Original Article

Environmental risk factors, protective factors and biomarkers for postpartum depressive symptoms: an umbrella review

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Abstract (287/300 words)

Background

Numerous environmental risk factors, protective factors, and biomarkers of postpartum depressive symptoms have been investigated, but their consistency and magnitude are undetermined, limiting translational impact.

Methods

This umbrella review (PROSPERO: CRD42021230784) systematically searched PubMed/MEDLINE, Embase, and the Cochrane Database of Systematic Reviews until 12/01/2021 to include systematic reviews and meta-analyses that examined associations between environmental (i.e., not purely genetic) risk/protective factors or biomarkers and postpartum depressive symptoms occurring within 1 year after childbirth. Summary effect estimates (odds ratio [OR], relative risk [RR], and Hedges' g), corresponding 95% confidence intervals (95% CI), heterogeneity I^2 statistics, 95% prediction intervals, small study effects, p-curves, p values under 10% credibility ceiling and sensitivity analyses were meta-analytically estimated. Methodological quality was assessed using AMSTAR 2. Levels of credibility of the evidence were assessed with established criteria.

Findings

We identified 30 articles, relating to 54 unique meta-analyses of 46 environmental risk/protective factors (154594 cases, 7302273 total population) and 9 biomarkers (2018 cases, 16757 total population). Credibility of evidence of association was convincing (class I) for antenatal anxiety (OR 2.49, 95% CI 1.91-3.25) and psychological violence (OR 1.93, 95% CI 1.54-2.42); and highly suggestive (class II) for intimate partner violence experience (OR 2.86, 95% CI 2.12-3.87), intimate partner violence during pregnancy (RR 2.81, 95% CI 2.11-3.74), smoking during pregnancy (OR 2.39, 95% CI 1.78-3.2), history of premenstrual syndrome (OR 2.2, 95% CI 1.81-2.68), any type of violence experience (OR 2.04, 95% CI 1.72-2.41), primiparity compared to multiparity (RR 1.76, 95% CI 1.59-1.96), and unintended pregnancy (OR 1.53, 95% CI 1.35-.75).

Interpretation

Convincing evidence indicates that psychological violence and antenatal anxiety are robustly associated with postpartum depressive symptoms, while no associated protective factors or biomarkers were detected. Further research is needed to investigate association with postpartum depressive disorders.

Funding

None

Introduction

Postpartum depression, also known as postnatal depression, is commonly defined as a depressive episode that occurs after pregnancy. For its diagnosis, the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V) does not include a specific diagnostic category but rather a "with peripartum onset" specifier to episodes of depression, which indicates major depressive episodes during pregnancy or within 4 weeks of childbirth.[1] In the International Classification of Diseases 11 (ICD-11), postpartum depression is included in "mental or behavioral disorders associated with pregnancy, childbirth or the puerperium."[2] In the clinical and research setting, however, postpartum depression is typically defined as the presence of depressive symptoms occurring up to 3, 6 or 12 months after birth rather than the DSM or ICD definition.[3] As one of the most common complications of pregnancy, the prevalence of postpartum depression is estimated to be approximately 9.2-19.2%,[4,5] with variability largely due to different diagnostic criteria and investigated population.[6] The disorder has profound impacts on the quality and function of the mother's life,[7,8] affecting her children's behavior, cognitive development, and physical health[9,10] and can lead to potentially fatal consequences for both the mother and their children.[11,12]

Because of this high personal, clinical, and societal burden, preventive approaches have been investigated. Understanding risk and protective factors associated with this condition is a prerequisite to advance preventive care.[13] Accordingly, numerous primary studies have explored genetic and non-purely genetic (environmental) factors, as well as biomarkers that might reflect their effects, showing that postpartum depression is caused by a complex interaction of genetic predisposition and environmental factors.[14-17] Although these studies have been summarized by meta-analyses, these are typically restricted to a single factor and do not carefully examine important biases including publication or reporting bias.[18,19] Therefore, the consistency and magnitude of environmental factors or biomarkers associated with postpartum depression are undetermined. Moreover, given that majority of previous studies used questionnaires such as the Edinburgh Postnatal Depression Scale (EPDS) rather than the DSM or ICD diagnosis, it would be more accurate to note that they investigated postpartum depressive 'symptoms' rather than 'disorder.' Two umbrella reviews[20,21] (i.e., reviews of systematic reviews or meta-analyses) have summarised environmental factors for postpartum depressive symptoms without quantitative analysis and full bias assessment. That is, no umbrella reviews have summarized the overall level of evidence by applying a hierarchical system which can account for several types of biases, which is essential for umbrella reviews.[22] Moreover, some previous meta-analyses included less objective diagnostic methods such as self-report or set too liberal cutoffs for postpartum depressive symptoms, which resulted in potential false positive and exaggerated effects. The current study aimed to overcome these limitations and organize the dispersed evidence by providing the first classification of evidence for environmental risk/protective factors and biomarkers for postpartum depressive symptoms.

Methods

We performed a systematic review in compliance with updated PRISMA guideline (appendix pp 2-3).[23] This review is registered with PROSPERO, number CRD42021230784, which is available online. The screening process, data extraction, and methodological appraisal of eligible articles were conducted independently by two investigators (JHK and SL), and any disagreement was resolved through discussion between four authors (JHK, JYK, SL and JIS).

Search strategy and selection criteria

We systematically searched PubMed/MEDLINE, Embase, and the Cochrane Database of Systematic Reviews from database inception to Jan 12, 2021, without any language restrictions. Full search strategies for each database are included in the appendix. (p 5) To find eligible articles among the searched articles, each investigator screened titles, abstracts, and full texts in order. We also manually searched the references of relevant articles. (figure 1)

We included systematic reviews providing meta-analyses that examined associations between postpartum depressive symptoms and environmental risk/protective factors, or biomarkers. The definitions of environmental risk/protective factors and biomarkers are presented in the appendix p 5. Since the majority of meta-analyses used questionnaires such as EPDS rather than DSM-V or ICD-11, we investigated 'postpartum depressive symptoms' that occurred within 12 months after childbirth. We included those that used validated diagnostic methods for postpartum depressive symptoms including not only DSM, ICD, and medical records but also EPDS, Center for Epidemiologic Studies Depression (CES-D), Beck Depression Inventory (BDI), etc. (details in the appendix p 7)

We excluded articles that did not study environmental risk/protective factors, or biomarkers of postpartum depressive symptoms; articles that did not provide meta-analyses; articles that did not provide sufficient data for re-analysis of meta-analysis (i.e., individual study estimates or data to calculate them). We also excluded non-human studies, purely genetic studies, primary studies, and conference abstracts. If more than one meta-analysis covered the same topic, we prioritized the one with the largest number of individual studies, then the most recent one, and lastly, the one with the largest number of cases with postpartum depressive symptoms. The list of articles excluded in the full-text screening stage was presented in the appendix pp 8-13.

Data extraction

From each eligible meta-analysis, we extracted the following data: author names; publication year; environmental risk/protective factor, or biomarker of interest; operationalization of depressive symptoms and applied cutoff for each individual study (DSM, ICD, psychometric questionnaires rater-administered); number of cases with postpartum depressive symptoms and total study population; maximally adjusted individual study estimates and corresponding 95% confidence intervals (95% CIs); metrics used in the original analyses (e.g. odds ratio [OR], relative risk [RR], weighted mean difference [WMD]); and study designs of individual studies (e.g. cohort, cross-sectional)

Data analysis

We conducted a series of statistical tests to examine the robustness and consistency of data in accordance with

previous umbrella reviews[24-27] and recent guidance for umbrella review.[22] We re-analyzed each eligible meta-analysis based on extracted individual study estimates, using metrics used in the original meta-analysis. We calculated the summary effect estimate, corresponding 95% CI, and p values under both random and fixed effects models. We further assessed whether p values < 0·001 or 0·000001.[28,29] To evaluate heterogeneity, we performed Cochran's Q test and calculated I^2 statistic (I^2 > 50% indicates high heterogeneity).[30] We assessed the existence of small study effects (i.e., larger studies significantly have more conservative results than smaller studies) with regression asymmetry test proposed by Egger and colleagues,[31] and small study effects was claimed at Egger p value < 0·1. We estimated the 95% prediction interval, the range in which we expect the effect of association will lie for 95% of future studies.[32] We performed p-curve analysis and assessed the distribution of statistically significant p values to detect publication bias or p-hacking among the individual studies,[33,34] and we claimed a set of individual studies to have evidential value when possibility of selective reporting was ruled out (p value of the right-skewness test for the half curve < 0.05 or p value of the right-skewness test < 0.1 for both the half and full curve).[34] We also performed random effects meta-analyses under 5%, 10%, 15%, and 20% credibility ceilings to account for potential methodological limitations of observational studies that might result in spurious significance.[35,36]

We performed sensitivity analyses of the validated cutoff score for diagnosing postpartum depressive symptoms by excluding individual studies that used lower cutoffs than the validated cutoff, which may lead to false positive and exaggerated effects. The validated cutoffs we applied for each included operationalization of depressive symptoms were presented in the appendix p 7. We also conducted sensitivity analyses of cohort studies (retrospective or prospective), prospective cohort studies, and study estimates adjusted for at least one confounder to further assess the robustness of the evidence. All sensitivity analyses were performed for associations graded as convincing or highly suggestive evidence. All statistical tests were two-sided and statistical significance was claimed at p < 0.05. All statistical analyses were performed by R version 4.0.4 and its packages. Methodological quality of each eligible article was assessed using AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews 2) by two independent investigators (JHK and SL) and any disagreements were solved by discussion.[37]

Determining the credibility of evidence

Referring to the classification system of recent umbrella reviews and recent guidance for umbrella review,[24-27] we classified the identified associations to five classes by their level of credibility, based on the results of our statistical analysis – convincing (class I), highly suggestive (class II), suggestive (class III), weak (class IV), and not significant (NS). (table 1) Criteria for classifying the level of evidence used p value under random effects model, number of postpartum depressive symptoms cases, p value of the largest study, small study effects, I^2 statistic, results of p-curve analysis, 95% prediction interval, and random effects p value under a 10% credibility ceiling.

Role of the funding source

There was no funding source for this study. All authors had full access to all the study data and the corresponding authors had final responsibility for the decision to submit for publication.

Results

From database inception to Jan 12, 2021, we identified 454 articles of which only 30 were appropriate for inclusion criteria.[38-67] (figure 1) Among the 30 articles, 54 unique meta-analyses were identified (45 risk/protective factors and 9 biomarkers; tables 2-3, appendix pp 16-36).

The 45 meta-analyses of environmental risk/protective factors were based on 154594 postpartum depressive symptom cases (median 1031 per meta-analysis, interquartile range [IQR] 551-5835, range 89-17954) and 7302273 total population (median 11758 per meta-analysis, IQR 4437-77838, range 875-2302311). Among them, 34 meta-analyses were based on cohort, of which 23 also included case-control or cross-sectional studies. The median number of study estimates were 8 (IQR 5-12, range 2-39). Effect metrics were either OR or RR. Among 45 associations, 43 (96%) associations were statistically significant with $p<0.05$, 35 of 45 (78%) with $p<0.001$, and 13 of 45 (29%) with $p<0.000001$. Among 43 statistically significant associations, 25 (58%) included more than 1000 postpartum depressive symptom cases. Only 14 of 45 (31%) associations showed no heterogeneity (I^2<50%). Among 45 associations, 3 were not available for Egger's test since they were represented by less than 3 individual studies. Then, 30 of 42 (71%) associations presented no small study effects. Further, 39 of 45 (87%) associations suggested no problem in p-curve analysis, 33 of 45 (73%) retained statistical significance with a 10% credibility ceiling, and the 95% prediction interval excluded the null value in 7 of 45 (16%).

Among 45 environmental risk/protective factors, 9 were associated with high level of evidence (class I or II). Only 2 factors were graded as convincing evidence (class I; table 2, figure 2): antenatal anxiety (OR 2.49, 95% CI 1.91-3.25) and psychological violence (OR 1.93, 95% CI 1.54-2.42). 7 were graded as highly suggestive evidence (class II; table 2, figure 2): intimate partner violence experience (OR 2.86, 95% CI 2.12-3.87), intimate partner violence during pregnancy (RR 2.81, 95% CI 2.11-3.74), smoking during pregnancy (OR 2.39, 95% CI 1.78-3.2), history of premenstrual syndrome (OR 2.2, 95% CI 1.81-2.68), any type of violence experience (OR 2.04, 95% CI 1.72-2.41), primiparity compared to multiparity (RR 1.76, 95% CI 1.59-1.96), and unintended pregnancy (OR 1.53, 95% CI 1.35-.75). Remarkably, 4 of 9 (44%) factors with high level of evidence were such type of violence against mother. Other factors were also included such as preterm birth, pre-pregnancy obesity, cesarean section (class III), low income, poor social support, and poor marital relationship (class IV). Meanwhile, active husband participation in maternal healthcare/services during pregnancy and postpartum showed protective effect against postpartum depressive symptoms with statistical significance. (class IV)

The 9 meta-analyses of biomarkers were based on 2018 postpartum depressive symptom cases (median 201 per meta-analysis, IQR 200-215, range 168-404) and 16757 total population (median 1793 per meta-analysis, IQR 1741-1793, range 1432-2375). All 9 meta-analyses were based on cohort, of which 4 also included case-control or cross-sectional studies. The median number of study estimates were 5 (IQR 5-6, range 3-7). Effect metrics were either OR, RR, or Hedge's g. Among 9 associations, only 3 (33%) were statistically significant with $p<0.05$ and no association with $p<0.0001$. No association included more than 1000 postpartum depressive symptom cases, and only 3 of 9 (33%) associations showed no heterogeneity. All association were available for Egger's test and 7 of 9 (78%) presented no small study effect. However, all but one suggested problem in p-curve analysis, and no association retained statistical significance with a 10% credibility ceiling and exclude the null value in the 95% prediction interval. Accordingly, no association was graded as convincing or highly suggestive evidence, but weak or non-significant.

Quality assessment

AMSTAR 2 quality assessment was available for all associations. Among 30 articles, 26 reported environmental risk/protective factors and 4 biomarkers. Of 26 meta-analysis articles of environmental risk/protective factors, only 3 (11%) were graded as high quality, 2 (8%) moderate, 7 (27%) low, and 14 (54%) critically low. Of 4 meta-analysis articles of biomarkers, 1 (25%) was graded as low, and 3 (75%) critically low. Among factors with high level of evidence, only 2 (intimate partner violence experience and history of premenstrual syndrome) were graded as high quality.

Sensitivity analyses

Sensitivity analyses of validated cutoff score for meta-analyses with high level of evidence (class I or II) were conducted. After excluding individual studies that used lower cutoff than validated one, 7 of 9 (78%) factors retained their level of evidence: antenatal anxiety (class I), intimate partner violence experience, intimate partner violence during pregnancy, smoking during pregnancy, history of premenstrual syndrome, any type of violence experience, and unintended pregnancy (class II), whereas the rest were downgraded to class III or IV.

Sensitivity analyses of 1) cohort (retrospective and prospective), 2) prospective cohort, and 3) adjusted study estimates for meta-analyses with high level of evidence (class I or II) were also conducted. In the cohort sensitivity analyses, 5 factors retained their level of evidence: antenatal anxiety, psychologic violence (class I), any type of violence experience, primiparity compared to multiparity, and unintended pregnancy (class II), whereas the rest were downgraded to class III or IV, or inappropriate for subgroup analysis since they included fewer than 2 cohort studies. In the prospective cohort subgroup analysis, the same factors retained the level of evidence except for antenatal anxiety (class I to III). In the sensitivity analyses of adjusted study estimates, which was unavailable for one (intimate partner violence experience), 5 of 8 (63%) factors graded as class II: psychologic violence, intimate partner violence during pregnancy, any type of violence experience, primiparity compared to multiparity, and unintended pregnancy, while whereas the rest were downgraded to class III or IV. All statistical details of sensitivity analyses were presented in the appendix pp 14-15.

Discussion

To the best of our knowledge, this study is the first umbrella review based on a state-of-the-art evidence grading strategy, which systematically and quantitatively collected and assessed the hierarchy of evidence for environmental risk/protective factors and biomarkers for postpartum depressive symptoms. Only 9 associations of environmental risk factors showed evidence of high credibility (antenatal anxiety, psychological violence [class I], intimate partner violence experience, intimate partner violence during pregnancy, smoking during pregnancy, history of premenstrual syndrome, any type of violence experience, primiparity compared to multiparity, and unintended pregnancy [class II]).

Various types of violence against the mother (psychological violence [class I]; intimate partner violence experience, intimate partner violence during pregnancy, and any type of violence experience [class II]) were associated with a higher risk of postpartum depressive symptoms. Of note, psychological violence was downgraded to class III in the sensitivity analysis of validated cutoff score, while others not. Though the underlying mechanism is unclear, given that violence against the mother is a type of stress, stress-related neuroendocrine dysfunction and gene-stress interaction are the most plausible explanations. The former suggests unbalanced secretion of glucocorticoids, the final product of hypothalamic-pituitary-adrenal (HPA) axis which is activated by stress response, may affect psychological function, leading to depression.[68,69] The latter proposes that reduced activity of brain-derived neurotropic factors by stress events may lead to diminished function of brain regions, including those involved in emotional processing and cognition, and subsequent changes in mood and depression eventually.[70-72] Of note, the majority of factors related to violence against mother including not only class I or II but also others, have effects sizes larger than 2. In this regard, violence experience of the mother may be robust predictors of postpartum depressive symptoms despite a large heterogeneity. These findings emphasize the necessity of screening for domestic and intimate partner violence and mindful care to promote maternal mental health.

Antenatal anxiety[49] showed convincing evidence for increased risk of postpartum depressive symptoms with the effect size larger than 2 (OR 2.64, 95% CI 2.02-3.46), retaining convincing evidence in sensitivity analysis of validated cutoff score. What requires attention is the factor is simply anxiety, which represents the symptoms rather than the disorder. Indeed, individual studies in the meta-analysis include not only those that used the diagnostic criteria of anxiety disorder, but also those that used questionnaires for anxiety and cut-off systems (e.g. state trait anxiety inventory-trait score > 45). Of note, the latter ones distinguished excessively anxious mothers from those experience anxiety in a normal range by setting certain cut-off scores such as mean plus one standard deviation or top 25th percentile. Meanwhile, regarding the association between anxiety disorder and postpartum depressive symptoms, antenatal social phobia[73], generalized anxiety disorder[73], and panic disorder[74] are also suggested to be independent risk factors for postpartum depressive symptoms respectively. Although robust biological mechanism is not yet suggested, considering that 1) no biases were detected in our analyses even though individual studies seemed to be quite heterogeneous in various aspects, 2) anxiety symptoms are frequently reported in pregnancy and even considered normal experience of pregnancy often, and 3) problematic anxiety symptoms in pregnancy were not well distinguished from normal anxiety, the anxiety symptoms of mothers should not be loosely considered to be a normal adaptive course of pregnancy.

Smoking during pregnancy[43] was associated with an increased risk of postpartum depressive symptoms with highly suggestive evidence, retaining the level of evidence in sensitivity analysis of validated cutoff score while downgraded to weak in other sensitivity analyses. In regard to its biological mechanisms, anti-estrogenic effect of smoking by disrupting endogenous estrogen biosynthesis and bioavailability was proposed[75,76] given that women are prone to mood fluctuation during the period when hormone levels(especially sex steroid hormone such as estrogen and progesterone) change rapidly.[77] HPA axis activation due to immune system alteration,[78-80] increased oxidative stress,[81,82] and nicotine acetylcholine receptors[83] induced by smoking are other potential mechanisms. Meanwhile, numerous investigations have been conducted regarding the various patterns of smoking cessation and risk of postpartum depression. Salimi et al.[84] reported odds of postpartum depressive symptoms in women who quit smoking during the last 3 months of pregnancy but resumed after parturition (OR 1.28, 1.06-1.53) and who did not quit at all (OR 1.48, 1.26-1.73) compared to who quit during the last 3 months of pregnancy and remained after parturition. Although accepting a less rigorous definition of postpartum depression, this finding demonstrated that smoking cessation is important not only before or during pregnancy but also in the postpartum period for the prevention of postpartum depressive symptoms. In addition, passive smoking should be avoided as well.[85] Of note, potential confounders of association should be accounted such as prenatal stressful events which may be associated with both smoking and postpartum depressive symptoms.[57,86]

History of premenstrual syndrome[42] was associated with an increased risk of postpartum depressive symptoms with highly suggestive evidence, retaining the level of evidence in sensitivity analysis of validated cutoff score while downgraded to weak in other sensitivity analyses. This association ought to be noted because premenstrual syndrome represents high prevalence of around 70%.[87] Regarding its underlying mechanisms, increased sensitivity to hormonal fluctuation was suggested to be the most plausible one.[88,89] Two reproductive steroid hormones, estrogen and progesterone, were considered to have a major role.[88,90] The levels of both hormones increase before the luteal phase and during pregnancy, but rapidly decreases in the luteal phase and after parturition, and this kind of fluctuation contributes to the development of premenstrual syndrome and postpartum depressive symptoms respectively, in those vulnerable to it.[91,92] The point is that the hormonal fluctuation itself in patients with premenstrual syndrome or postpartum depressive symptoms is not the matter as they demonstrated to have a normal hormone level, that is, the problem is patients' vulnerability to hormonal fluctuation.[93] Although may not be applied to late-onset postpartum depressive symptoms since the level of hormones recover steady state, this explanation seems to be most persuasive given that depression of women from puberty to menopause is more prevalent than men in same age, but this is reversed in childhood or after menopause.[94-96] Meanwhile, other mechanisms were also proposed such as inadequate vitamin D status[62,97] and cytokine effects.[90]

Primiparity[60] is associated with a higher risk of postpartum depressive symptoms compared to multiparity with highly suggestive evidence, which was confirmed in all subgroup analyses except validated cutoff score analysis. Notably, it seems to more plausible to explain the association as postpartum depressive symptoms were related to behavioral tendency of multiparity distinguished from primiparity or subsequent events associated with the first pregnancy, rather than primiparity itself. Indeed, some reasons were suggested why postpartum depressive symptoms is more prevalent in primiparas than multiparas. First, multiparas may be more experienced in adapting stress or other adversities accompanied by pregnancy and parturition. Second, given that history of postpartum

depression may be another risk factor of postpartum depressive symptoms despite its low level of evidence (class IV),[47] those who have experienced postpartum depression would endeavor not to repeat such tragedy by receiving psychological education, taking preventive measures against depression, or being reluctant to conceive again. Third, primiparous women are at an increased risk of having anxiety, sexual problems, and others, which may eventually lead to postpartum depressive symptoms.[98] Although the abovementioned factors may not fully account for the issue and some more unidentified factors may exist, this association have a major implication for healthcare professionals or national health care plan to pay more attention to mothers who got pregnant for the first time.

Unintended pregnancy[58] showed highly suggestive evidence in higher risk of postpartum depressive symptoms, which was confirmed in all sensitivity analyses. This may be explained in the regard that women who conceive unintentionally seem to experience psychosocial stress due to concerns after pregnancy such as interruptions in educational, career, or other life aspirations.[99,100] Stress-related neuroendocrine dysfunction and gene-stress interaction were the two most plausible biological mechanisms that underlie the association between unintended pregnancy and postpartum depressive symptoms. The detailed explanation of these suggested mechanisms was already presented in the above. (see second paragraph in discussion) Further, other behavioral mechanisms were also suggested. First, mothers conceive without intention tend to start late and seldom complete prenatal care, which can be detrimental to maternal mental health.[101] Second, a pregnancy that is unexpected and thus unplanned may lead to adjustment stress in the mother, leading to concerns about maternal and fetal health and even conflicts regarding maintaining versus terminating the pregnancy.[99] Third, mothers with unintended pregnancies tend to smoke more and take fewer vitamins than those who have planned pregnancies[101], which plausibly explains their higher risk of postpartum depressive symptoms given that smoking[43] and lack of vitamin D supplementation[102] were significantly associated with postpartum depressive symptoms.

The present study has some limitations. First, as all meta-analyses were based on observational studies, the associations here reported do not necessarily imply causality. We could not exclude potential confounders and caution is required in interpreting the findings. Second, most of the identified associations showed large heterogeneity. This may be due to the unstandardized operationalizations and various cutoff point for postpartum depression. Our sensitivity analyses confirmed that psychological violence and primiparity compared to multiparity no longer presented a strong association with postpartum depressive symptoms when excluding studies that used invalidated cutoff score. Operationalization of environmental factors was also inconsistent across several studies and some of them required temporal or contextual specifiers or be influenced by changes in the contextual environment (e.g., cumulative exposure to potentially traumatic experiences). The lack of standardized assessment measures to reliably record environmental exposures may prevent their usability in research and clinical settings. Accordingly, a significant advancement of knowledge would likely be reached by global collaborative harmonization efforts to standardize the multimodal (e.g. psychopathological, neurobiological, neurocognitive) measurement of these exposures.[13] Third, there is no assumption that the identified factors are independent. Fourth, we could only address the associations which were available synthesized by meta-analysis; that is, we may have inevitably missed some environmental factors or biomarkers.

Despites these limitations, our umbrella review identified convincing evidence indicating that antenatal anxiety and psychological violence are robustly associated with postpartum depressive symptoms, while no protective

factors or biomarkers showed robust evidence. Since these associations cannot imply causality, further well-designed primary studies with ICD/DSM-established operationalization of postpartum depression are needed to confirm these findings.

Declaration of interests

We declare no competing interests in relation to the current manuscript.

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None.

Contribution

JHK, JYK, SL, and JIS designed the study. JHK, JYK, SL, and JIS did the literature search and screening, extracted, analysed, and interpreted the data, and made the figures and tables. All authors drafted and critically revised the manuscript. All authors gave approval to the final version of the manuscript for publication. All authors approved the final version of the manuscript for publication.

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