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The Association between Vitamin D Deficiency and Perinatal Depression: A Systematic Review and Meta-Analysis

ABSTRACT

Objective: To conduct a meta-analysis on the connection between vitamin D deficiency and perinatal depression.

Methods: A comprehensive literature search was conducted across several databases, including PubMed, Web of Science, Embase, Cochrane Library, China National Knowledge Infrastructure, and VIP database. Two reviewers independently assessed the risk of bias in articles using the Cochrane collaboration's tool, with analysis performed via RevMan software.

Results: After reviewing major databases, 13 studies were included. Three studies assessed prenatal depression and vitamin D levels, showing significantly lower levels in the depression group compared to controls (Standardized Mean Difference [SMD] = −0.41, 95% Confidence Interval [CI] −0.57 to −0.25) with minimal heterogeneity, thus a fixed effects model was used. Another three studies explored postpartum depression and vitamin D, revealing considerable heterogeneity (I^2 = 96%, P < .01), leading to the use of a random effects model; these indicated much lower vitamin D levels in the depression group (SMD = −1.62, 95% CI −2.62 to −0.62). Seven studies examined the link between postpartum depression and vitamin D deficiency, again showing significant heterogeneity (I^2 = 92%, P < .01) and lower vitamin D levels in depressed women (SMD [Standardized Mean Difference] = 2.28, 95% CI 1.60-3.25), with no significant publication bias detected.

Conclusion: Reduced vitamin D levels are significantly associated with the incidence of perinatal depression. Pregnant women with reduced vitamin D levels have a relatively higher risk of depression. This signifies that vitamin D levels may figure prominently in maintaining maternal mental health.

Keywords: Vitamin D deficiency, perinatal period, depression, meta-analysis

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Introduction

Prenatal depression is a new type of psychological disorder in pregnant women that has emerged in recent years. Due to physiological and psychological changes after pregnancy, such as changes in estrogen levels and pregnancy reactions, some pregnant women have unreasonable expectations for life. When their inner needs are not met, various negative emotions are generated. If these emotions are not well-regulated, they can eventually develop into prenatal depression. Postpartum depression is a familiar psychological obstacle that influences approximately 10%-15% of new mothers. The global average incidence rate of postpartum depression is about 12%, and the incidence rate of developed countries is lower than that of developing countries. There are regional differences in the incidence of postpartum depression in China.[1] According to the meta-analysis, the incidence rate is about 10.7%. Postpartum depression not only takes a serious toll on the body and mental health of postpartum female, but may also affect the relationship between mother and baby, infant and child development, and family harmony in the end.[2] Women with postpartum depression bear greater psychological pressure, are more prone to anxiety, and have a serious bearing on

their quality of life.[3] To that end, studying the pathogenesis of postpartum depression and finding effective prevention and treatment methods have important clinical significance and social value. In this day and age, research has revealed that the deficiency of vitamin D is inextricably with the germination and development of postpartum depression.[4] Vitamin D is a fat-soluble vitamin with multiple biological activities, which not only participates in calcium and phosphorus metabolism but also has regulatory effects on the nervous system, immune system, and other systems. Vitamin D deficiency might give rise to a series of physiological and psychological problems, such as neurotransmitter imbalance and intensified inflammatory response, thereby increasing the risk of depression.[5] Numerous surveys have shown[6,7] that vitamin D is linked to prenatal and postpartum depression. As one of the dietary factors affecting depression during pregnancy, some investigations have revealed[8] that vitamin D makes a salutary difference in alleviating depression. The academic community has proposed several possible mechanisms for this: vitamin D as a hormone that can stimulate nerve tissue. A study has found that there are a large number of vitamin D receptors in the human brain, and when these receptors are insufficient, they can alter some neurotransmitters related to depressive behavior.[9] Vitamin D can regulate neuronal calcium levels, which are linked with the onset of depression. When the concentration of vitamin D is low, the concentration of calcium ions will increase, and then exacerbating depression. Vitamin D also has a bearing on neuroimmune regulation and neural plasticity, both of which are related to human emotions. Although surveys have signified a certain connection between vitamin D deficiency and postpartum depression, there is still several controversy in the existing research results. One study suggests that current evidence was insufficient to determine the role of vitamin D in perinatal depression.[10] Therefore, a comprehensive and quantitative evaluation of existing research is conducted through meta-analysis in order to draw more reliable conclusions and provide a scientific basis for clinical practice and policy formulation. The correlation between vitamin D levels and postpartum depression has been a hot topic in recent years. However, the specific mechanism is not yet fully understood and further research is needed to explore. However, the specific dose–response relationship is not yet clear, and further research is needed to confirm it. In this study, we used meta-analysis to systematically evaluate relevant studies and explore the correlation between vitamin D levels and postpartum depression. This method can improve the reliability and accuracy of research results, providing strong evidence support for clinical doctors and policymakers. The following chapters will provide a detailed introduction to the literature search, research methods, results, and discussions.

MAIN POINTS

- *The association mechanism between vitamin D deficiency and perinatal depression: Vitamin D, as a neuroactive substance, can affect depressive symptoms through the following pathways: (1) regulating neurotransmitter balance; (2) affecting the expression of nerve growth factors; (3) participating in immune regulation; (4) improving oxidative stress.*
- *Novel insights: This article finds that the association between vitamin D deficiency and perinatal depression has a dose effect, meaning that the lower the vitamin D level, the more severe the depressive symptoms. In addition, supplementing with vitamin D has potential value in preventing and treating perinatal depression.*
- *Clinical significance: For pregnant women and postpartum women with vitamin D deficiency, it is recommended to engage in moderate outdoor activities, increase vitamin D intake, and supplement treatment if necessary. This will help reduce the incidence rate of perinatal depression and improve maternal and infant health.*

Material and Methods

Database and Search Strategy

For the sake of comprehending the correlation from multiple perspectives as a whole between vitamin D deficiency and postpartum depression, this survey conducted an extensive search on multiple databases. Use relevant keywords to search on PubMed (Using MeSH topic keyword search and free word search), Embase (Topic search), China National Knowledge Infrastructure (CNKI), and Wanfang (Search for keywords, free words, and keywords+free words) databases. The search strategy followed a mixture of subject words and free words to ensure the breadth of research objects. Covers relevant research from the establishment of the database to 2023. The English search terms were ("Vitamin D" OR "Vitamin D2" OR "Vitamin D3" OR "Cholecalciferol" OR "Ergocalciferol" OR "25-hydroxyvitamin D" OR "1,25-dihydroxyvitamin D" OR "Calcitriol" OR "Anti Rickets Vitamin" OR "Dietary Supplements" OR "Sunlight Exposure" OR "Vitamin D Deficiency" OR "Vitamin D Insufficiency" OR "Hypovitaminosis D") AND ("Postpartum Depression" OR "Postpartum Mood Disorder" OR "Postnatal Depression" OR "Perinatal Depression" OR "Antenatal Depression" OR "Maternal Depression" OR "Prenatal Depression" OR "Postpartum Mood" OR "Perinatal Mood" OR "Antenatal Mood" OR "Maternal Mood" OR "Prenatal Mood.") Finally, the results of the Chinese and English searches will be imported into the literature management software EndNote version X7 (Clarivate Analytics, Philadelphia, Pennsylvania, USA).

(("Vitamin D" OR "Cholecalciferol" OR "Anti Rickets Vitamin" OR "Ergocalciferol" OR "Dietary Supplements" OR "Vitamin D Deficiency" OR "Vitamin D Insufficiency" OR "Hypovitaminosis D") AND ("Postpartum Depression" OR "Anxiety Disorder" OR "Postpartum Depression Status" OR "Postpartum Anxiety" OR "Perinatal Depression" OR "Antenatal Depression" OR "Maternal Depression" OR "Prenatal Depression")).

Literature Screening Criteria

This study adopted strict literature screening criteria to ensure the quality of the included studies. The inclusion criteria mainly include: (1) research types: cohort studies, case–control studies, cross-sectional studies, etc.; (2) research subject: it was found that perinatal women aged 23-40 suffer from depression within 1 year after pregnancy and postpartum, with a duration of more than 2 weeks; regardless of race, age, or country; (3) research content: exploring vitamin D deficiency. The relationship between syndrome and postpartum depression; and (4) document language: Chinese or English. The exclusion criteria mainly include: (1) duplicate publications or studies with incomplete data; (2) using non-raw data for research; (3) review, case reports, meeting documents, etc.; (4) the study includes patients with severe physical illnesses, women who have previously suffered from mental illness and drug, drug, and/or alcohol abuse or suicidal tendencies; and (5) this survey includes women with adverse neonatal outcomes, 5-minute Apgar score <5, assisted ventilation for more than 6 hours, neonatal seizures, birth trauma, neonatal death, and other conditions.

Literature Screening

The 2 authors screened the retrieved articles according to unified screening criteria. The headline, abstract, duplicates, and text of each retrieved article were checked. The screening outcomes of the 2 researchers were contrasted, and the ultimate inclusion was decided through discussion. When consensus could not be reached, there will be a third experienced author will be asked to make the last decision. All the information collected for each document included was as follows: year of publication, author name, number of subjects, age of subjects, duration of treatment, baseline Hamilton Depression Rating Scale (HAMD), intervention in the test and control groups, and outcome measures.

Quality Assessment

Documents' quality was assessed by 2 scholars independently with the Newcastle–Ottawa Scale (NOS), which is separated into 2 evaluation criteria: cohort surveys and case–control surveys, and risk of bias was assessed on the basis of the kind of the original research of the naiad, comprising population option, comparability, and assessment of the outcomes. ≥6 was set as high-quality surveys, and <6 was set as low-quality surveys.

Statistical Methods

Statistical analysis was conducted using Review Manager 5.3 (The Cochrane Collaboration, London, United Kingdom) and Stata12.0 software (StataCorp LLC, College Station, USA). Quantitative data uses weighted mean difference (WMD) as the effect indicator, while qualitative data uses odds ratio (OR) value as the effect indicator. Point estimates and 95% CI are given for each effect size. Q-test is used to determine whether there is heterogeneity in the literature, and I is used to quantify the size of heterogeneity. When $P \leq .100$ and $I^2 > 50.00\%$, heterogeneity is considered to exist, and a random effects model is used for data consolidation; When $P > .100$ and $I^2 \leq 50.00\%$, it is considered that there is no heterogeneity, and a fixed effects model is used for data consolidation. Heterogeneity sources were analyzed using subgroups, stability of outcome measures was evaluated using sensitivity analysis, and publication bias was evaluated using Begg's and Egger's tests. Inspection level $\alpha = 0.05$.

Results

Literature Inclusion Process

Four hundred twenty-five articles in total were included after consulting major databases, and 215 articles remained after eliminating duplicate articles. After browsing the headlines and abstracts, there are 215 articles in total remained after preliminary screening. After browsing the full text and re-screening, 42 articles were included, and 13 articles were included in the last place. The documents inclusion process is shown in Figure 1.

Basic Information on Included Literature

Thirteen documents in total were comprised in this survey, ranging from 2012 to 2020. A total of 7 documents used the cohort study type, and 6 documents used the case–control study type. Among them, 5 documents had an NOS score of 6. The NOS score of 3 documents is 7 points. See Table 1 below for details.

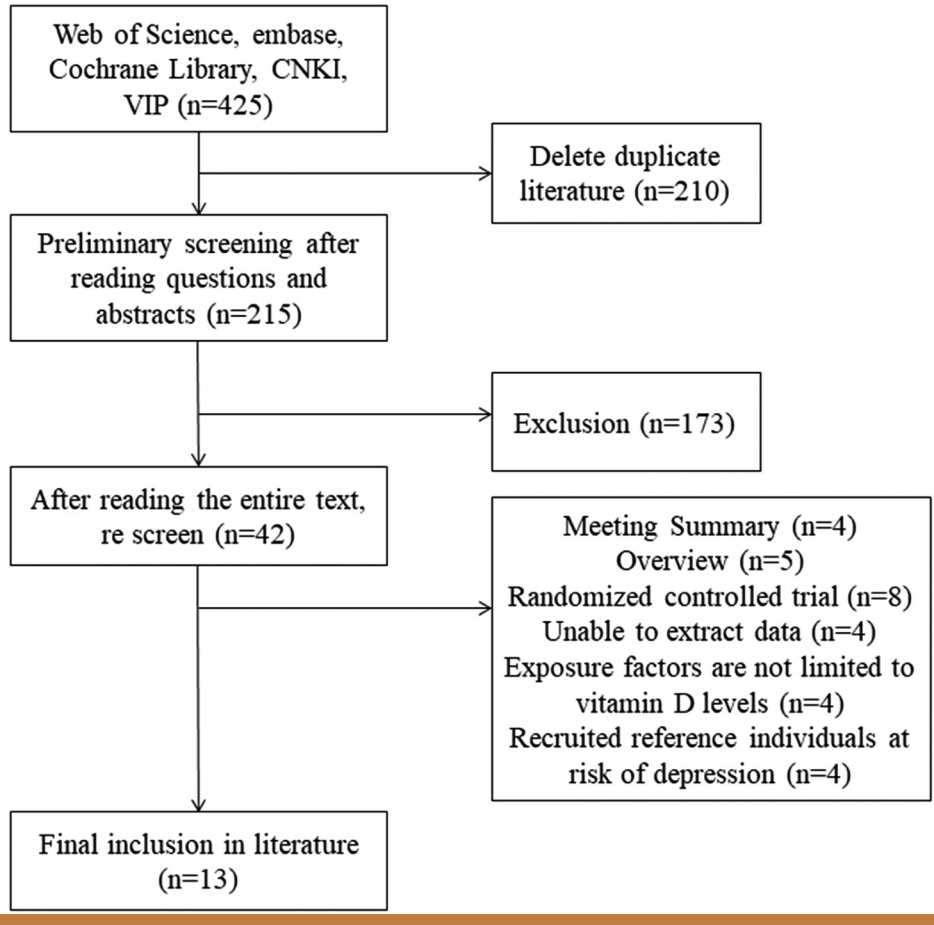

Figure 1. Documents inclusion process.

Table 1. General Information Included in the Literature

Authors	Years	Nation	Type of Study	Number of Examples	Depression Diagnosis	Vitamin D Deficiency Value	Vitamin D Measurement Method	Outcome Indicators	NOS Score
Brandenbarg et al[11]	2012	Netherlands	Array research	1133/2968[a]	CES-D ≥ 16	50 nmol/L	ELISA	Antenatal depression	7
Cassidy-Bushrow et al.[12]	2012	USA	Case–control study	74/104[a]	CES-D ≥ 16	50 nmol/L	CLIA	Antenatal depression	6
Cunha Figueiredo et al[13]	2017	Brazil	Array research	36/143[a]	EPDS ≥ 13		LC-MS	Antenatal depression	7
Abedi et al[14]	2018	Iran	Case–control study	60/60[b]	BDI ≥ 11	75 nmol/L	ELISA	Antenatal depression	8
Du et al[15]	2019	China	Case–control study	60/120[b]	HAMD > 17		HPLC-MS	Antenatal depression	6
Liu[16]	2020	China	Case–control study	200/200[b]	EPDS > 13		CL	Antenatal depression	7
Fu et al[17]	2015	China	Array research	29/184[b]	EPDS ≥ 12	25.5 nmol/L		Antenatal depression	8
Gould et al[18]	2015	Australia	Array research	97/940[b]	EPDS > 12	50 nmol/L	LC-MS	Antenatal depression	8
Gur et al[19]	2014	Türkiye	Array research	41/154[b]	EPDS ≥ 12	50 nmol/L	ELISA	Antenatal depression	8
Nielsen et al[20]	2013	Denmark	Case–control study	598/875[b]	Taking antidepressant medications	50 nmol/L	LC-MS	Antenatal depression	8
Pillai et al[21]	2020	India	Case–control study	330/330[b]	EPDS ≥ 10	75 nmol/L	ELISA	Antenatal depression	6
Robinson et al[22]	2014	Australia	Array research	162/554[b]	EPDS ≥ 6	50 nmol/L	LC-MS	Antenatal depression	6
Murphy et al[23]	2010	USA	Array research	56/41[c]	EPDS ≥ 9	80 nmol/L	RIA	Antenatal depression score	6

Data from cohort research have been converted to case–control data.
BDI, Beck Depression Inventory; CES-D, Center for Epidemiologic Studies Depression Scale; CL, chemiluminescence; CL, chemiluminescent assay; CLIA, chemiluminescent immunoassay; ELISA, enzyme-linked immunosorbent assay; EPDS, Edinburgh Postnatal Depression Scale; HAMD, Hamilton Depression Scale; HPLC-MS, high performance liquid chromatography–mass spectrometry; LC–MS, liquid chromatography–mass spectrometry; NOS, Newcastle–Ottawa Scale; RIA, radioimmunoassay.
[a]Indicates antenatal depression group/control group.
[b]Postpartum depression group/control group.
[c]Lower vitamin level group/higher vitamin level group.

Meta-Analysis

The Connection between Antenatal Depression and Vitamin D Levels: Three articles in total were included, which evaluated the connection between antenatal depression and vitamin D levels. No heterogeneity between surveys was detected ($I^2 = 30\%$, $P = .36$); therefore, a fixed-effects model was opted. The vitamin D level of pregnant females in the antepartum depression group was sharply lower than the control group (Standardized Mean Difference [SMD] = −0.41, 95% CI −0.57 to −0.25). See Figure 2 below.

The Connection between Postpartum Depression and Vitamin D Levels: Three articles in total were included, which evaluated the connection between postpartum depression and vitamin D levels. Heterogeneity between studies was detected ($I^2 = 96\%$, $P < .01$); therefore, a random effects model was used. The vitamin D level of pregnant females in the postpartum depression group was sharply lower than that in the control group (SMD = −1.62, 95% CI −2.62 to −0.62). See Figure 3 below.

The Relationship between Postpartum Depression and Vitamin D Deficiency: A total of 7 articles were included, which evaluated the connection between postpartum depression and the amount of people with vitamin D deficiency. Heterogeneity between surveys was detected ($I^2 = 92\%$, $P < .01$), on this account a random effects model was opted. The overall summary analysis indicated that the vitamin D level of pregnant women in the postpartum depression group was sharply lower than the control group (SMD = 2.28, 95% CI 1.60-3.25). See Figure 4 below.

Sensitivity Analysis

After re-running the meta-analysis after excluding individual studies one by one, none of the studies showed significant changes and were generally stable and reliable. Meta-analysis comparing the difference in vitamin D levels of the antenatal depression group and the control group after excluding the Brandenbarg[11] study revealed a decrease in heterogeneity ($I^2 = 16.2\%$, $P = .359$), and still discovered a link of serum vitamin D levels and antenatal depression (WMD = −4.64, 95% CI: −7.12 to −2.15, $P < .001$). Meta-analysis comparing the discrepancy in vitamin D levels between the postpartum depression group and the control group found a slight decrease in heterogeneity after excluding the Abedi et al[14] study ($I^2 = 78.00\%$, $P = .011$), and the conclusions were unchanged. Meta-analysis comparing the discrepancy in the amount of vitamin D deficiencies between the postpartum depression group and the control group found a significant decrease in heterogeneity after excluding the Pillai et al[21] study ($I^2 = 24.80\%$, $P = .256$), conclusions unchanged.

Assessment of Publication Bias

According to Begg's test results, the *P* values were .734, >.999, >.999, respectively, The results of Egger's test showed *P* values of .600, .938, and .354, respectively, indicating that there was no significant publication bias in all studies. See Table 2.

Discussion

Maternal mental health issues have attracted widespread attention, with depression being one of the most common mental illnesses. Maternal depression is a common psychological problem during pregnancy and postpartum, affecting about 10%-15% of pregnant women.[24] Depression during pregnancy may lead to adverse

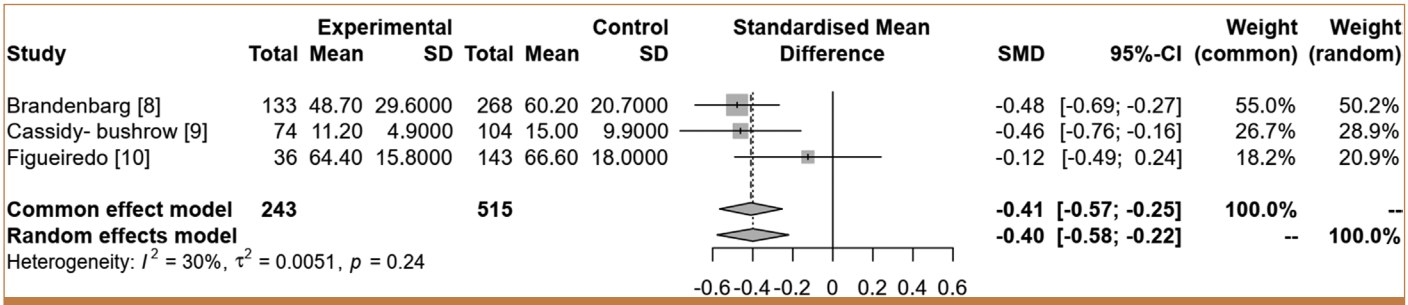

Figure 2. Meta-analysis of the connection between prenatal depression and vitamin D levels. SD, Standard Deviation; SMD, Standardized Mean Difference; CI, Confidence Interval.

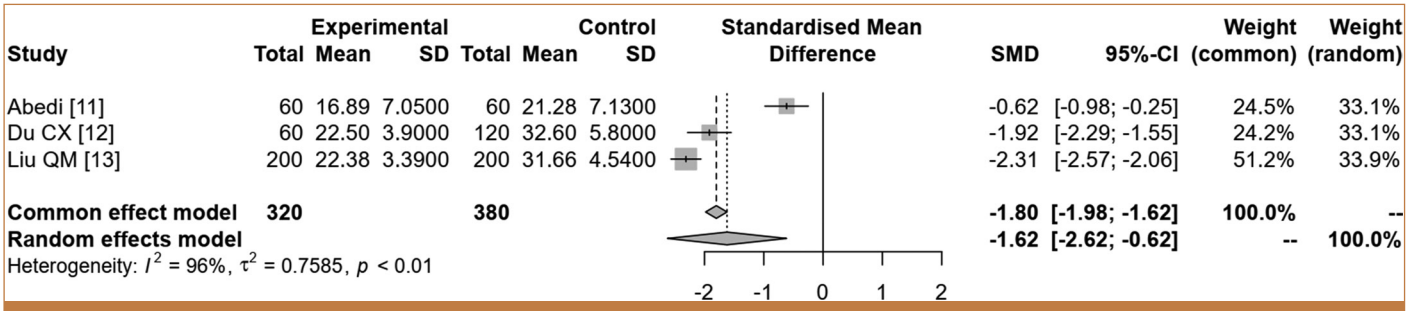

Figure 3. Meta-analysis of the connection between prenatal depression and vitamin D levels.

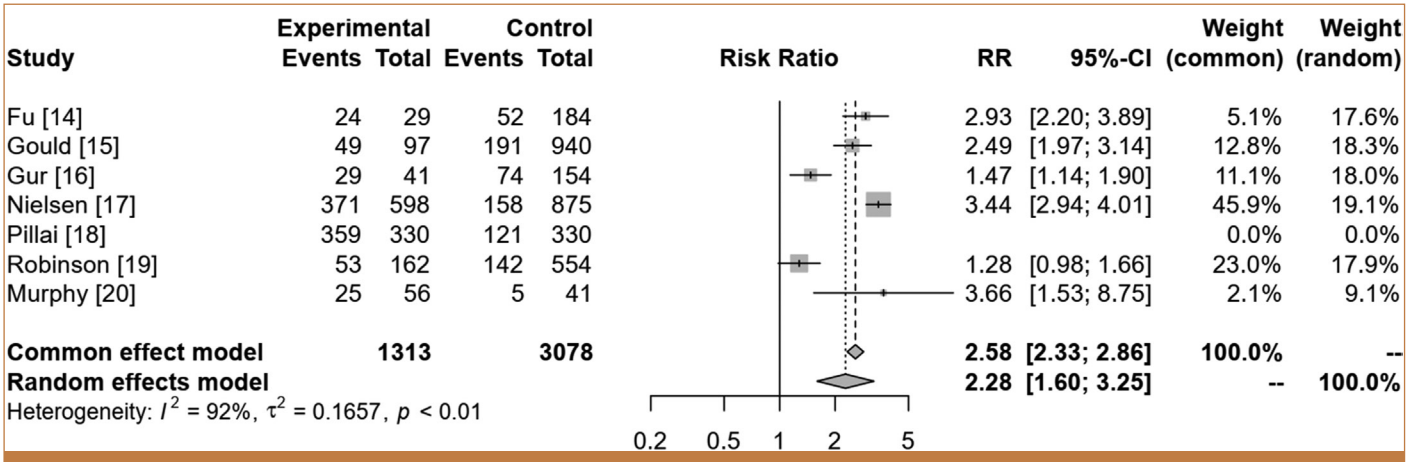

Figure 4. Meta-analysis of the relationship between postpartum depression and vitamin D deficiency.

outcomes such as poor fetal development and premature birth; postpartum depression will affect the mother–infant relationship, parenting ability, and family harmony. Therefore, it is of great significance to pay attention to maternal mental health. Vitamin D, as an important nutrient, makes a significant difference in maintaining human physiological functions and mental health. These years, mounting research have focused on the correlation between vitamin D levels and maternal depression.[25,26] Based on the above

Table 2. Subgroup Analysis of Publication bias in the Relationship between Postpartum Depression and Vitamin D Levels

	Number of Documents	Begg's Test _		Egger's Test _	
Research Content		*Z*	*P*	*Z*	*P*
Antenatal depression	4				
Prenatal depression / VD levels in control group	4	0.34	.734	0.62	.600
Postpartum depression					
Postpartum depression / VD levels in control group	6	–0.34	> .999	0.09	.938
With postpartum depression/ VD deficiency in the control group	2	< 0.01	> .999	1.05	.354

VD, Vitamin D.

background, this study systematically evaluates the connection between vitamin D levels and maternal depression and provides scientific basis for the application of vitamin D intervention measures in clinical practice. In addition, this study will also explore the role of vitamin D receptor gene polymorphisms and vitamin D metabolites in the connection between vitamin D and maternal depression, with the aim of providing new ideas for revealing the pathogenesis of maternal depression.

In this study, by meta-analysis, vitamin D levels were lower in both prenatal and postpartum depression groups than in the control group, and the risk of vitamin D deficiency was also higher in the postpartum depression group than in the control group, suggesting that statistically obvious correlation has been found between vitamin D levels and maternal depression and that lower levels of vitamin D are prone to ascend the risk of developing prenatal and postpartum depression. The setting of the vitamin D deficiency cut-off value in the subgroup analyses may have contributed to the heterogeneity of the Meta-analysis comparing the difference in the amount of people with vitamin D deficiency in the postpartum depression group and the control group, and the lack of information on the number of births, age at delivery, and mode of delivery in most of the studies may also have contributed to the heterogeneity of the results. The inclusion of maternal blood samples in the literature consisting of serum and cord blood and the lack of a transformed relationship between the two in the available studies may have brought about a bias in the vitamin D levels collected.[27] Continued surveys on the mechanism of vitamin D and maternal depression, as well as larger population-based epidemiologic surveys, are supposed to go further to characterize the correlation of serum vitamin D levels and maternal depression, and to provide a stronger basis for the prevention and remedy of maternal depression.

As a fat-soluble vitamin, duplica vitamin D maintains bone health mainly by promoting the absorption and utilization of calcium and phosphorus. However, these years, surveys have found that vitamin D also has various physiological functions such as regulating neurotransmitters, the immune system, and inflammatory response.[28] Vitamin D deficiency may lead to chronic diseases like bone disease, cardiovascular disease, and diabetes, and is also closely related to a variety of psychological diseases, such as depression and anxiety.[29] When the skin is exposed to the sun, the body will get vitamin D, while the vitamin D obtained from food sources is relatively small. Vitamin D is synthesized from the food or skin and then hydroxylated to 25-hydroxyvitamin D (25OHD), the predominant circulating form of vitamin D and the most fabulous index of vitamin D status.[30] With the aim of being fully activated, 25OHD undergoes through a second hydroxylation to 1,25-dihydroxyvitamin D. This active form is a nuclear steroid that binds to vitamin D receptors found in many tissues and plays a role in neurological function provides a biological possibility.[31] The original suggestion that vitamin D makes a difference in mood barriers came from seasonal affective disorder, a mood disorder characterized by depression during the winter when synthesis of vitamin D is low in the winter sun.[32] Research has also shown[33] that low levels of vitamin D are a risk element for postpartum depression. Not only low serum vitamin D during pregnancy is linked to postpartum depression, but low serum vitamin D levels 24-48 hours after delivery are also a risk element for postpartum depression, and serum vitamin D levels are also a risk element for postpartum depression.[34] Vitamin D levels <10.2 ng/mL are the cutoff values for predicting postpartum depression. However, those who were given 400 U of vitamin D every day and increased exposure to sunlight 2 weeks before delivery had lower depression scores in the observation group compared with pregnant women who did not receive any intervention.[35] That is, vitamin D supplementation can decline the incidence of postpartum depression.

Conclusion

In conclusion, lower vitamin D levels were significantly connected with the incidence of perinatal depression, and the risk of maternal depression was relatively higher in sufferers with lower vitamin D levels. This suggests that vitamin D levels may also make a pivotal difference in maintaining maternal mental health.

Data Availability Statement: *The datasets for this study are available from the corresponding author on reasonable request.*

Ethics Committee Approval: *N/A.*

Informed Consent: *N/A.*

Peer-review: *Externally peer-reviewed.*

Author Contributions: *Concept – Y.Y., L.Q., P.H.; Design – Y.Y., L.Q., X.Z.; Supervision – Q.S., P.H., X.Z.; Materials – Y.Y., L.Q., Q.S., P.H.; Data Collection and/or Processing – Y.Y., L.Q., Q.S., P.H., X.Z.; Analysis and/or Interpretation – Q.S., P.H., X.Z.; Literature Search – Y.Y., Q.S., X.Z.; Writing – Y.Y., L.Q., Q.S., P.H., X.Z.; Critical Review – L.Q., Q.S.*

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist Item	Location Where Item Is Reported
Title			
Title	1	Identify the report as a systematic review.	1
Abstract			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
Introduction			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	1
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	2
Methods			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	2
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and, if applicable, details of automation tools used in the process.	2
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and, if applicable, details of automation tools used in the process.	2
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	2
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	2
Study risk of bias assessment	11	Specify the methods used to assess the risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and, if applicable, details of automation tools used in the process.	2
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	2
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	2
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	2
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	2
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	2
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	2
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	3
Reporting bias assessment	14	Describe any methods used to assess the risk of bias due to missing results in a synthesis (arising from reporting biases).	3
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	3

Results			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	3
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	3
Study characteristics	17	Cite each included study and present its characteristics.	3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots.	4
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	4
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	4
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	4
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	5
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	5
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	6
Discussion			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	7
	23b	Discuss any limitations of the evidence included in the review.	8
	23c	Discuss any limitations of the review processes used.	9
	23d	Discuss implications of the results for practice, policy, and future research.	10
Other Information			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	13
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	13
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	13
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	13
Competing interests	26	Declare any competing interests of review authors.	13
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	13

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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