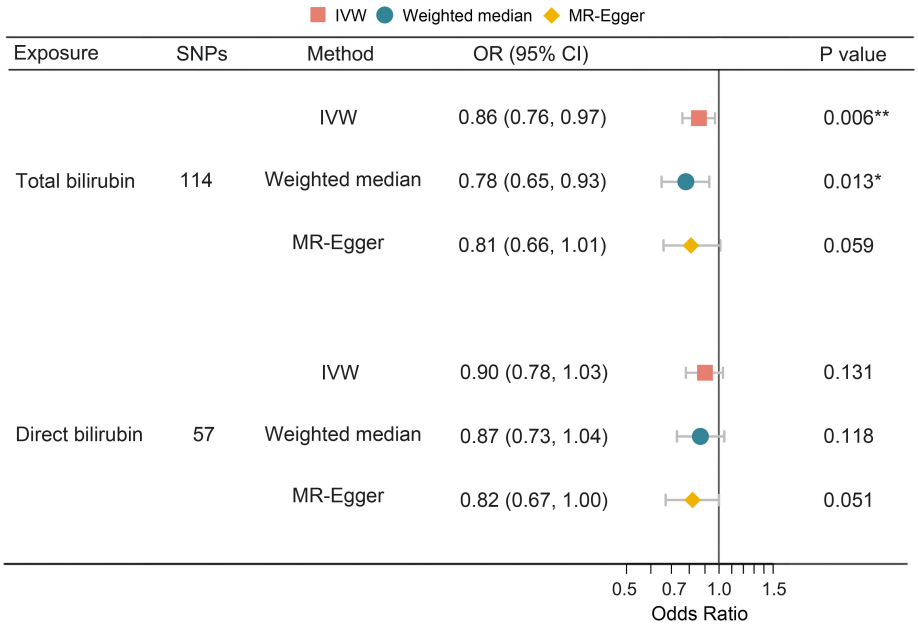

FIGURE 3
Univariate MR analysis of the causal effect of bilirubin on PPD. MR, Mendelian randomization; PPD, postpartum depression; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; IVW, inverse variance weighting. *, P < 0.05; **, P < 0.01.

TABLE 3 Sensitivity analysis of causality between bilirubin and postpartum depression.

Exposure	Outcome	Weighted median		MR-Egger regression		Heterogeneity[a]	MR-PRESSO outlier detect[b]		Pleiotropy[c]
		OR/Beta (95% CI)	P Value	OR/Beta (95% CI)	P Value		OR (95% CI)	P Value	
TB	PPD	0.779 (0.653, 0.930)	0.006	0.814 (0.659, 1.005)	0.059	I^2 = 25.2%; Cochrane's Q = 151; P_{het} =0.010	No significant outliers		Intercept = 0.002; P_{ple} = 0.576
DBIL	PPD	0.869 (0.728, 1.036)	0.118	0.815 (0.667, 0.996)	0.051	I^2 = 28.6%; Cochrane's Q = 77; P_{het} = 0.026	No significant outliers		Intercept = 0.005; P_{ple} = 0.195
PPD	TB	-0.020 (-0.041, -0.010)	0.083	0.052 (-0.030, 0.131)	0.230	I2 = 16.7%; Cochrane's Q = 12; het = 0.285	No significant outliers		Intercept = -0.008; Pple = 0.092
PPD	DBIL	-0.023 (-0.041, 0.020)	0.071	0.024 (-0.062, 0.113)	0.593	I2 = 0.1%; Cochrane's Q = 10; Phet = 0.470	No significant outliers		Intercept = -0.005; Pple = 0.320

a Heterogeneity in the random effect IVW methods was reported. Mild heterogeneity was observed in both the SNPs of total bilirubin and direct bilirubin.
b There is no outlier needed to be corrected.
c MR-Egger was used to detect Pleiotropy. No pleiotropy was observed (P>0.05).
PPD postpartum depression, TB total bilirubin, DBIL direct bilirubin, OR odds ratio, CI confidence interval, MR mendelian randomization.

psychological, and physiological predictors were proposed and verified by clinical studies (8). Combining observational and Mendelian randomization study, we described the association and causality between bilirubin and PPD for the first time.

In our observational cohort, a decreased serum level of total bilirubin was associated with an increased risk of PPD, while the serum level of direct bilirubin was not. Meanwhile, bidirectional two-sample MR and MVMR with published GWAS data confirmed the true causality of total bilirubin on PPD. On the other hand, the occurrence of PPD resulting in a decrease in serum bilirubin should be modestly interpreted considering the ambiguous outcomes of reverse MR. As secondary results, gestational diabetes mellitus and lower educational attainment were associated with an increased risk of PPD.

For a very long period of time, bilirubin has been considered a waste product of heme catabolism with neurotoxicity, and serum bilirubin level has been used as an ominous sign of liver disease, until Stocker et al. reported the antioxidant capacity of bilirubin in 1987 (14). Heme, one of the decomposed products of erythrocytes, was catabolized to produce biliverdin, which is reduced to indirect bilirubin, also known as unconjugated bilirubin. Then, unconjugated bilirubin is released into the circulation and is combined with albumin before entering the hepatocyte, where it is conjugated with glucuronic acid to form conjugated bilirubin or direct bilirubin. After that, direct

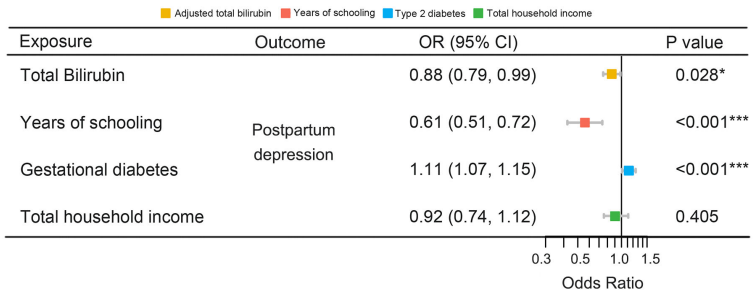

FIGURE 4
MVMR of the causal effect of bilirubin on PPD. MVMR, multivariable Mendelian randomization; PPD, postpartum depression; OR, odds ratio; CI, confidence interval. *, P < 0.05; ***, P < 0.001.

bilirubin is excreted by the hepatocyte into the biliary tract, and a disorder of bilirubin excretion would result in elevated direct bilirubin in the serum, which is called obstructive jaundice (46).

Oxidative stress (OS), defined as the imbalance between the production of reactive oxygen species (ROS) and endogenous antioxidants, was widely considered as one of the major hypotheses of the pathogenesis of depression (47). ROS overload could induce the expression of heme oxygenase (HO-1), which catalyzes the decomposition of heme. As a result, increased bilirubin is able to reduce ROS via redox (48). OS has been proposed to be one of the major causes of depressive disorder, and representative biomarkers of OS were increased in patients with depression (49). Similar results were reported in PPD in recent studies, indicating the elevated status of OS in PPD patients (50). Urinary biopyrrin, the production of the oxidation reaction of bilirubin with reactive oxygen, has been used as an oxidative stress marker (51). A higher level of urinary biopyrrin was found in patients with depression and schizophrenia, which suggested more consumption of bilirubin caused by OS in psychiatric disorders (52).

Based on the aforementioned studies and the results of the present research, decreased bilirubin might impair the antioxidant defense system, inducing oxidative damage in pregnant women, which could possibly lead to PPD. As ROS mainly causes damage inside the cells where direct bilirubin is difficult to reach, the true antioxidant is indirect bilirubin, which accounts for most of the total circulation bilirubin under physiological conditions (47). The level of bilirubin could increase due to liver dysfunction, which occurred in up to 3% of pregnant women (53). Decreased total and direct bilirubin levels were usually due to anemia. In Japanese participants with self-reported depression, a higher rate of self-reported history of iron deficiency anemia was observed, which was in accordance with our theory (54). The relationship between indirect bilirubin and PPD should be further investigated.

In the previous MR research, a significant causal effect of major depressive disorders on total bilirubin was reported, which implied a sophisticated relationship between depression and bilirubin (25). Given that most of the serum levels of bilirubin of participants in the observational study and MR analysis were within normal limits,

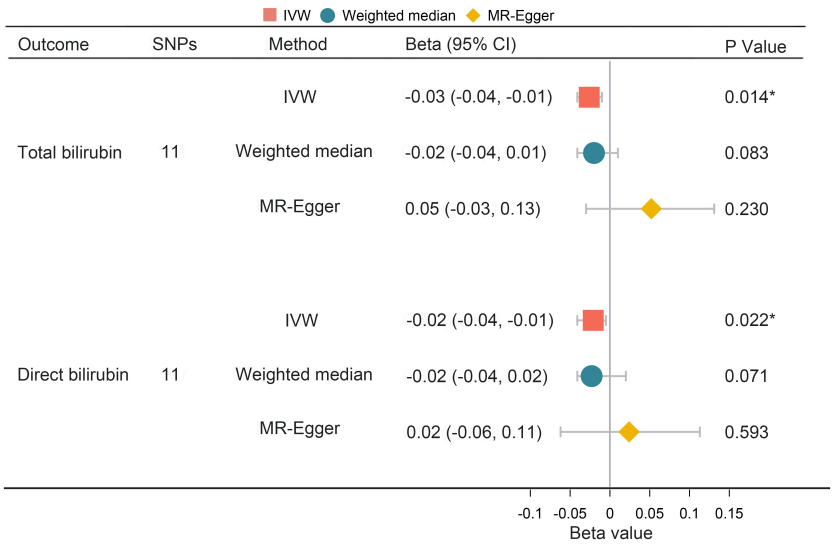

FIGURE 5
Univariate MR analysis of the causal effect of PPD on bilirubin. MR, Mendelian randomization; PPD, postpartum depression; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; IVW, inverse variance weighting. *, P < 0.05.

the acute neurotoxic effect of high-level bilirubin had little impact on our research. In poststroke and diabetes patients who also suffered from depression, elevated bilirubin was observed (16–18). This opposite association was not equal to true causality; instead, bilirubin might function as a protector against depression in the pathologic state. Further research might provide more clues on this matter. Recently, multidimensional evidence suggested that bilirubin was more than just an antioxidant; it also might serve as a messenger of cell signal transduction, metabolism modulation, and immune regulation (55). Mechanisms other than OS might be involved in the pathogenesis of PPD.

There were several highlights in our research. First, our PPD cohort was built with the standard protocol of medical care based on evidence-based clinical guidelines, and a quality control of follow-up was executed. Second, the major results of the observational study were confirmed by MR analysis, which minimized the confounding effect and reverse causality. Moreover, no pleiotropic effect was detected in the sensitivity analyses, which indicated that causal estimates were not induced by confounders. Finally, consistent positive results were observed in both the Asian cohort (observational study) and the European cohort (MR study), suggesting that the causal association of bilirubin with PPD is robust and generalizable.

On the other hand, limitations should be declared equally. First, two different diagnostic criteria of PPD were applied in our cohort and the FinnGen database, and the criteria in our cohort lacked the diagnosis of depression by a psychiatrist after childbirth. Second, participants with incomplete results of perinatal examinations were excluded from the observational study, which might be a source of selection bias. Third, there was a potential overlap in GWAS for PPD and gestational diabetes mellitus in MVMR, which might cause fake positive results. Furthermore, mild heterogeneity was observed in the SNPs of both total and direct bilirubin. However, the use of the random-effect IVW method and the absence of horizontal pleiotropy suggested that our results were unlikely to be disturbed by heterogeneity. Fourth, the observational cohort only included participants who were within the normal levels of bilirubin; thus, whether the abnormally increased bilirubin is protective for depression in postpartum women remained to be discovered. Lastly, while the causal relationship of bilirubin on PPD was hinted at by a clinical cohort and further validated by MR analysis, many potential unadjusted confounders in the MR study could be behind this association. A well-designed multicenter prospective PPD cohort was needed to generate credible data.

In a nutshell, our results suggested a clinical association between total bilirubin and PPD, and decreased total bilirubin was likely to be a cause of PPD. Further studies regarding the biological function of bilirubin and its association with PPD are warranted.

5 Conclusion

In conclusion, the present research demonstrated that the decreased serum level of total bilirubin was associated with an increased risk of PPD. The importance of serum bilirubin levels on PPD surveillance and prevention should be addressed and further studies are required.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation. All the cited GWAS data was downloaded from public database.

Ethics statement

The studies involving humans were approved by the Ethics Committee of West China Second University Hospital, Sichuan University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YL: Writing – original draft, Writing – review & editing. ZW: Writing – original draft, Writing – review & editing. DL: Writing – original draft, Writing – review & editing. BL: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

Our sincere thanks to the developers and maintainers of UK Biobank, FinnGen, MRC-IEU, and SSGAC; the R software and Python contributors; all the related algorithms and websites; and all the participants in this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2024.1277415/full#supplementary-material

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frontiers | Frontiers in Psychiatry

TYPE Perspective
PUBLISHED 10 June 2024
DOI 10.3389/fpsyt.2024.1364845

OPEN ACCESS

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RECEIVED 03 January 2024
ACCEPTED 06 May 2024
PUBLISHED 10 June 2024

CITATION
Athan AM (2024) A critical need for the concept of matrescence in perinatal psychiatry.
Front. Psychiatry 15:1364845.
doi: 10.3389/fpsyt.2024.1364845

A critical need for the concept of matrescence in perinatal psychiatry

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The concept of matrescence, akin to adolescence but for mothers, has gained increasing attention in perinatal psychiatry, marking a paradigm shift towards understanding the holistic development of mothers. Matrescence encompasses the myriad psychological, social, cultural, and existential changes which occur as women transition into motherhood. Despite advances in maternal mental health, a bias towards pathologizing maternal experiences persists in research and practice. This commentary advocates for the integration of matrescence into perinatal psychiatry, drawing from the work of Dana Raphael and contemporary scholarship. Matrescence offers a strengths-based framework that acknowledges both the challenges and opportunities of motherhood, emphasizing the normative aspects of a mother's self-development. By adopting matrescence terminology and nosology, clinicians and researchers can enhance traditional psychiatric classifications. Additionally, matrescence underscores the importance of considering ecological systems and historical factors in maternal well-being, highlighting the need for comprehensive and compassionate healthcare services. Embracing matrescence as a fundamental concept in perinatal psychiatry holds promise for improving maternal mental health outcomes and promoting the flourishing of mothers worldwide.

KEYWORDS

matrescence, transition to motherhood, maternal mental health, perinatal psychiatry, Perinatal Mood and Anxiety Disorders (PMADs), reproductive health education

Introduction

Since the inception of psychiatry at the end of the 19th century, its various theoretical orientations have shifted in prominence but rarely has the mother as a figure of interest for the well-being of individuals and the broader societal fabric lost her primacy. Mothers have been identified as primary agents in the developmental trajectories of their offspring and as sources of negative impact when in distress. Regrettably, this scholarly fascination has historically led to the stigmatization and medicalization of maternal experience without the same attention paid to their well-being. Over the past six decades, with the establishment of entities such as the International Society for Psychosomatic Obstetrics and Gynecology, the Marcé Society, and Postpartum Support International, the field of perinatal psychiatry has made significant

contributions to recognizing the pivotal role of reproductive transitions in women's health, facilitated by a global consortium of researchers, clinicians, educators, and advocates (1–4). This unfolded in parallel with social justice activism that ultimately led to legislative actions mandating the universal screening of new mothers for depression and their active participation in clinical research (5–8). By the turn of the 21st century, the field of maternal mental health had grown beyond its myopic focus on child outcomes to encompass a wider classification of diagnoses (e.g., perinatal mood and anxiety disorders or PMADs), clinical windows (e.g., prenatal onset), pathophysiologies (e.g., traumatic childbirth), interventions (e.g., zuranolone), and trainings (e.g., specialized curricula)— this time to alleviate the distress of the mothers themselves (9–11). Epidemiological data revealed that vulnerability in motherhood was ubiquitous with estimates between 15% to 21% of the general population experiencing depression, and up to 80% of mothers reporting distress of some kind (12). This paradigmatic shift from viewing the mother merely as a functional object to recognizing her as a psychological *subject* marked a belated but critical turn.

Despite these notable advancements, it is imperative to acknowledge that a deeply rooted biomedical "psychiatry bias" in maternal mental health research and practice still remains, inviting critical reflection (13). Ongoing theoretical innovation is necessary to advance bold ideas that can evolve outdated explanatory frameworks and guide scientific exploration now in the direction of building *resilience*. In 2018, the World Health Organization (WHO) underscored the mental health of mothers as a fundamental component of their overall health, defining maternal well-being not merely as a reductionistic absence of mental illness, but as the capacity for *flourishing* (14). There exists an urgent need for a strengths-based framework that studies the normative aspects of a mother's self-development and acknowledges both the positive and negative outcomes with equal consideration. Such an expanded viewpoint provides a more comprehensive appreciation of mothers as complete individuals capable of thriving if given the optimal environmental conditions. Using a term known as *matrescence* from the archives of women's health literature and, notably, from a different discipline, is a timely intervention (15). The process of becoming a mother, or *matrescence*, was first introduced in the 1970s by Dana Raphael, Ph.D., a female medical anthropologist who studied birth and breastfeeding and also coined the word 'doula'. It was largely neglected until half a century later when the author revived it to complement diagnostic views in maternal mental health and expanded its definition further (15). Matrescence must once again evolve beyond its original conceptualization in order to offer a new lineage of thinking for the field of perinatal psychiatry. The larger promise of matrescence may be in its ability to reshape entrenched societal beliefs and, by extension, how health systems nurture maternal welfare by providing a more comprehensive and compassionate approach to their care.

Matrescence terminology and nosology

In her pioneering yet overlooked work, *Becoming a Mother, A New/Old Rite de Passage in Reproduction, Power, and Change* (1975), Raphael stated,

> *"The critical transition period which has been missed is matrescence, the time of mother-becoming … Giving birth does not automatically make a mother out of a woman … The amount of time it takes to become a mother needs study" (16, p.65-70).*

Raphael's words serve as a call to inquire further into the nature of maternal psychological maturation and to integrate these insights into modern psychiatric theory and practice. The delayed explication of matrescence may be due, in part, to the lack of language available to describe new motherhood as a "life crisis" without cloaking it entirely in negative terminology. Like the term adolescence from the Latin word "adolescere", meaning "to emerge, grow, or mature", it may share similar defining features of developmental growth or regression true of any life transition. The more common terms of postpartum or perinatal are borrowed from the obstetric establishment and as such form a natural pairing with words of infirmity (e.g., postpartum depression). It illuminates how over time the study of maternal development has been saddled with a conceptual basis that has shaped it into a 'curative discipline' based on the medical model of disease, and to which some argue it largely owes its transformation into the subfield of perinatal psychiatry (17). Establishing its own unique nosology instead may help matrescence gain similar recognition and relevance. A standardized framework would also enable systematic investigation by others, enhance the quality and comparability of studies, and could play a vital role in education and awareness efforts.

The act of transcending disciplinary boundaries to adapt concepts from other fields is a key strategy for theoretical innovation. This approach not only enriches our understanding but also broadens our interpretative frameworks for the better (see *reproductive identity*) (18, 19). It is also an opportune moment as the classification of PMADs is currently being subjected to greater scrutinty (1). While more studies aim to distinguish conditions like postpartum depression from nonpuerperal major depression, comparisons to non-pathological human development remain curiously sparse. This discrepancy highlights a fundamental lack of understanding about what is *normative* during this life stage. More attention is needed as to whether general maternal distress is a distinct affective state, a subclinical presentation, or part of a normal continuum across the spectrum of illnesses from "baby blues" to psychosis (20). The utility of a developmental orientation such as matrescence is in helping to discern between normal and abnormal reactions to common experiences like fatigue or mood changes when interpreting the concerns of new mothers. For example, the term "perinatal distress" often serves as a vague catch-all that may incorrectly suggest impending illness (21). Recognizing it instead as a universal phenomenon of psychological disorientation to a major life change could clarify its meaning and reduce its potential overuse. In such an acute time of flux, distinguishing between psychiatric disorders and developmentally appropriate reactions can become challenging and potentially obscure the theoretical and practical boundaries between them (see Figure 1).

This conceptual "fuzziness" also extends into the history of nonspecific constructs often used to describe maternal psychology such as "transition to motherhood", "becoming a mother", "maternal role attainment", or "maternal identity formation" (22). Using agreed-upon, succinct and clear terms such as Raphael's *matrescence* and *matrescents* may reduce confusion, improve communication, and assist keyword searches when exploring these diverse bodies of literature. In terms of its timing and scope, precocious puberty and assisted reproductive technologies have widened the reproductive window and made it possible to become a mother even younger and older than previous generations. The exact length of matrescence is therefore individual, recurs with each child, and may last a lifetime with no clear endpoint. Integrating additional terminology from the field of developmental psychology could further improve cohesiveness and distinguish the various ages and stages of motherhood, similar to what is noted for young adulthood: *emerging motherhood* (infants to school-aged offspring), *middle motherhood* (adolescent offspring), and *late motherhood* (adult offspring). Notably, most research on maternal psychology predominantly centers around the early years of motherhood, leaving a gap in our understanding of late motherhood or the dynamics of parenting during menopause, especially considering the rising trend of delayed childbearing. This lack of comprehensive exploration suggests potential areas for future research to delve into the various phases of motherhood. For example, borrowing insights from the literature on grief could shed light on topics such as mourning the loss of one's former self or the emotional impact of the empty nest syndrome.

Raphael (16) gave us another clue that motherhood was a *holistic* experience with multidimensional significance: "The matrescent rite de passage can be examined as a biological fact, as a cultural event … The physiological stage of matrescence begins at the moment a female delivers a live infant. But, human beings are never limited by biological fact!" (16, pg. 66). Adolescence is widely recognized as a significant developmental period between childhood and adulthood that shares these equivalent all-encompassing changes. Although the comparison to adolescence is imperfect, theories from this field can provide valuable guidance in understanding the unique and distinct aspects of matrescence. Still, many questions remain unanswered. Is it a discrete life transition like adolescence or a complex life-long experience? If acute, what are the anticipated developmental tasks, and how does it then shape later adult development across the lifespan of a mother (and perhaps even into grandmothering)? What has been evidenced to date is that people who experience preconception, pregnancy, birth, surrogacy, adoption, and early parenting, undergo alterations not only in the few domains Raphael initially proposed but across *all* of the domains of human existence. With this in mind, the updated definition of matrescence for the 21st century offered here, as a first step in this longer inquiry process, is: a lifespan, developmental transformation that is biological, neurological, psychological, social, cultural, economic, political, moral, ecological, existential, and spiritual in nature. Furthermore, creating a comprehensive nosology for matrescence should also involve classifying both the developmental challenges *and* opportunities possible within each of these domains (see Box 1).

Positive perspectives matter to patients

The exploration of the *positive psychology of motherhood* represents an essential aspect of matrescence that warrants further investigation into the opportunities for personal growth

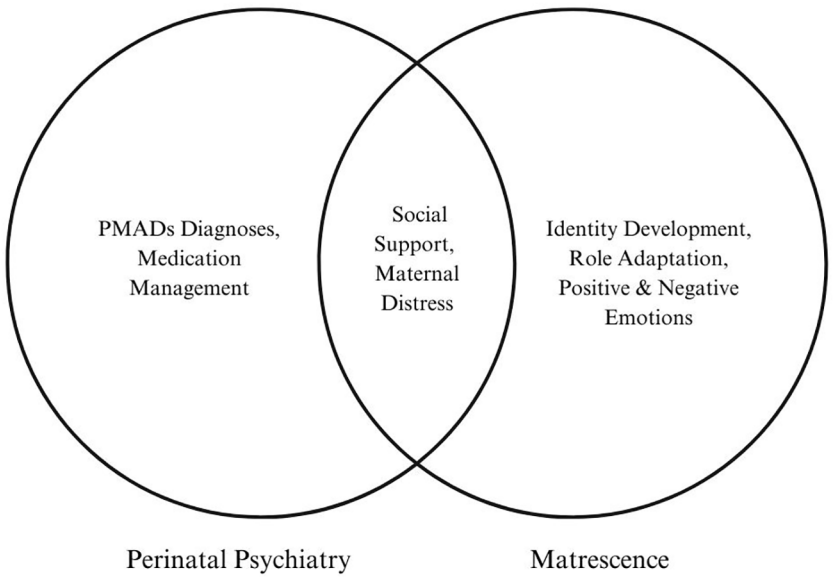

FIGURE 1
Clinical versus developmental perspectives.

BOX 1 Developmental domains of matrescence.

Conventional bio-psycho-social domains
Biological. Pregnancy, childbirth, and infant feeding involve intricate hormonal cascades (e.g., progesterone, estrogen, prolactin, relaxin, cortisol, and oxytocin) that affect the brain and body much like puberty. Physical challenges such as chronic bending, lifting, feeling "touched out," and sleep deprivation can also alter body appearance and self-perception (23).
Neurological. Changes in the maternal brain's structure and function indicate another phase of human neuroplasticity. Neuroscientists describe this as 'pruning and tuning,' a process that streamlines and optimizes the brain, making it more efficient, empathetic, attuned, and socio-emotionally intelligent (24). This challenges the derogatory concept of 'baby brain,' mistakenly associated with cognitive decline (25).
Psychological. Heightened emotional sensitivity, caretaking responsibilities, and the 'mental load' can overwhelm coping abilities and lead to feelings of inadequacy. Rumination, perfectionism, and hypervigilance may become maladaptive. Adjustment involves integrating identity shifts and setting more realistic expectations, leading to enhanced ego resilience over time (26).
Social. The arrival of children can prompt relationships to change considerably (e.g., divorce, losing/gaining friends, mending family ties) (27–31). Issues of social comparison and group belonging (e.g., social media, peer pressure, cliquish behavior) based on child-rearing preferences may also become more central and contribute to social anxieties typical of adolescence (32).
Cultural. Cross-cultural factors such as variations in the Value of Children (VOC) and postpartum practices, can help or hinder maternal development (33, 34). Culturally competent care respects regional preferences and helps mothers analyze influences to discover personal preferences. Such care should promote equity and inclusion across all child-rearing models and family structures, including LGBTQ+ parenting (35).
Economic. Mothers may face professional setbacks or unpaid labor due to their parental status, which exacerbates existing gender biases (36–38). Terms like "leaky pipeline", "maternal wall", or "maternal wage penalty" describe phenomena such as premature workforce exit, leading to activism for fair pay and family-leave policies (39). Others turn to "mompreneuriship" as solutions or seek roles with social impact (40).
Expanded ideological domains
Moral. Ethical concerns grow as mothers contemplate the fairness and systemic oppression within societal structures (workforce, healthcare, childcare) (41, 42). The COVID-19 pandemic further exposed these disparities and stronger advocacy for equity and justice (43). Such awakened awareness may lead to greater compassion for others, coupled with a reduced tolerance for violence in media, reflecting a deep empathy for families affected by tragedies such as war.
Ecological. Climate change may drive mothers to adopt environmentally conscious behaviors, ranging from recycling to engaging in political protests (44–46). They may also report an attitudinal shift, from anthropocentric to ecocentric, developing an aversion to overconsumption and a desire for a deeper connection with nature and all living beings in a reciprocal relationship (47).
Existential. A maternal existential perspective sees self-realization as continuously evolving, not fixed (48, 49). This reassessment of life priorities, personal freedom, and choice often connects back to the responsibilities of parenting. Establishing practical boundaries can nurture a new ethic of care that considers both mother and baby, moving from self-sacrifice to mutual interdependence (50).
Spiritual. An increased engagement with spiritual practices or religious faith may develop, including transformative experiences like "born again" events, or the transpersonal phenomena of indigenous traditions (e.g., synchronicities, ancestral communication). Integrating spiritual views into coping with reproductive grief (e.g., infertility, miscarriage) may offer comfort (51–54).

available to mothers. Perinatal patients often challenge clinical interpretations that solely pathologize their maternal experiences. Intolerance for this one-sidedness is gaining momentum as more mothers publicly share their stories and global public health initiatives such as Maternal Mental Health awareness campaigns increasingly use empowering and destigmatizing language (5). Today, Positive Youth Approaches (PYA) teach adolescents that they can adopt a growth mindset during their time of identity difussion. The "disorienting dilemma" of matrescence should be similarly viewed as a fertile period of self-discovery, experimentation, and subsequent mastery for mothers (55). For example, managing a central preoccupation like the desire for autonomy versus healthy interdependence can be reframed as an occasion to explore their personal values and to become more clear in their direction, meaning, and purpose. This may herald a more pivotal turning in their overall worldview, a *metanoia* that is more akin to an existential conversion– a fundamentally transformed outlook in life, or a moral evolution.

To that end, the repackaging of the nosology outlined in Box 1. into an innovative self-assessment tool that acknowledges the bivalent, dual, or paradoxical nature of motherhood would help identify not only areas of vulnerability and symptoms as is the convention in a psychiatric evaluation but also the coexistence of self-perceived virtues and strengths. Unfortunately, explicitly "probing for the positive" is not how mental health practitioners are commonly trained, and as such they likely miss accounting for the subtle psychological gains (e.g., tolerance for ambiguity) experienced by mothers alongside the more obvious losses (e.g., sleeplessness). This "benign neglect" could be considered an ethical violation as the psychological and philosophical literature has validated a range of indicators for maternal subjective well-being and post-traumatic growth, and even the presence of *perinatal flourishing* (18). Denying the full range of maternal experience may have unforeseen consequences such as too many false positive diagnoses of depression in light of widespread screening. It may also unwittingly lead mothers to believe their failures are more

important than their achievements. Designing a more comprehensive "positive and negative" assessment would be a useful adjunct to the widely used Whooley Screening Questions or Edinburgh Postnatal Depression Scale (EPDS). Such an innovation would also be in keeping with John Cox's recommendation that organizations such as the Marcé Scientific Society or Global Alliance for Maternal Mental Health create forums for thinking about new scale development (56). Interestingly, in the appendix of Cox's ten updated recommendations for the optimal administration of the EPDS are instructions on how to thoroughly ask and listen to answers:

> "*When used to assess a mother in the community, the practitioner should discuss the responses with her, listen to her story, ascertain whether clinical depression or another mental disorder is present – and consider referral and/or further listening visits" (25, p.128).*

Perhaps swapping out "another mental disorder" with "matrescence" would be a step in the right direction for a more mother-centered, supportive, and developmentally-informed attitude. An interesting challenge moving forward, therefore, is how to best build the capacity of professionals to help mothers integrate the transformative effects of matrescence into their overall self-understanding while also preparing to assist them through impaired functioning when warranted.

In conclusion, it is important to emphasize this stage of development as a critical window for establishing lifelong positive health behaviors. Developmental factors such as the timing of the first pregnancy or whether a mother has been given a proper 'head start,' by equipping her with comprehensive matrescence education and not just childbirth preparation, can profoundly impact the course of motherhood. Future maternal functioning depends in part on past exposures, with each stage affecting the next and leading to a weathering effect of cumulative distress over time. This developmental cascade requires redesigning healthcare services to include prevention and early intervention programs, seamless linkages to professionals—especially during peak times of need—and sequential, stepwise care. Such a life course perspective must also extend its focus beyond individual-level assets and consider the broader ecological systems in which mothers are situated. It should critique the quality of their own holding environment and incorporate historical factors (e.g., COVID-19). Just as with adolescence, the experiences of matrescence can be severely altered by how well or poorly a mother is socially or economically resourced, placing her on a vastly different trajectory in terms of her well-being (57).

The promise of matrescence

Today, a growing number of scientists are studying reproductive health issues, driven by advancements in women's representation in the sciences, as well as their increased economic and political influence. These efforts are the unfinished work of generations of scientists, many of whom were mothers themselves, who were not afforded protected time from family life or adequate funding to pursue their hypotheses in earnest. Meanwhile, matrescence has also come a long way since its initial introduction to the scientific community in the 1970s, gaining significant traction and recognition. Its resurgence has catalyzed fresh discoveries across various fields, from neuroscience to economics and has been embraced by contemporary scholars as a good fit for reframing their inquiries (58). However, this has also led to fragmentation, with numerous disconnected discussions lacking a centralized platform for a more fruitful exchange of complementary perspectives. Lewis Gordon, as cited by Mantuori, notes that

> *"The emergence of disciplines has often led to the forgetting of their impetus in living human subjects" (59, p.45).*

The prospect of matrescence serving as an academic container to consolidate its disparate strands of scholarship into a newly named specialization is promising. E.O. Wilson similarly advocated for 'a unification of knowledge … a consilience,' since bridging the gaps between disciplines can enhance the depth and diversity of understanding of any subject (60). A parallel process to what was done for adolescence more than a century ago, now for matrescence, could promulgate the same progress (61). Cross-disciplinary collaboration is also essential for maintaining checks and balances, especially for more dominant disciplines like psychiatry that may inadvertently skew scientific discourse, social trends, or grant allocations towards its own objectives. Efforts should be *inquiry-driven* rather than *discipline-driven* as a reminder that the priority should be a common commitment to improving the well-being of mothers.

Matrescence has also captured the interest of the private sector, leading to the development of various profitable outputs such as beauty products, luxury wellness services, trade books, and expensive online educational programs. This trend has opened up avenues for its commercialization with little ethical oversight. It is therefore necessary to protect and ensure robust support for all new mothers, not just the privileged few. The evolving science of matrescence, combined with grassroots activism and a reproductive justice perspective, demands a radical reimagination of our collective obligation to empower every mother to thrive, regardless of their socioeconomic status. This will require a multi-pronged approach: 1) establishing foundational knowledge of its unique developmental tasks and coping mechanisms; (2) identifying environmental factors that either facilitate or impede its optimal progression; (3) overhauling healthcare systems to ensure greater integration of services; (4) enforcing ethical guidelines for the treatment of mothers as a protected group; 5) expanding access to public health education initiatives; 6) training competent professionals in the specialization of maternal well-being. As was once said of adolescents, until society embraces this responsibility, the promise of matrescence will remain unfulfilled for millions of women. These issues will only continue to gain importance, and with them, the need for bold ideas like matrescence that can better sustain the reproductive life satisfaction of parents and the future environmental conditions that support them.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

AA: Conceptualization, Visualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Psychiatry

TYPE Original Research
PUBLISHED 09 July 2024
DOI 10.3389/fpsyt.2024.1326151

OPEN ACCESS

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RECEIVED 22 October 2023
ACCEPTED 12 June 2024
PUBLISHED 09 July 2024

CITATION
Albertini JGL, Benute GRG, Francisco RPV and Galletta MAK (2024) Factors associated with depression during pregnancy in women receiving high- and low-risk prenatal care: a predictive model. *Front. Psychiatry* 15:1326151. doi: 10.3389/fpsyt.2024.1326151

Factors associated with depression during pregnancy in women receiving high- and low-risk prenatal care: a predictive model

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Introduction: Depression during pregnancy can put strain on pregnant women's interpersonal relationships, the formation of emotional bonds with the fetus, and the adaptation to the new routine and social role post-pregnancy. Some studies have associated socioeconomic factors, emotional factors, interpersonal relationships, perceived social support, gestational risk, and the occurrence of certain diseases during pregnancy with higher risk of depression.

Objectives: This study aimed to investigate the prevalence of depression during pregnancy and associated factors in low- and high-risk prenatal patients at a Brazilian university hospital.

Methods: This study presents a retrospective and prospective cross-sectional design. A total of 684 prenatal psychological analysis records from a Brazilian tertiary university service were retrospectively evaluated to assess depression through the PRIME-MD questionnaire between 2002–2017. Between 2017 and 2018, 76 patients treated at the same service were prospectively evaluated with the aforementioned instrument. Medical records were accessed to obtain labor and birth data. Multivariate analyses assessed the association between sociodemographic, gestational or obstetric, and health variables and the presence of depression during pregnancy.

Results: A total of 760 pregnant women were included in the study, with a depression prevalence of 20.66% (n = 157). At the time of assessment, 48 (21.05%) women from the low-risk pregnancy group and 109 (20.49%) from the high-risk pregnancy group were depressed. The mean age was 30.01 ± 6.55 years in the group with depression and 29.81 ± 6.50 years in the group without depression. In the univariate analysis, there was an association of risk for depression with absence of paid work, absence of a partner, low family income and diagnosis of epilepsy, being a protective factor the presence of diabetes during pregnancy. However, in the multivariate analysis, a lower family income, not having a partner at the time of the assessment, and the prevalence of

10.3389/fpsyt.2024.1326151

epilepsy were independently associated with an increased risk of depression during pregnancy.

Conclusion: This study showed that 1 in 5 women had depression during pregnancy, with no association with obstetric risk, but those women living in unfavorable economic conditions, without a partner, and having epilepsy were at increased risk of depression.

KEYWORDS

depression, pregnancy, high-risk pregnancy, epilepsy, diabetes, epidemiological models

1 Introduction

Pregnancy is a normal physiological phenomenon and a significant life experience for many. Within this context, some women may experience the expected transformations for this condition, meaning that maternal and fetal risk is within the average identified in the general population, resulting in a low-risk pregnancy, while others may have a higher risk for unfavorable outcomes, thus constituting a high-risk pregnancy (1). Factors associated with high-risk pregnancy include individual characteristics, maternal diseases, and unfavorable socioeconomic conditions (2).

Both low- and high-risk pregnancies present several physical, hormonal, psychological, and social integration changes that lead to intense transformations and can affect the woman's mental health in ways still requiring further studies to be fully understood (3–5). Depression is the most prevalent psychiatric disease during pregnancy. A common characteristic among depressive disorders is the presence of a sad or depressed mood, with a lack of interest or pleasure in practically all activities and feelings of guilt and low self-esteem (6, 7).

The prevalence of depression during pregnancy ranges between 9% (8) and 61.4% (9), with lower indices in low-risk pregnancies (8, 10) and higher indices in high-risk pregnancy (8, 9). These percentages may vary depending on the geographic location, level of development of each country, method used in the study, and the instrument used to assess depressive symptoms (11). Data from a meta-analysis study (7) published in 2021 estimate that the mean global prevalence of depression during pregnancy is 20.7% (95% CI 19.4–21.9%), reducing to 15% when only major depression is considered, thus constituting one of the most common clinical complications in pregnancy.

Considering the peculiarities of depressive symptoms and their repercussions on the pregnant woman's daily life, for example, on her behavior, self-perception, and understanding of pregnancy, a growing number of studies (3, 12, 13) have investigated the possible impacts of depression during pregnancy, uggesting that it would lead to worse obstetric results and unfavorable neonatal outcomes.

Several authors have studied risk factors for depression during pregnancy, classifying them as biological and psychosocial risks (14) that include mainly a history of mental disorder (15, 16), history of domestic violence or abuse (17, 18), lack of social support (16, 19, 20), unplanned current pregnancy (21), smoking, and history of miscarriage (22).

The influence of socioeconomic aspects seems to be quite significant. Previous systematic review and meta-analysis studies, such as that by Nisar et al. (20), associated lower socioeconomic levels with depression in Chinese pregnant women. In particular, higher education levels and better living conditions were protective factors. Simultaneously, other meta-analyses (7) demonstrated that unemployment is also associated with depression during pregnancy and that greater attention should be given to this group, particularly in low- and middle-income countries, because prevalence data is higher in these geo-economic conditions.

However, few studies on factors predisposing to gestational depression have been conducted in Latin America. Guidelines and recommendations from European (23), North American (24), and Canadian (25) organizations and societies suggest screening for depressive symptoms during prenatal care as an important opportunity for the early identification and treatment of signs and symptoms of depression during pregnancy. The most commonly used standardized tool for this purpose is the Edinburgh Postnatal Depression Scale (EPDS), a self-report screening instrument used with various cutoff scores to detect signs of risk or a high probability of a major depressive disorder diagnosis. However, such results are more precisely applicable to the postnatal period, and a review on this topic (26) indicated that, in the assessment of pregnant women, the EPDS result should be associated with a clinical evaluation by a specialized professional. Building on this premise, the use of the PRIME-MD in evaluating depressive symptoms in pregnant women becomes a more favorable possibility as it contains within its structure the DSM-III diagnostic criteria for major depressive disorder, serving as a guide for specialized clinical interviews.

Understanding the influence of depression in pregnancy and the possible associated factors in 102 specific populations are relevant to improving the care provided to these women, helping

reduce 103 deleterious effects on the mother-baby dyad (22). There are few publications in Latin 104 America, especially in Brazil, exploring factors related to antenatal depression, and even fewer 105 exploring depression in populations at high obstetric risk (27–29). Therefore, this study aimed to investigate the prevalence of depression 108 during pregnancy and associated factors in low- and high-risk prenatal patients in a Brazilian 109 university hospital.

2 Methods

A time series study with retrospective and prospective data between 2002 and 2018 was 112 conducted in a public tertiary university hospital in São Paulo, SP, Brazil, with the project previously 113 approved by the institution's Research Ethics Committee under number 68144317.2.0000.0068. As of June 2017, a psychological screening service was implemented to identify women who needed specialized mental health care among patients starting prenatal care. The care protocol used in the psychological screening service also consisted of an initial semi-structured interview and the PRIME-MD depression module.

The study included all patients evaluated by the PRIME-MD depression module between January 2002–June 2018, including both phases. The exclusion criteria were: not completing the interview, not completing the depression assessment via PRIME-MD, having received a fetal malformation diagnosis in the current pregnancy, and reporting a prior diagnosis of mood disorder or other mental disorders. Therefore, of 1,091 psychological records containing depression evaluation by the PRIME-MD identified in the retrospective part of the research, 407 were excluded, leaving 684 pregnant women in the study. In the prospective part, 373 depression evaluations were conducted in psychological screening, with 297 cases excluded and 76 pregnant women included. Therefore, a total of 760 pregnant women were included in the study. Figure 1 shows the study flowchart.

Several demographic, social, clinical, and obstetric variables were surveyed to investigate a possible association with a diagnosis of depression by the PRIME-MD. The following demographic variables were recorded: age, education level, religion, and marital status. Furthermore, the participant's personal and family per capita income were presented in minimum salaries corresponding to the period during which the pregnant woman was evaluated (minimum salary, MS, in 2018 was BRL 954, i.e., around USD 3,000). The following obstetric variables were analyzed: parity, previous miscarriages, complications, and gestational age at the time of psychological evaluation. A high risk pregnancy was considered when there was a risk of death or morbidity both for the mother and fetus, including intercurrent clinical pathologies (hypertension, diabetes, heart disease, thyroid disease, infectious diseases, thrombophilia, neoplasms, asthma, epilepsy, collagenosis) or obstetric history of risk. The remaining pregnant women were included in the low obstetric-risk group.

The Primary Care Evaluation of Mental Disorders - PRIME-MD is an instrument composed of five modules (mood, anxiety, eating, somatoform disorders, and alcohol abuse or dependence disorders), which can be used independently. The PRIME-MD mood module's main objective is identifying whether the patient is in a major depressive episode, as it contains the criteria established by the DSM for this diagnosis. The Portuguese version, revised by Dr. Robert Leopold Spitzer, its creator, has

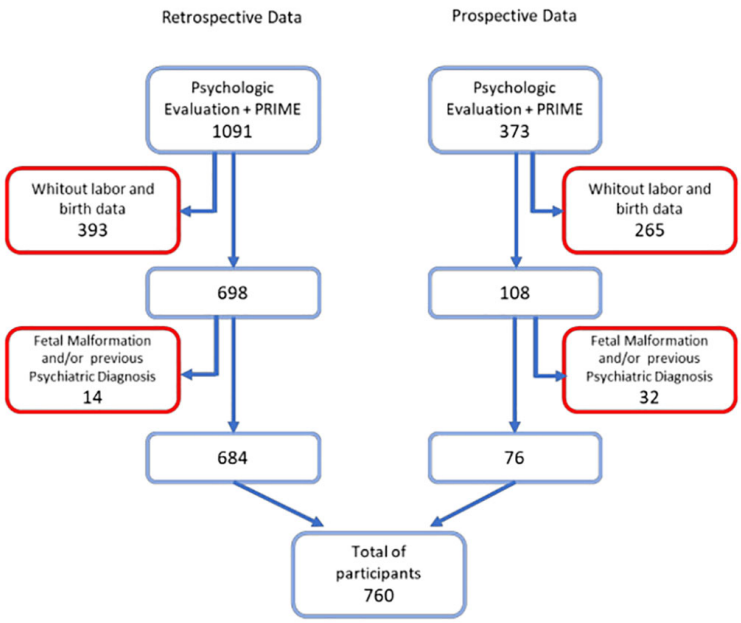

FIGURE 1
Data collection flow chart. Embedded text: Retrospective data; PRIME-MD psychological evaluation; No labor and birth data; Fetal malformation or previous psychiatric diagnosis and the total number of participants; Prospective data.

demonstrated good accuracy (sensitivity and specificity) for major diagnostic groups in primary care settings. For the present study, the module that evaluates mood disorders, specifically Major Depression, was used (30, 31) and considered positive for depression when at least five out of nine symptoms evaluated by the PRIME-MD were present, of which it must necessarily include the presence of sad and depressed mood or lack of interest/pleasure in situations previously experienced as pleasurable.

Qualitative variable results were presented as relative (percentage) and absolute (n) frequencies.

Quantitative variables were presented as the mean, median, minimum, and maximum values and standard deviation.

Distribution tests were conducted for quantitative variables to verify data normality. Quantitative variables were compared between groups using the Student's t-test for parametric variables or the Mann–Whitney test for non-parametric variables. The Kruskal-Wallis non-parametric test was used to reach more than two groups.

Pearson's chi-square or Fisher's exact tests assessed the association between two categorical variables. The correlation coefficient between two quantitative variables was evaluated by Pearson's statistical test or, in the case of non-normality, by Spearman's statistical test.

The association of these variables with depression during pregnancy was demonstrated by odds ratio with CI95%, crude or adjusted to the predictive model. A predictive model for depression was used to analyze risk factors independently associated with depression during pregnancy, which was constructed with the variables most significant in univariate analysis. This analysis used a logistic regression model of characterization variables and health data with $p < 0.200$, through the backward stepwise model. Regression model adequacy was verified using the Hosmer-Lemeshow test.

The significance level was set at 5%—results with a p-value less than 0.05 were considered significant. The IBM SPSS software version 20. was used for data analyses.

3 Results

Between 2002 and 2017, pregnant women undergoing outpatient prenatal care referred for psychological assessment and those receiving face-to-face psychological care were included in an initial care protocol consisting of a semi-structured interview and assessment of mood using the major depressive disorder module of the Portuguese version of the Primary Care Evaluation of Mental Disorders (PRIME-MD) (30, 31), and these assessments were attached to the patient's medical records. The retrospective cohort was generated through the review of evaluations carried out with the same instrument in cases referred by OG doctors, who provide prenatal care to these patients, for Psychology evaluation. The prospective cohort consisted of the psychological screening assessment of pregnant women at the time of the first prenatal consultation, without prior medical referral.

The total prevalence of depression in the study sample (n = 760) was 20.66% (n = 157). This rate did not consider if the pregnant woman was in the low (21.1%) or high (20.5%) obstetric risk group. Considering only the population diagnosed with depression (n = 157; 100%), 84.71% (n = 133) were in the high-risk group.

Table 1 presents the study population characterization data, variables evaluated, the association with depression during

TABLE 1 Distribution of characterization, sociodemographic, and health data in mean, minimum and maximum values; relative and absolute frequencies; ORcrude (CI95%); and symptoms associated with depression during pregnancy.

Sociodemographic and pregnancy data	Depression		*p*	ORcrude (CI95%)
	Yes	No		
Age				
Median (Min–Max)	31 (18-45)	30 (18-45)	0.721**	0.996 (0.976-1.016)
Personal income - minimum salaries				
Up to 1 minimum salary/month	7/25 (28.0)	18/25 (72.0)	0.092***	Ref.
Between 1 and 5 minimum salaries/month	48/266 (18.0)	218/266 (82.0)		0.566 (0.224-1.431)
Between 6 and 10 minimum salaries/month	4/13 (30.8)	9/13 (69.2)		1.143 (0.224-4.951)
No income	63/240 (26.3)	177/240 (73.8)		0.915 (0.365-2.295)
Family Income—Per capita minimum salaries				
≥ 2 minimum salaries/month	80/458 (17.5)	378/458 (82.5)	**0.002*** **	Ref.
< 2 minimum salaries/month	59/209 (28.2)	150/209 (71.8)		1.858 (1.264-2.734)

(Continued)

TABLE 1 Continued

Sociodemographic and pregnancy data	Depression		*p*	ORcrude (CI95%)
	Yes	No		
Gestational age at the time of evaluation				
Median (Min–Max)	24/49 (7-40)	25/49 (4-40)	0.597**	0.996 (0.976-1.016)
Gestational age at the time of evaluation				
First trimester	12/76 (15.8)	64/76 (84.2)	0.183	Ref.
Second trimester	83/354 (23.4)	271/354 (76.6)		1.633 (0.841-3.172)
Third trimester	58/308 (18.8)	250/308 (81.2)		1.237 (0.627-2.441)
Age				
< 20	9/47 (19.1)	38/47 (80.9)	0.953	Ref.
20 a 35	113/548 (20.6)	435/548 (79.4)		1.097 (0.515-2.6335)
> 35	35/165 (21.2)	130/165 (78.8)		1.137 (0.502-2.573)
Schooling				
Up to 5 years (elementary school)	80/333 (24.0)	253/333 (76.0)	0.140	Ref.
Up to 12 years (high school)	55/299 (18,4)	244/299 (81.6)		0.713 (0.485-1.048)
Over 12 years (university)	22/125 (17.6)	103/125 (82.4)		0.675 (0.400-1.141)
Relationship status (with partner)				
With partner	129/656 (19.7)	527/656 (80.3)	**0.029**	1.761 (1.061-2.923)
Without partner	25/83 (30.1)	58/83 (69.9)		
Paid activity				
Yes	74/403 (18.4)	329/403 (81.6)	**0.037**	1.469 (1.023-2.109)
No	76/306 (24.8)	230/306 (75.2)		
First pregnancy	46/262 (17.6)	216/262 (82.4)	0.126	0.742 (0.507-1.088)
Nulliparous woman	61/343 (17.8)	282/343 (82.2)	0.076	0.723 (0.505-1.035)
High-risk pregnancy				
Yes	133/629 (21.1)	496/629 (78.9)	0.92*	1.184 (0.731-1.919)
No	24/130 (18.5)	106/130 (81.5)		
Previous Abortion (yes)	49/223 (22.0)	174/223 (78.0)	0.564	1.119 (0.764-1.637)
Religion (yes)	103/517 (19.9)	414/517 (80.1)	0.198*	1.294 (0.873-1.917)
Complications in previous pregnancies	54/269 (20.1)	215/269 (79.9)	0.198*	1.319 (0.865-2.014)
Diseases in current pregnancy	132/623 (21.2)	491/623 (78.8)	0.464*	8.838 (0.521-1.347)

(Continued)

TABLE 1 Continued

Sociodemographic and pregnancy data	Depression		*p*	ORcrude (CI95%)
	Yes	No		
High-risk pregnancy				
Diabetes	39/240 (16.3)	201/240 (83.8)	**0.040*** **	0.659 (0.442-0.983)
Hypertension	35/170 (20.6)	135/170 (79.4)	0.980*	0.995 (0.652-1.516)
Cardiopathy	10/59 (16.9)	49/59 (83.1)	0.464*	0.769 (0.380-1.555)
Thyroid diseases	10/50 (20.0)	40/50 (80.0)	0.905*	0.957 (0.468-1.960)
Infectious diseases	10/30 (33.3)	20/30 (66.7)	0.080*	1.983 (0.909-4.327)
Thrombophilia	7/30 (23.3)	23/30 (76.7)	0.715*	1.175 (0.495-2.790)
Neoplasms	7/29 (24.1)	22/29 (75.9)	0.643***	1.230 (0.516-2.934)
Asthma	6/17 (35.3)	11/17 (64.7)	0.136**	2.138 (0.778-5.875)
Epilepsy	5/8 (62.5)	3/8 (37.5)	**0.012****	6.579 (1.555-27.834)
Collagenosis	3/24 (12.5)	21/24 (87.5)	0.444**	0.539 (0.159-1.830)
Repeat miscarriage	3/18 (16.7)	15/18 (83.3)	0.472**	0.764 (0.218-2.671)

HC-FMUSP, 2002–2018.
*Student's t-test; **Mann-Whitney test; ***Chi-square test; ****Fisher's exact test.
The bold values refer to p-values less than 0.05.

pregnancy, and the ORcrude and confidence intervals. There was no statistically significant difference between pregnant women with or without depression symptoms when considering the associated gestational risk (p= 0.492).

The analyses indicated a statistically significant association between per capita family income in minimum wages and depression, where the majority of participants in the depression group had income lower than 2 minimum salaries/month (p = 0.002). The pregnant women who reported not engaging in paid work had a higher risk of belonging to the depression group (OR 1.469; CI95% 1.023–2.109). Similarly, not having a partner showed a statistically significant association with depression, with greater risk for participants without a partner at the time of the evaluation (OR 1.761; CI95% 1.061–2.923). Regarding clinical variables, there was a significant statistical association between depression and the diagnosis of diabetes and epilepsy. The group without diabetes showed a greater chance of depression during pregnancy than the group with diabetes (OR 0.659; CI95% 0.442–0.983). Having epilepsy was associated with a greater risk of depression during pregnancy (OR 6.579; CI95% 1.555– 27.834).

Variables considered clinically relevant vis-à-vis depressive symptoms during pregnancy were also included. A stepwise backward model with 11 stages was included, maintaining the variables "religion," "nulliparous," and "diabetes" to adjust the model (Hosmer-Lemeshow = 0.685). The results of this analysis with the respective ORadjusted are presented in Table 2.

Thus, the final predictive model analysis showed that the chance of having depression in the group of pregnant women without a partner was 1.86-fold higher (CI95% 1.041–3.334). Prevalence of epilepsy was also an independent factor, with more than four-fold more significant chance of depression during pregnancy (OR = 4.758, CI95% 1.055–21.455). The variable family income < 2 MS, related to a worse socioeconomic condition, also maintained statistical significance in the predictive model com 1.78-fold increased chance of a participant this group having depression during pregnancy.

TABLE 2 Logistic regression model for the association between significant variables and depression during pregnancy adjusted for the control variables religion, being nulliparous, and having diabetes.

	B	*P*	*OR*	(CI95%)
Without partner	0.622	**0.036**	1.863	(1.041-3.334)
Epilepsy	1.560	**0.042**	4.758	(1.055-21.455)
Family incomes < 2 MS	0.577	**0.005**	1.780	(1.193-2.658)

HC-FMUSP, 2002–2018.
The bold values refer to p-values less than 0.05.

4 Discussion

The general prevalence of major depression in the sample was 20.66%. The scientific literature (8, 9) presents wide depression rate variation during pregnancy. However, the results of this study are comparable with other international studies (32, 33) that used assessment instruments constructed with the same theoretical assumptions (Structured Clinical Interview for DSM Disorders (SCID) or PRIME-MD). A North American study (32) using the SCID, an instrument used to diagnose depressive disorders, identified that 20% of pregnant women evaluated in the second trimester met the criteria for major depressive disorder. Rashid and Mohd (34) conducted a cross-sectional study with 3,000 Malaysian pregnant women undergoing prenatal care in all gestational trimesters. They identified a 20% prevalence of depressive symptoms, which corroborates ours findings. Still in this sense, a Korean study with 1,262 women assessed using the Edinburgh Postpartum Depression Scale (EPDS) identified that 20.2% of them scored above ten for depressive symptoms (35). Silva et al. (36) conducted a study in 2012 with 1,109 low-risk pregnant women in the second and third trimester of pregnancy reporting rates similar to ours, with the identification of depressive symptoms in 20.5% of the sample also using the EPDS, but with a cutoff point of 13.

Conversely, compared with the present study, some works (37, 38) with similar instruments presented lower prevalence results, indicating that different methodologies (such as inclusion or exclusion criteria and instrument evaluated) can explain, at least partially, different results. An important point is the chosen instrument for assessing depressive symptoms that can identify symptoms (symptom scales) or diagnose depressive disorder (diagnostic scales) and can focus decisively on the data obtained in studies and, consequently, on different rates of depression during pregnancy found in the literature. Specifically, there is an issue regarding using self-report instruments for symptomatological investigation, such as the EPDS, that identifies a more significant number of cases compared to clinical assessments using diagnostic instruments, such as the PRIME-MD. Juhas et al. (37) used the same instrument as in the present study (PRIME-MD). Nonetheless, they only had a sample of high-risk pregnant women, identifying that 11% of participants scored for depression, signaling the importance of specific group studies to discuss the specificity of each population. Similarly, the first longitudinal study in Latin America (8) to evaluate perinatal depression showed different findings compared to the present study, reporting lower depression rates. Their longitudinal study, when evaluating depressive symptoms using the Patient Health Questionnaire (PHQ-9), found that the percentage of participants exhibiting symptoms of depression was 16.6%. Another study (39) assessing major depression with the SCID showed a rate of 6.4%. Furthermore, other possible factors associated with depression prevalence variations in pregnant women include aspects related to different contexts of economic, social, cultural, and healthcare development of the studied population (7). One of the relevant aspects regarding the prevalence of depression was the choice of instrument, as it allowed a parameter based on the Diagnostic and Statistical Manual of Mental Disorders - DSM III-R (40) criteria, which could analyze pregnant women both at low and high gestational risk during all gestational trimesters.

As for data characterization, being without a partner was a significant difference factor in the univariate analysis between groups concerning depression, maintaining the association in the final predictive model with an even higher adjusted OR (ORadjusted = 1.863; 95% CI 1.041–3.334). Of the pregnant women with depression, around 30% reported not having a partner at the time of evaluation. Extensive literature (36, 41) on depression during pregnancy indicates relationship status as a critical associated factor. A study (42) with Dutch pregnant women identified a similar association between depression and not living with a partner at the beginning of pregnancy. However, this association was not maintained throughout pregnancy. Another study (43) with pregnant women treated at a university hospital in the city of São Paulo identified that participants with a partner had an 89% lower risk of depression during pregnancy.

An aspect related to the presence or absence of a partner indicated as necessary is the extent to which the relationship can be considered a protective factor. Studies such as the one by Redinger et al. (44) concluded that pregnant women reporting that their partners made life more difficult had a prevalence of depressive symptoms three-fold higher than the other women evaluated. These findings indicate that the gestational experience cannot be restricted only by women's health. Instead, it needs to be expanded to consider their social support network and intimate relationships. Further, whether these relationships can be healthy, thus reducing or increasing the risk of mental disorders. In this scenario, the quality of the relationship and how this relationship can make the pregnancy experience difficult or easier should be assessed. One of the aspects of most significant clinical concern due to the potential risk to the maternal-fetal dyad is the presence of intimate partner violence, with physical, sexual, or psychological harm. Several studies (45–48) indicate that pregnant women exposed to threats or aggression have a greater chance of low adherence to prenatal care and of mental disorders, in particular, perinatal depression.

Per capita family income was another variable that showed a significant difference between groups, with the group with depression reporting lower mean family income than the group without depression, both in univariate (OR = 1.858; CI95% 1.264–2.734) and multivariate (OR 1.780; CI95% 1.193–2.658) analysis. This result corroborates other studies (49–51) reporting the impact of income, both of the pregnant women and the family, on the onset of depressive symptoms. A study by Choi et al. (49) indicated that unfavorable socioeconomic conditions were associated with a higher prevalence of depression in pregnant women. Similarly, Podvornik et al. (50) demonstrated an association between low socioeconomic status and depression during pregnancy in Slovenian women. Socioeconomic indicators and poverty measurement indices relate to a more significant presence of mental disorders. However, studies such as the one by Nasreen et al. (52) with women from Bangladesh identified no specific association with depression during pregnancy, diverging from our findings. Likewise, a study (53) with pregnant Indian women identified no statistical association between family income and depression during pregnancy.

The present study also indicated that having a paid job was a protective factor against the diagnosis of depression, with more than half of the participants in the group with depression stating that they had no paid work at the time of the evaluation. However, the association was not reflected in the multifactorial analysis of the predictive model. Meanwhile, studies such as the one by Algahtani et al. (54) demonstrated that unemployment increased the chance of depressive symptoms in Saudi women who had experience of paid work or were students. However, there is a lack of more extensive studies on pregnant women that consider individual aspects and broader socioeconomic contexts. During the study period, Brazil was experiencing an economic recession, with a significant gross domestic product (GDP) drop (55), unemployment rates of 12.2 million people, and unemployment levels of 11.6% of the population. Indexes from the last quarter of 2018 were twice as high as before the economic crisis in 2014 (55). This panorama may have influenced findings related to the sample characterization data in this study. It is essential to understand that depression during pregnancy is a multifactorial disorder requiring an approach and treatment that considers the patient's social and economic aspects.

Of the maternal health variables analyzed in the present study, being in the group with a high-risk pregnancy, that is, having a disease associated with the current pregnancy, did not prove to be a risk factor for depression during pregnancy compared with a low-risk pregnancy. Unlike our findings, other studies (43, 56, 57) indicate that having a disease associated with pregnancy is a risk factor for depression during pregnancy. One of the most relevant aspects related to different results in the present study is the specific characterization of the group with low-risk women, mainly composed of women working in the institution's own health department, which may generate bias.

Although the mental health of pregnant healthcare workers is an aspect little studied in the literature, it appears that there would be high rates of depression during pregnancy (58–60). One explanation would be a possible greater burden of physical and emotional stress which, associated with low social support, could lead to depression (61), but the impact of this association is yet to be determined, and there is still theoretical space for discussion about stress and its association with depression during pregnancy (62) Pregnant women exposed to stressors such as turbulent situations and psychological threats, who cannot adapt flexibly, appear to be at increased risk of depression during pregnancy.

On the other hand, we could think that such women, as they are often healthcare professionals, would be better able to take care of their own well-being, seeking to reduce work stress with alternative measures that encourage relaxation and a certain disconnection from problems. Such women would also have better knowledge of general guidelines and could better manage their health condition with better self-care conditions, which could improve their mental health condition. Therefore, which of these two trends would be the most prominent is something that needs to be further investigated, under different contexts.

Regarding diseases associated with the current pregnancy, diabetes was a statistically significant difference factor in univariate analysis; however, this difference did not remain significant in multivariate analysis as the presence of the variable improved the model, acting as an adjustment factor. The results of the present study indicated that being diabetic was a protective factor against depression during pregnancy, contradicting the literature (63–65) on the topic, which signals an association between these two variables. Notwithstanding, other authors could not establish an association between diabetes and depression (66, 67). The bidirectional relationship that may exist between depression and diabetes should also be noted. Studies with non- pregnant women indicate diabetes as a risk factor for depression (63, 66). However, depression is also a risk factor for the onset of diabetes (65). Furthermore, questions about the biological mechanisms underlying the two diseases could be shared (66). All the transformations and implications in a woman's life form the hypothesis that diabetes, whether pre-existing or gestational, may increase the risk of depressive symptoms; however, evidence on the subject remains inconclusive.

We envision that diabetic patients in our sample could establish a secure positive bond with the multidisciplinary team, especially after following the guidance and implementing necessary lifestyle changes to achieve glycemic control with guidance and follow-up regarding diet control and monitoring of blood glucose levels through fingerstick tests. This could potentially reduce anxiety and stress, thereby lowering the risk of gestational depression. A study by Marquesim (66) at a university in São Paulo and another by Castro (67) at a university in Portugal reinforce this possibility. Even with the quality-of-life impairment and stress associated with this clinical condition, these patients presented depression rates equal to those of the general pregnant woman population. However, these conjectures and hypotheses require further studies to guide this specific group of pregnant women better.

Considering patients who reported having epilepsy, the univariate analysis identified, and the predictive model confirmed an increased risk of depression during pregnancy. We identified some studies that corroborate our findings. A study conducted in Norway (68) with 329 pregnant women with epilepsy and 106,224 without epilepsy reported a higher rate of depression in pregnant women with epilepsy than those without epilepsy.

Bjork et al. (69) identified higher rates of depressive symptoms in pregnant women with epilepsy, especially those who used more anticonvulsant medications. However, a recent prospective study (70) with pregnant women and women in the postpartum period compared women with epilepsy during pregnancy, pregnant women without epilepsy, and non-pregnant epileptic women. They observed no statistically significant difference between the three groups regarding the presence of depression diagnosed by the SCID. As discussed about the relationship between depression and diabetes, studies on epilepsy and depression point to a bidirectional association and indicate the need for a deeper analysis of this possible interaction. Some studies suggest that epilepsy and its resulting seizures induce frontal and temporal hypofunction, serotonergic and/or glutamatergic dysfunction, as well as hypofunction in the hypothalamic-pituitary-adrenal axis, processes that may be implicated in the occurrence of depressive symptoms. Although the present study did not assess the use of anticonvulsant medications, it is important to note that some studies (69, 70) indicate that their use may be associated with

significant mood alterations and that polytherapies, epilepsy activity, and its severity appear to be bidirectionally related to the presence of psychiatric disorders. On the other hand, levetiracetam, which is known to cause behavioral changes (e.g., aggression, agitation, anger, anxiety, apathy, depression, hostility, and irritability), as well as psychotic symptoms, it only recently began to be used in our patients and was not present among the participants in the present study, during the period in which the research was carried. Furthermore, we can extrapolate and reflect on some possible risk aspects in these patients, such as loss of control, worsening of quality of life, and the potential increased number of seizures during pregnancy, requiring therapeutic regimen changes and leading to greater insecurity. These factors could increase depressive symptom rates.

The results of this study show that, in addition to classic risk factors associated with low family income and absence of a partner, epilepsy was found to increase the risk of depression, whereas diabetes was a factor that posed reduced risk. This study presents a relevant case series in a tertiary service where high- and low-risk obstetric patients are treated according to a well-established and safe protocols. These findings can guide similar services to increase attention to the profiles mentioned here. Early identification of depressive symptoms in high-risk pregnancy is increasingly relevant, particularly in relation to worse maternal and fetal outcomes (27, 38, 49) and for hindering the fullest and healthiest gestational experience possible for each mother-baby dyad and the entire adjacent family nucleus.

However, there are still questions about how to diagnose antenatal depression early. Some recommendations (71, 72) and studies question the implementation of universal depressive symptom screening, mainly using standardized scales to identify symptoms. The lack of more specific and reliable studies justifying universal screening is examined, with the possibility of unnecessary interventions and negative impact on pregnant women, who could become more stressed by the screening procedures. However, most scholars on the subject (73) argue that health professionals and prenatal services, in general, would be adequately qualified to identify depression symptoms and, based on this, carry out the necessary treatments and referrals. Corroborating this opinion, several studies (74, 75) showed that psychological screening can be an effective strategy for mental health care during pregnancy to help identify initial symptoms and for reaching women who, for socio-cultural, emotional, and even medical reasons, would have difficulties identifying symptoms, attributing them to the pregnancy.

Some limitations of this study included the lack of exploration of other risk factors identified in the literature associated with depression during pregnancy, such as assessing the stress perceived by the patient, as well as stressful life events, specific family conflicts, or even domestic violence by a partner. In terms of the participants' health aspects, a limitation was the lack of information regarding current medication treatment related to existing illnesses, which would add relevant variables to the discussion. Furthermore, in this study, the interview to assess depression in pregnant women took place at a single stage of pregnancy, hindering the identification of whether the disease improved or worsened and how many patients underwent some psychotherapeutic or psychiatric intervention before giving birth. There is no consensus regarding the gestational trimester in which depression would be most prevalent; however, early and late pregnancy is reported as the most susceptible (76), although some studies (77, 78) indicate that this prevalence tends to increase as the pregnancy advances. Longitudinal studies are needed to answer this question, especially in high-risk pregnant women, with additional investigation indicating the cause-effect direction.

The present study reported a high rate of antenatal depression, with approximately one case in every five pregnant women, without difference between low- and high-risk pregnant women, possibly because many low-risk pregnant women were hospital employees with high workload stress levels. Although similar studies corroborate the data, such results highlight the importance of the topic, confirming depression during pregnancy as one of the leading clinical complications during the gestational period in comparison with data on the Brazilian population (79). Other important aspects of this study are the significant sample size and face-to-face interviews with trained psychologists, who administered a diagnostic instrument based on the DSM III (40) when most studies (90%) use a screening scale and self-report to identify depressive symptoms.

However, despite the relevant rates presented here, few physicians notice the presence of depression during prenatal care, and even fewer initiate appropriate treatment (80). Therefore, it is often underdiagnosed, severely affecting maternal or fetal health. Health professionals still make errors and have deficiencies in recognizing, diagnosing, and treating depression during pregnancy, consequently impacting the pregnant woman and newborn. Unfortunately, depression during pregnancy is a common and underdiagnosed condition because its symptoms are often attributed to the pregnancy, and the mental health support necessary is still poorly understood.

Thus, this study brings new information to help recognize the disease and establish early treatment. First, it reinforces the notion that unfavorable economic conditions and the lack of a partner are important risk factors. Moreover, high-risk pregnancy may not be a preponderant risk factor, but some diseases, such as epilepsy during pregnancy, may be an additional risk factor. In all cases, further research is needed on the impact of prenatal care on pregnant women with previous and intercurrent illnesses.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by CAPPESQ - Comissão de Ética para Análise de Projetos de Pesquisa do

HCFMUSP HCFMUSP Ethics Committee for Analysis of Research Projects. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JA: Writing – original draft, Project administration, Investigation, Conceptualization. GG: Writing – review & editing, Supervision, Project administration, Conceptualization. RF: Writing – review & editing, Resources. MG: Writing – review & editing, Validation, Supervision, Conceptualization.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We thank all pregnant women for participating in this study. We would also like to thank Miss Stela Verzinhasse Peres for helping us with various statistical aspects.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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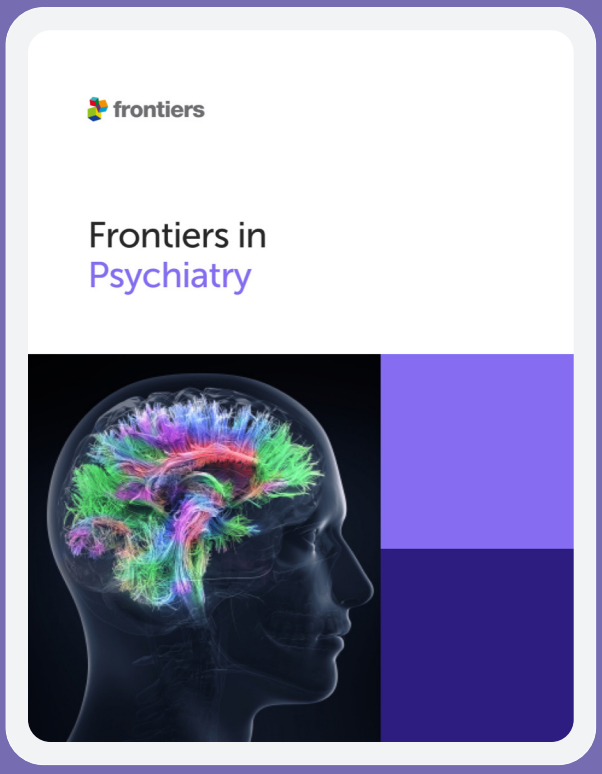

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