

1 **A sum of its parts: A systematic review evaluating**
2 **biopsychosocial and behavioral determinants of**
3 **perinatal depression**

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21 **Abstract**

22 **Introduction** Depression is one of the most common yet underdiagnosed perinatal complications and
23 our understanding of the pathophysiology remains limited. Though perinatal depression is considered to
24 have a multifactorial etiology, integrative approaches to investigation are minimal. This review takes an
25 integrative approach to systematically evaluate determinants and potential interactions among
26 determinants of perinatal depression across four domains (i.e., biological, behavioral, environmental,
27 social) and appraise the quality of methods applied. **Methods** Four databases (i.e., PubMed, CINAHL,
28 APA PsycInfo, and Web of Science) were systematically searched to identify studies examining
29 determinants of perinatal depression in adult perinatal persons (≥ 18 years). Articles were excluded if the
30 outcomes were not focused on perinatal persons and depression or depression symptoms, the evaluation
31 of depression was specific to a discrete facet of the perinatal period with probable psychological
32 consequences (e.g., abortion, fetal/infant loss, adoption), or was considered grey literature. The Critical
33 Appraisal Skills Programme and AXIS tools were used to guide and standardize quality appraisal
34 assessments and determine the level of risk of bias. **Results** Of the 454 articles identified, 25 articles
35 were included for final review. A total of 14 categories of determinants were investigated: biological (5),
36 behavioral (4), social and environmental (5). Though only 28% of studies simultaneously considered
37 determinants under more than one domain, a pattern of interactions with the tryptophan pathway
38 emerged when determinants across domains were aggregated. Concerns for risk of bias were noted or
39 were unclear for three types of bias: 13 (52%) selection bias, 3 (12%) recall bias, and 24 (96%)
40 measurement bias. **Conclusions** Future research is needed to explore interactions among determinants
41 and the tryptophan pathway; to strengthen the methods applied to this area of inquiry; and to generate
42 evidence for best practices in reporting, selecting, and applying methods for measuring determinants and
43 perinatal depression.

44 **Introduction**

45 The leading underlying cause of perinatal death is mental health conditions [1]. Depression is
46 one of the most common conditions to occur perinatally as it impacts every one in five perinatal persons
47 [2, 3]. Perinatal depression denotes the manifestation of affective, somatic, and/or cognitive symptoms,
48 ranging in severity, that can occur at any time point in the perinatal period (i.e., conception-12 months
49 postpartum) and impairs one’s ability to complete daily activities [2–4]. While impairment in
50 functioning is already of concern due to the increased physiological, psychological, and financial
51 demands generated by this life-stage, distal outcomes (i.e., suicide, opioid use disorder) continue to
52 contribute to the alarmingly unabated maternal mortality rates in the US where 80% of these deaths are
53 considered preventable [1, 5, 6]. For instance, suicide, a leading cause of maternal mortality, has tripled
54 over the last decade and accounts for ~20% of perinatal deaths [6, 7], whereas opioid use disorder
55 accounts for one of the most frequent causes of accidental death [1, 5, 8]. Yet, depression remains the
56 most underdiagnosed perinatal complication in the US [2] suggesting advancements in our
57 understanding of the risk for and development of the condition requires timely attention and response.

58 The heterogeneous nature of depression symptoms coupled with the stark overlap of “normal”
59 pregnancy symptoms make early detection and intervention difficult. Therefore, the prevalence of
60 perinatal depression is likely underrepresented in part due to the lack of diagnostic expertise in the
61 clinicians who are most likely to interact with at-risk individuals, high variability in existing screening
62 practices, and underreporting of symptoms due to perceived stigma [9–11]. Still, 10-20% of perinatal
63 persons are reported to experience depression [3, 12–14].

64 A majority of research on the etiology of perinatal depression has attempted to dissect it into two
65 broad camps (i.e., internal factors, external factors) [13]. Investigations are further reduced and often

66 limited to factors respective to a single domain (e.g., biological, behavioral, social, environmental) [12,
67 13, 15–17]. Evidence suggests interactions among external factors and biological factors can contribute
68 to the onset of pathology [18]. For instance, lower levels of education, income, and occupation status
69 have been associated with elevations in inflammatory markers, chronic disease states, and metabolic
70 dysregulation [19]. Yet, the factors most commonly explored in relation to perinatal depression are
71 largely external (e.g., social, environmental, behavioral), such as, social determinants of health, personal
72 or family history of a psychiatric condition, low socioeconomic status (SES), stress, poor social support,
73 intimate partner violence (intimate partner violence), and multiparity [12, 20, 21]. Due to the limited
74 understanding of biological factors that may contribute to depression in perinatal populations, biological
75 theories of depression (i.e., immune response, inflammation, tryptophan metabolism) in the general
76 population may be useful in informing initial directions for investigations including biological factors in
77 perinatal specific depression [19, 22–25].

78 Since perinatal depression is considered to have a multifactorial etiology, siloed approaches to
79 investigation may inadvertently omit significant findings related to interactions among factors from
80 differing domains that can advance our understanding of risk and onset. In an era of team science,
81 integrative approaches to investigation are not only feasible but desirable to address some of the world’s
82 most complex health problems, like perinatal depression. This review aggregates existing literature
83 across various scientific domains and uncovers novel interactions that warrant further investigations into
84 the etiology and risk for this complex condition. Advancements in knowledge of distinct determinants
85 and interactions will not only improve our ability to detect existing symptoms but will also progress our
86 aptitude for determining risk status and implementing risk mitigation strategies [10]. Therefore, the
87 purpose of this review is to take an integrative approach to systematically evaluate a) what social,
88 environmental, behavioral, and biological determinants (i.e., immune response, inflammation,

89 tryptophan metabolism) have demonstrated a relationship with perinatal depression b) how such
90 determinants effect perinatal depression, and c) the quality of the methods used in the included studies.

91 **Methods**

92 **Search Strategy**

93 The literature search took place in December 2022. The following databases were searched for
94 articles that encompassed all or some of the specified determinants: PubMed, CINAHL, APA PsycInfo,
95 and Web of Science. The following search terms were used across all databases in the Title/Abstract
96 field: (depression or depressive or mdd or major depressive disorder or clinical depression or unipolar
97 depression) AND (social or environmental or behavioral) AND (determinants or characteristics or
98 factors) AND (tryptophan or serotonin or kynurenine or immunology or immune response or immune
99 system or inflammation or inflammatory response or cytokines) AND (metabolites or metabolomics or
100 metabolism) AND (pregnan* or prenatal or perinatal or antenatal or postpartum or postnatal or matern*
101 or peripartum or intrapartum).

102 The study selection process was guided by the Preferred Reporting Items for Systematic Reviews
103 and Meta-analyses (PRISMA) methodology [26]. Search results and duplicates were managed using the
104 open-source reference management software Rayyan [27]. Microsoft Excel was used as a screening and
105 data extraction tool to organize articles among the six authors (KDL, MLW, SG, TCN, KL, OFR), and
106 allowed the primary author to successively cross-check articles screened to confirm eligibility decisions
107 before proceeding to full-text review and quality appraisal.

108 **Inclusion and Exclusion Criteria**

109 Articles from any date were included if they focused on a timeframe within the perinatal period
110 (i.e., conception-12 months postpartum), had participants that were 18 years or older, were available in
111 the English language, investigated factors that belonged to at least one of the four domains (i.e.,
112 biological, behavioral, environmental, social), and had an outcome of depression or depression
113 symptoms. We define the four domains as follows: 1) biological: individual features unique to a person
114 that have a biological basis (e.g., genetics, brain chemistry, hormone levels) 2) behavioral: either a
115 conscious or unconscious action or inaction in response to internal or external stimuli (e.g., dietary
116 intake, smoking, physical activity) 3) environmental: physical surroundings or conditions a person lives
117 or functions within (e.g., access to resources, air pollution, poor water quality, crime) 4) social: one's
118 experiences with relationships or interactions with others (e.g., racism/discrimination, intimate partner
119 violence, social support) [28, 29]

120 Articles were excluded if they were non-peer-reviewed publications, review/meta-analyses, and
121 commentaries. Further, articles were excluded if outcomes were not specific to pregnant/postpartum
122 individuals (i.e., partner, support persons, infant), determinants investigated were not related to
123 depression or depression symptoms (e.g., post-traumatic stress disorder), and the outcome or evaluation
124 of depression or depression symptoms were specific to a discrete facet of the perinatal period with
125 implied potential for psychological consequences (i.e., abortion, fetal/infant loss, surrogacy, adoption).

126 **Article selection and quality appraisal**

127 After all articles were compiled and duplicates were removed, six authors (KDL, MLW, KAL,
128 SG, TCN, OFR) independently screened the titles and abstracts to determine which articles met
129 inclusion criteria. All articles were then subsequently cross-checked by the primary author to make a
130 final determination on inclusion. Of the articles that remained after the title and abstract screening, five
131 authors (KDL, MLW, SG, TCN, OFR) independently completed a full-text review. Any concerns

132 related to inclusion during any of the screening processes were resolved by discussion among the
133 primary author and the respective co-author.

134 Quality appraisal screening was independently conducted by two authors (KDL, TCN) to
135 ascertain any methodological or risk of bias concerns. Since quality appraisal assessments can be
136 subjective in nature, we selected two commonly used quality appraisal tools (i.e., Critical Appraisal
137 Skills Programme [CASP] and AXIS), respective to study design, to guide and standardize the process
138 [30, 31]. The studies were then categorized as having a low, moderate, high, or unclear risk of bias per
139 three types of bias (i.e., selection bias, recall bias, measurement bias). The types of bias and levels of
140 risk are defined in **Table 1**.

141 **Table 1. Definitions of types of bias and level of risk**

Term	Definition
Selection bias	any non-random error in methodological decisions that influence how a study sample is acquired.
Recall bias	occurs when the data collected from the participant may not be an accurate representation of the event or information being investigated given the lapse in time from when the event occurred to when the participant is being asked to recount information about the event.
Measurement bias	any non-random error in how an outcome is measured or evaluated.
Low risk of bias	sufficient information about the methods of investigation is provided, and there are minimal concerns related to risk of bias that could compromise the validity of the findings.
Moderate risk of bias	a majority of information about the methods of investigation are provided and/or a few concerns related to risk of bias were noted that could potentially influence the validity of the findings.
High risk of bias	a significant amount of essential information about the methods of investigation are not provided and/or a considerable number of concerns related to risk of bias were noted that likely compromise the validity of the findings.
Unclear risk of bias	too few methodological details were reported by the investigators to allow for a genuine determination of the level of risk of bias.

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143 **Data extraction and synthesis**

144 The following data were extracted from the included articles: country, purpose or aims, study
 145 design, recruitment and sampling method, perinatal period investigated, number of time points, sample
 146 description, what determinants were investigated, methods for measuring determinants and depression,
 147 method of analysis, and findings related to the relationship among determinants and depression or
 148 depression symptoms. Once data extraction was complete, the data were organized by descending date
 149 respective to the time-period investigated (i.e., pregnancy, postpartum, perinatal) and then synthesized.

150 Results and discussion

151 The PRISMA flow diagram provides an overview of the search results **Fig 1**. Twenty-six articles
 152 remained for full-text review and quality appraisal screening. One article was excluded [32] during
 153 quality appraisal screening due to methodological concerns making the total articles included 25 [33–
 154 57]. An overview of included articles with statistical values of significant findings per perinatal period
 155 can be found in **Tables 2-4**.

156 **Fig 1. PRISMA flow chart diagram.**

157 **Table 2. Summary of included articles (pregnancy).**

PREGNANCY				
First Author	Purpose/Aims	Design [#]	Factor Domain	Summary of significant findings (<i>values</i>)
Miyake ² (2022) (N = 1744) <i>Japan</i>	Examine the association between tryptophan intake and depressive symptoms during pregnancy.	Cross-sectional ¹	Bh	<p>Tryptophan intake was <i>positively associated</i> with being unemployed ($p = 0.0001$), household income ($p = 0.002$), education ($p = 0.01$), and intake levels of saturated fatty acids ($p \leq 0.0001$), eicosapentaenoic acid plus docosahexaenoic acid ($p \leq 0.0001$), calcium ($p \leq 0.0001$), vitamin D ($p \leq 0.0001$), isoflavones ($p \leq 0.0001$), fish ($p \leq 0.0001$) and <i>negatively associated</i> with having ever smoked ($p = 0.0006$) and cereal intake ($p \leq 0.0001$). Age was <i>negatively associated</i> to the prevalence of depressive symptoms during pregnancy in a crude analysis ($p = 0.02$).</p> <p>Compared with tryptophan intake in the <u>lowest quartile</u>, tryptophan intake in the <u>highest quartile</u> was related to a ↓ prevalence of depressive symptoms during pregnancy. The <i>inverse exposure – response</i> relationship was also significant in the <i>crude analysis</i>.</p>

				<p>↑ tryptophan intake was independently <u>negatively associated</u> with the prevalence of depressive symptoms during <u>pregnancy</u>: the <i>adjusted PRs</i> (95% CIs) for depressive symptoms during <u>pregnancy</u> in all <u>four quartiles of tryptophan intake</u> (<i>Crude PR</i> (95% CI), 1.00; 0.95 (0.74–1.22); 0.87 (0.67–1.12); 0.57 (0.42–0.76), $p=0.0001$); (<i>Adjusted PR</i> (95% CI), 1.00; 0.99 (0.76–1.28); 0.94 (0.71–1.25); 0.64 (0.44–0.93), $p=0.04$)).</p> <p>These results were not changed when controlling for dietary factors.</p>
<p>®Venkatesh² (2019) (N = 462) US</p>	<p>1) Determine whether antenatal depression was associated with two biomarkers of oxidative stress, 8-OHdG and 8-Isoprostane, and five biomarkers of inflammation. 2) assess whether the association between antenatal depression and SPTB was mediated by those biomarkers found to be significant in the primary aim.</p>	<p>Prospective²</p>	<p>B</p>	<p>Spontaneous preterm birth (SPTB) was 2 times more frequent among those with depression compared to those without (12.4 vs. 6.3%, OR: 2.1 [95% CI: 1.10-4.04], $p = 0.02$)</p> <p>Those with depression had ↑ levels of specific gravity corrected 8-isoprostane compared to those without depression (<i>geometric mean</i>: 299.96 pg/mL vs. 237.01 pg/mL, $p = 0.001$).</p> <p>Those with depression who had <u>prenatal antidepressant exposure</u> had ↓ levels of 8-isoprostane compared to those who had depression <u>without antidepressant exposure</u> (<i>geometric mean</i>: 362.40 pg/mL, $p = 0.03$); however, both groups (<u>antidepressant exposure vs. not</u>) had ↑ 8-isoprostane levels compared to those without <u>prenatal depression</u> (237.01 pg/mL, ANOVA $p = 0.02$).</p> <p>Prenatal depression was associated with SPTB (AOR: 2.09, 95% CI: 1.09-4.03, $p = 0.02$). The association between 8-isoprostane and <u>prenatal depression</u> with SPTB were ↓ when analyzed in the same <i>regression model</i>, which is suggested by the authors to indicate <i>partial mediation</i> of 8-isoprostane on the relationship between <u>prenatal depression</u> and SPTB (AOR for 8-isoprostane: 3.72, 95% CI: 2.14-6.46, $p < 0.001$; AOR <u>prenatal depression</u>: 1.68, 95% CI: 0.85-3.34, $p = 0.13$). After <i>bootstrapping</i> over 1,000 iterations, it was found that 27% of the effect of <u>prenatal depression</u> on SPTB was explained by 8-isoprostane.</p> <p>No significant findings were noted for 8-OHdG or inflammatory markers.</p>
<p>Chang (2018) (N = 33) Taiwan</p>	<p>Investigate if subjects with depression in pregnancy had higher levels of pro – inflammatory markers and lower levels of anti-inflammatory markers.</p>	<p>Case control¹</p>	<p>B</p>	<p>Compared to controls, those with <u>prenatal depression</u> had ↓ levels of omega-3 polyunsaturated fatty acid (3-PUFAs) ($p = 0.026$), EPA ($p = 0.019$), and DHA ($p = 0.02$). They also had ↑ n-6/n-3 ratios.</p> <p>TNF-α was the only inflammatory marker found to be significantly ↑ for those with <u>prenatal depression</u> versus those without ($p = 0.016$).</p> <p>No <i>correlation</i> between depression severity PUFAs and inflammatory markers were found. Depression duration was <i>negatively correlated</i> with total n-3 PUFAs, EPA and DHA ($r = -0.415, -0.395, -0.392, p < 0.05$). Current depression was <i>positively correlated</i> with n-6/n-3 ratio and TNF-α ($r = 0.458, 0.443, p < 0.01$).</p>

<p>©Finy² (2018) (N = 214) US</p>	<p>Examine the association between childhood abuse, low socioeconomic status (SES) and inflammatory markers during pregnancy</p>	<p>Cross-sectional¹</p>	<p>B, S</p>	<p>Childhood abuse history was <i>positively associated</i> with CRP and IL-6. Current SES and CRP and IL-6 were <i>negatively associated</i> (p's < 0.01).</p> <p>Depressive symptoms were <i>positively correlated</i> with IL-6 ($r = 0.23$, $p < 0.01$).</p>
<p>©Miller² (2018) (N = 170) US</p>	<p>To evaluate the association between psychotropic medication and maternal serum inflammatory biomarkers in women with antenatal depressive symptoms (ADS) in the mid-trimester.</p>	<p>Cross-sectional¹</p>	<p>B</p>	<p>Those with <u>untreated depression</u> were more likely to be from a racial/ethnic minority group, to have a \downarrow household income, to be publicly insured, have a \downarrow educational level, and \downarrow likely to be married. Further, they were \uparrow likely to be employed than those with depression <u>non-responsive to treatment</u> but were \downarrow likely to be employed than those with depression <u>responsive to treatment</u>.</p> <p>There were no differences noted in serum levels of IFNγ, IL13, IL6, IL8, or CRP, but TNF-α differed across the groups. <i>Post-hoc</i> analyses indicated those <u>non-responsive to treatment</u> ($p = 0.02$) and <u>untreated depression</u> ($p = 0.01$) had \downarrow TNF-α compared to those <u>responsive to treatment</u>. No differences noted between <u>untreated depression</u> and those <u>non-responsive to treatment</u> ($p = 0.76$).</p> <p>When controlling for race/ethnicity, income, and marital status, a <i>linear regression</i> demonstrated both those with depression who were <u>non-responsive</u> to treatment and those who had <u>untreated</u> depression had \uparrow TNF-α compared to those <u>responsive to treatment</u> ($\beta = 0.27$, 95% CI: 0.02-0.52 and $\beta = 0.23$, 95% CI 0.02-0.44).</p>
<p>©Ross (2017) (N = 90) US</p>	<p>Examine the association between pregnant women's close relationships and cytokine profiles in the third trimester.</p>	<p>Prospective²</p>	<p>B, S</p>	<p><i>Correlations</i> between cytokines varied within <u>each trimester</u> and ranged from $r = 0.660 - r = -0.469$ with a <i>mean</i> $r = 0.322$ indicating a good proportion of variance in each cytokine is unique.</p> <p>Romantic partner (RP) relationships with positive features (i.e., support/closeness) were associated with \downarrow levels of inflammatory cytokines; RP relationships low in both positive and negative features (indifferent) were <i>associated</i> with cytokine profiles indicating \uparrow inflammation.</p> <p>Positive RP relationship was negatively associated with IL6:IL10 ratio. Further, when positive RP features were \uparrow and there were \downarrow RP negative features, the estimated IL6:IL10 ratios were lowest indicating a potential buffering or protective effect of positive RP relationships.</p> <p>Positive and negative RP relationships were <i>associated</i> with IL10 levels ($b(SE) = 0.031$ (0.009), $p = 0.001$; $b(SE) = 0.017$ (0.007), $p = 0.017$).</p> <p>Positive and negative RP relationships were <i>associated</i> with IFNγ levels ($b(SE) = 0.131$ (0.041), $p = 0.002$; $b(SE) = 0.095$ (0.032), $p = 0.004$)</p> <p>Neither positive and negative RP relationships were <i>associated</i> with IL13, IL8, IL6, and TNF-α levels.</p>

				<p>↑ positive RP relationship was associated with ↓ depressed mood ($r = -0.35, p = 0.001$) and perceived stress ($r = -0.41, p < 0.001$) whereas ↑ negative RP relationship was associated with ↑ depressed mood ($r = 0.51, p < 0.001$), perceived stress ($r = 0.53, p < 0.001$), and pregnancy distress ($r = 0.29, p = 0.005$).</p>
<p>@Christian (2009) (N = 60) US</p>	<p>Examine associations among perceived stress, current depressive symptoms, and serum inflammatory markers among pregnant women from primarily lower socioeconomic backgrounds.</p>	<p>Cross-sectional¹</p>	<p>B, Bh</p>	<p>When controlling for pre-pregnancy BMI, ↑ depression scores were associated with ↑ levels of IL-6 ($\beta = .23, t(2, 55) = 1.98, p = 0.05$).</p>
				<p>↑ depression scores were marginally associated with ↑ TNF-α levels ($\beta = 0.24, t(2, 58), p = 0.06$).</p>
				<p>Depressive symptoms were <i>positively correlated</i> with perceived stress ($r = 0.050, p < 0.01$).</p>
				<p>Those classified as unhappy about their pregnancies had ↑ depressive symptoms compared to those who were happy about their pregnancy (<i>mean CES-D = 22, SD = 10; mean CES-D = 16, SD = 10, p = 0.04</i>).</p>
				<p>Those reporting ↓ social support had ↑ depressive symptoms ($p < 0.05$), and those with ↑ frequent hostile and insensitive social interactions also had ↑ depressive symptoms ($p < 0.01$).</p>
				<p>After <i>controlling</i> for social support, hostile and insensitive social interactions remained associated with depressive symptoms ($\beta = 0.17, r(1, 59) = 1.25, p = 0.21$).</p>

158 Author² = secondary analysis; Design[#] = Design + Number of timepoints investigated; Domain of factors investigated in relation to depression: B =
 159 Biological, Bh = Behavioral, E = Environmental, S = Social ; *Values (when provided)* = statistical values respective to analysis; Factors investigated in
 160 relation to depression **bold**; Timeframe and/or groups investigated underlined.
 161 @Study reported race/ethnicity

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Table 3. Summary of included articles (postpartum).

POSTPARTUM				
First Author	Purpose/Aims	Design [#]	Factor Domain	Summary of significant findings (<i>values</i>)
<p>Achytes (2022) (N = 130) US</p>	<p>Investigate whether a pro-inflammatory status in plasma, together with changes in the kynurenine pathway activity, is associated with the development of severe depression and suicidal behavior in the post-partum.</p>	<p>Case-control¹</p>	<p>B, Bh</p>	<p>↑ IL-6, IL-8 ↑ PPD (<i>OR IL-6 = 3.0, 95% CI = 1.37 – 6.6; OR IL-8 = 3.32, 95% CI = 1.32 – 8.34, per pg/ml increase</i>)</p>
				<p>↓ IL-2 ↑ PPD (<i>OR = 2.34, 95%CI = 1.35–4.05, p = 0.002, per pg/ml decrease</i>)</p>
				<p>↓ serotonin ↑ odds of PPD (<i>OR = 1.43 per nM decrease in serotonin, 95% CI: 1.07 – 1.92, p = 0.016</i>)</p>
				<p>↑ Kynurenine/serotonin ratio ↑ PPD (<i>OR = 1.35 per unit increase, 95% CI: 1.03 – 1.79, p = 0.038</i>)</p>
				<p><i>Sensitivity analysis</i> using depression scores: models for IL-8, IL2, serotonin, serotonin/kynurenine, and quinolinic acid were significant; (<i>linear regression, Beta 3.9, Standardized Beta 0.22, p = 0.006</i>), (<i>linear regression, Beta –2.3, Standardized Beta –0.23, p = 0.005</i>), (<i>linear regression, Beta –1.3, Standardized Beta –0.24, p = 0.003</i>), (<i>linear regression, Beta –1.1, Standardized Beta 0.22, p = 0.009</i>), (<i>linear regression, Beta –4.3, Standardized Beta –0.18, p = 0.022</i>)</p>

				<p>↓ serotonin was associated with current and history of suicidal behavior and ↑ odds of completed suicide attempt during pregnancy. (OR : 0.51[0.32, 0.8]1, p = 0.005), (OR: 0.50 [0.29, 0.87], p = 0.013), (OR: 0.51, [0.31, 0.84], p = 0.007)</p>
<p>Dhiman² (2021) (N = 660) India</p>	<p>Explore the association between vitamin B12 and probable PPD in South Indian population.</p>	<p>Cross-sectional¹</p>	<p>B</p>	<p>Those with probable depression were ↑ likely to belong to the middle SES group (p = 0.002), had more than one child (p = 0.002), be dissatisfied with their marriage (p < 0.001), be dissatisfied with the gender of their child (p < 0.001), and had ↑ rates of cesarean delivery (p = 0.014). They also reported ↓ milk (p < 0.001), meat (p = 0.012), and egg (p = 0.002) intake.</p>
				<p>Median total B12 levels and cB12 were ↓ in cases compared to controls (p < 0.001). Methyl malonic acid (MMA) – marker of functional deficiency of vitamin B12 – was ↑ cases compared to controls (p = 0.002).</p>
				<p>After <i>adjusting</i> for SES, marital dissatisfaction, unplanned pregnancy, and type of delivery, the <i>regression model</i> indicated the likelihood of postpartum depression to ↓ by 0.39 for ever unit ↑ in total vitamin B12 (OR = 0.394; 95% CI: 0.189-0.822, p = 0.009) and by a factor of 0.29 (OR = 0.293; 95% CI: 0.182-0.470, p < 0.001) for cB12. MMA (OR = 2.04; 95% CI: 1.53-2.11, p < 0.001) and 5-methyl tetrahydrofolate (THF) (OR = 3.18; 95% CI: 1.42-6.08, p = 0.001) were found to be predictors of PPD.</p>
				<p>After <i>adjusting</i> for SES, marital dissatisfaction, unplanned pregnancy, and type of delivery, a significant <i>negative</i> association among serotonin and depression remained (β = -0.16, p = 0.005), as did a <i>positive</i> association among MMA (β = 0.161, p = 0.001), homocysteine (hcy) (β = 0.155, p = 0.005), and THF (β = 0.118, p = 0.010) and depression.</p>
				<p>The <i>path analysis</i> model with total vitamin B12 as the predictor, depression score as the outcome variable, and MMA as the <i>mediator</i> was significant (p < 0.001).</p>
<p>Rihua² (2018) (N = 84) China</p>	<p>To determine associations between PPD and plasma neurotransmitters.</p>	<p>Case control¹</p>	<p>B</p>	<p>There were significant differences in education and mode of delivery among those with PPD and those <u>without</u>.</p>
				<p>Plasma levels of serotonin (5-hydroxytryptamine or 5-HT) and neuropeptide Y (NPY) were ↓ in those with PPD compared to controls (p < 0.05 or p < 0.01) whereas norepinephrine (NE) and substance P (SP) were ↑ in PPD cases versus controls (p < 0.05). No differences were found for dopamine (DA).</p>
				<p>A <i>negative correlation</i> among depression scores and serotonin and NPY (p < 0.05 or p < 0.01) were present as well as a <i>positive correlation</i> among depression scores with NE and SP (p < 0.01 or p < 0.01).</p>
<p>Veen (2016) (N = 42) Netherlands</p>	<p>To investigate if alterations in tryptophan degradation in the postpartum period are</p>	<p>Case control¹</p>	<p>B</p>	<p>Those considered to be “healthy” postpartum participants were ↑ likely to be breastfeeding at the time of blood collection (p < 0.001).</p>

	<p>associated with the occurrence of postpartum depression and postpartum psychosis.</p>		<p>Physiological postpartum period: <u>Healthy postpartum</u> (PP) participants had ↓ serum levels of kynurenic acid (KA) compared to <u>healthy non-PP controls</u> ($p < 0.001$).</p> <p>All <u>PP</u> participants had ↑ levels of 3-OH-kynurenine (3HK) ($p = 0.011$); the KA/kynurenine (KYN) ratio was ↓ in <u>healthy PP</u> participants ($p < 0.001$) suggesting a strong inhibition of the kynurenine aminotransferases (KAT) enzymes during the first <u>2 months PP</u>.</p> <p>The 3HK/KYN ratio was ↑ in <u>healthy PP</u> participants with a median time of <u>22 days PP</u> ($p = 0.021$), but not in <u>healthy PP</u> participants with a median time of blood collection <u>40 days PP</u>. The authors suggest this indicates ↑ activity of the kynurenine-3-monooxygenase (KMO) enzymes in the <u>first month</u> of the physiological <u>PP period</u> and then the gradual returning to “normal” levels.</p> <p>The serotonergic pathway (5HIAA)/KYN ratio was ↓ in <u>healthy PP</u> participants suggesting that the breakdown of tryptophan (TRP) is <i>biased towards</i> the KYN pathway and <i>away from</i> the serotonergic pathway in the physiological <u>PP period</u> ($p = 0.009$).</p> <p>“Healthy” <u>PP participants</u> had ↓ serum levels of TRP ($p < 0.001$), and ↑ levels of KYN ($p = 0.002$) compared to <u>healthy non-PP</u> participants, and consequently the TRP breakdown index was also ↑ ($p < 0.001$).</p> <p>KYN was ↓ in <u>cases</u> compared to <u>controls</u> ($p = 0.001$), and accordingly <u>cases</u> had a ↓ tryptophan breakdown index compared to <u>controls</u> ($p = 0.035$).</p>
<p>Comasco (2011) (N = 272) Sweden</p>	<p>Examine whether genetic variations in the monoaminergic neurotransmitter system, together with environmental stressors, contribute to the development of PPD symptoms</p>	<p>Case control²</p>	<p>B, S</p> <p><i>Associations</i> between genetic polymorphisms and PPD symptoms were significant only at the <u>6-week time point</u>, not at <u>6 months</u> (data not shown).</p> <p>COMT-Val¹⁵⁸Met with ↑ risk for Met carriers was <i>associated</i> with <u>PPD</u>.</p> <p>Previous psychiatric contact, significant life events, and maternity stressors were <i>associated</i> with <u>PPD</u> symptoms.</p> <p>Gene-by-gene interactions were present for COMT-MAOA in relation to PPD symptoms. Low MAOA activity carriers with the Met variant of COMT was related to PPD symptoms; high MAOA activity variant was <i>associated</i> with PPD symptoms only when <u>combined</u> with the Met allele of COMT; short 5HTT allele was <i>associated</i> with PPD symptoms only when <u>combined</u> with the Met allele of COMT.</p> <p>COMTVal¹⁵⁸Met was <i>associated</i> with PPD symptoms in the presence of previous psychiatric contact and maternity stressors, while MAOA-uVNTR was <i>associated</i> with PPD symptoms only in the presence of maternity stressors.</p> <p>The <i>logistic regression analysis</i> demonstrated an <i>association</i> among PPD symptoms and COMTVal¹⁵⁸Met, previous psychiatric contact, and maternity stressors. The <i>model explained 30% variance</i>. After stratifying for previous psychiatric contact, the gene-environment</p>

				interaction model indicated those with previous psychiatric contact had a <i>main effect</i> of COMT-Val¹⁵⁸Met and 5HTT-LPR with an <i>explained variance</i> of 40%.
Bailara (2006) (N=50) France	Assess the correlation of intensity of baby blues, with the intensity of metabolic changes and brain tryptophan availability	Cross-sectional ¹	B	Total plasma TRP exhibited a <i>mild</i> (+19%) ↑. An abrupt ↑ in competitor amino acid concentrations (+77% isoleucine , +55% leucine , +52% tyrosine) led to a ↓ in brain tryptophan availability (BTAI) . The BTAI ↓ between the <u>prenatal</u> and <u>postpartum</u> period (-15%, <i>p</i> < 0.01) and was <i>associated</i> with PP blues symptoms. The change in BTAI was <i>negatively correlated</i> with the intensity of postpartum blues (<i>r</i> = -0.283, <i>p</i> < 0.05).
Moses-Kolko ² (2008) (N=16) US	To measure brain serotonin-1A (5HT1A) receptor binding potential (BP) in healthy and depressed postpartum women.	Cross-sectional ¹	B	There was an effect of breastfeeding status on hypothalamic-pituitary-ovarian axis hormone concentrations estradiol , progesterone , LH , FSH , and prolactin [<i>Wilks' lambda</i> = 0.2056; <i>F</i> (5, 10) = 7.73, <i>p</i> = 0.003]. A <i>post-hoc analysis</i> showed breastfeeding was <i>associated</i> with ↓ estradiol [<i>F</i> (1, 14) = 8.31, <i>p</i> = 0.01], progesterone [<i>F</i> (1, 14) = 4.33, <i>p</i> = 0.06], and FSH concentrations [<i>F</i> (1, 14) = 5.18, = 0.04] and ↑ prolactin concentrations [<i>F</i> (1, 14) = 26.25, <i>p</i> = 0.0002]. Serotonin receptor (5HT1A) binding in the three <i>a priori</i> regions of interest (mesiotemporal cortex , left lateral orbitofrontal cortex , and subgenual anterior cingulate cortex) demonstrated a <i>main effect</i> of depression [<i>F</i> (3, 12) = 13.67, <i>Wilks' lambda</i> = 0.23, <i>p</i> = 0.0004]. <i>Post hoc analysis</i> detected significant depression effects on ↓ in the mesiotemporal cortex [21.6% mean decrease; <i>F</i> (1, 140) = 22.5, <i>p</i> = 0.0003], subgenual cingulate cortex [27.65 mean decrease; <i>F</i> (1, 14) = 23.4, <i>p</i> = 0.0002], and left lateral orbitofrontal cortex [17.9% mean decrease; <i>F</i> (1, 14) = 7.13, <i>p</i> = 0.018] regions. There were also associations with reductions in the secondary ROI [<i>F</i> (5, 10) = 3.24, <i>Wilks' lambda</i> = 0.38, <i>p</i> = 0.054], and the most significant ↓ were in the right lateral orbitofrontal cortex [23.4% mean decrease; <i>F</i> (1, 14) = 8.72, <i>p</i> = 0.011] and pregenual anterior cingulate cortex [23.4% mean decrease; <i>F</i> (1,14) = 17.2, <i>p</i> = 0.001].

165 Author² = secondary analysis; Design[#] = Design + Number of timepoints investigated; Domain of factors investigated in relation to depression: B =
 166 Biological, Bh = Behavioral, E = Environmental, S = Social ; *Values (when provided)* = statistical values respective to analysis; Factors investigated in
 167 relation to depression **bold**; Timeframe and/or groups investigated underlined.
 168 ®Study reported race/ethnicity
 169

170 **Table 4. Summary of included articles (perinatal).**

PERINATAL				
First Author	Purpose/Aims	Design [#]	Factor Domain	Summary of significant findings (<i>values</i>)
®Sha (2022) (N=114) US	To determine whether cytokines and kynurenine metabolites can	Prospective ⁴	B	↑ IL-1β , IL-6 , and QUIN were <i>associated</i> with ↑ depression severity and/or ↑ <i>odds</i> of having depression (<i>Percent change in OR(CI)</i> : 32.3% (7.0, 63.6), 58.4% (22.1, 111.7), 91.6% (15.0, 232.0))

	<p>predict the development of depression in pregnancy.</p>		<p>IL-6 performed best in <i>predicting</i> depressive symptoms; however, KYN, QUIN, KYN/TRP ratio (rKT) also produced good predictions ($AUC = 0.79$ and 0.8 by <i>Bayesian ordinal and logistic regression, respectively</i>; $ROC AUC > 0.7$). <i>Precision recall analyses confirmed predictive value of model.</i></p> <p>The <i>leave-one-out cross validation</i> method indicated the predictability of the model would be optimal from <u>mid- to late pregnancy</u> (2nd to 3rd trimester). The full model nominally outperformed individual markers for <i>predicting</i> risk of significant depressive symptoms. <i>Ordinal and logistic regression full models had ROC AUC = 0.83, PR AUC = 0.41.</i></p>
<p>®Kimmel (2022) (N = 30) US</p>	<p>Analyze trajectories of serotonin and tryptophan-related metabolites, bile acid metabolites, and microbial composition related to psychiatric history and current symptoms across the perinatal period.</p>	<p>Pilot³</p>	<p>Fiber consumption was slightly ↓ in cases compared to <u>controls</u> (determined too small a sample to calculate p-values).</p> <p>Mean serotonin level ↑ from <u>pregnancy to postpartum</u> ($p = 0.0002$ for 3rd trimester (V2) to 5-10 weeks postpartum (V3); $p = 0.002$ for 1st or 2nd trimester (V1) to V3). NEOP level trajectories followed a different pattern than serotonin by ↑ from V1 to V2 ($p < 0.0001$) and then ↓ postpartum ($p = 0.005$). Mean KYN ↑ from V1 to V2 ($p = 0.003$) and ↑ again from V2 to V3 ($p = 0.004$). The KYN/TRP ratio was ↑ at V2 and V3 compared to V1 ($p < 0.0001$; $p < 0.0001$). KA was ↑ at V3 compared to both V2 ($p = 0.003$) and V1 ($p = 0.0004$).</p> <p>Primary bile acids: Chenodeoxycholic acid (CDCA) ↑ from V2 to V3 ($p < 0.00011$) with an overall ↑ from earlier V1 to V3 ($p = 0.0003$); Glychenodeoxycholic acid (GCDCA) ↑ from V2 to V3 ($p < 0.0001$) and remained ↑ at V3 compared to V1 ($p < 0.0001$); Taurochenodeoxycholate (TCDCA) ↓ from V2 to V3 ($p = 0.001$); Glycocholic acid (GCA) ↑ from V1 to V2 ($p = 0.003$) and ↑ from V1 to V3 ($p = 0.005$); Taurocholic acid (TCCA) ↑ from V1 to V2 ($p < 0.0001$), and ↓ from V2 to V3 ($p < 0.0001$).</p> <p>Secondary bile acids: Glycoursodeoxycholic acid (GUDCA) ↓ from V2 to V3 ($p < 0.0001$) whereas GUDCA and Ursodeoxycholic acid (UDCA) ↑ from V2 to V3 ($p < 0.0001$; $p = 0.0003$) and GUDCA remained ↑ from V1 to V3 ($p < 0.0001$); Glycolithocholic acid (GLCA) ↑ from V2 to V3 ($p < 0.0001$) and levels of Glychoyocholic acid (GHCA) and GLCA were ↑ compared to the initial value in <u>pregnancy</u> ($p = 0.0001$; $p < 0.0001$; $p = 0.0005$)</p> <p>Tauro alpha-murchoic acid (TaMCA), Taurohyocholic acid (THCA), and tarodeoxycholate hydrate (TDCA) ↓ from V2 to V3 ($p < 0.0001$; $p = 0.0003$; $p < 0.0001$) and V3 were ↓ than earlier in <u>pregnancy</u> ($p < 0.0001$; $p = 0.0003$; $p = 0.002$). TUDCA, TDCA, and TCA were <i>associated</i> with change in NEOP from V1 to V2 ($q = 0.011$; $q = 0.021$; $q = 0.021$). TUDCA was also <i>associated</i> with change in TRP ($q = 0.004$), KYN ($q = 0.001$), and KA/KYN ratio ($q = 0.002$). These findings became stronger when excluding those in the first trimester.</p>

				<p>Metabolites and microbiome:</p> <p>Alpha diversity did not significantly change across the <u>perinatal period</u>. ↑ bile acid GUDCA and UDCA levels were associated with ↓ alpha-diversity across all 4 indices (<i>evenness, Faith's phylogenetic diversity, count of observed OTUs, Shannon entropy</i>).</p> <p>↑ CDCA was associated with ↓ alpha diversity for the <i>evenness index</i> and <i>Shannon index</i> only, and also only when <u>first trimester</u> participants were included.</p> <p>Certain bacterial genera were associated with UDCA and TUDCA, primarily in the order Clostridiales and family Cachnospiraceae. THcA was also associated with Riseburia.</p> <p>UDCA was the only metabolite associated with psychiatric history ($q = 0.033$).</p>
<p>©Tebeka² (2021) (N = 3,252) France</p>	<p>Assess the relationship between childhood trauma (CT) and perinatal depression, considering types of CT</p>	<p>Case control³</p>	<p>S</p>	<p>Those reporting childhood trauma (CT) were ↑ likely to be < 26 years old (8.1% vs. 4.5%; OR = 1.8; 95% CI: 1.2-2.6) > 39 years old (11% vs. 7%; OR = 1.9; 95% CI: 1.2-2.9), single (6.7% vs. 2.7%; OR = 2.6; 95% CI: 1.5-4.2), have a lower level of education (18.1% vs. 6.8%; OR = 3.0; 95% CI: 1.8-3.6), and ↑ likely to have been unemployed (14.1% vs. 6.1%; OR = 2.5; 95% CI: 1.8-3.6).</p> <p>Those with CT had a ↑ risk of either depression, anxiety, or suicide attempts compared those without (61.6% vs. 40.8%; OR = 2.3; 95% CI: 1.8-2.9), and a personal history of depression, anxiety, or suicide attempts were ↑ frequent in those with CT (depression: OR = 2.2; 95% CI: 1.7-2.7; anxiety: OR = 2.3; 95% CI: 1.7-3.0; suicide attempt: OR = 5.4; 95% CI: 3.5-8.4)</p> <p>Depression was ↑ common in those with a CT regardless of type of CT, and the difference was significant for emotional, physical, and sexual abuse as well as emotional neglect ($p < 0.05$ for each). The types of CT demonstrated specific associations with different timing of depression onset. Emotional neglect was associated with depression during <u>pregnancy</u> (aOR = 2.1; 95% CI: 1.2-3.8, $p = 0.012$); sexual abuse with both <u>early and late onset</u> PPD (aOR = 2.3; 95% CI: 1.2-4.6; aOR = 2.4; 95% CI: 1.2-4.9, respectively); emotional abuse was associated only with late PPD (aOR = 2.7; 95% CI: 1.4-5.1).</p> <p>A <i>dose effect</i> was present between CT types and risk of depression. When 1 type of CT was present there was a ↑ risk of depression (aOR = 1.6; 95% CI: 1.1-2.3, $p = 0.015$), whereas, when 2+ types of CT were present the risk further ↑ (aOR = 2.1; 95% CI: 1.3-3.3) even after adjusting for history of depression and sociodemographic covariates.</p>
<p>Nazzari (2020) (N = 97) Italy</p>	<p>1) Describe the cross-sectional and longitudinal association between</p>	<p>Prospective⁴</p>	<p>B</p>	<p>↑ prenatal Kyn levels were associated with ↓ depressive symptoms in <u>late pregnancy</u> (estimate = - 0.002, SE = 0.001, $p = 0.03$) after adjusting for maternal age.</p>

	<p>tryptophan, kynurenine, and kynurenine/tryptophan ratio and depression symptoms in late pregnancy through the first year postpartum 2) examine the role of inflammatory (IL-6) and stress (cortisol) markers in moderating any associations 3) determine if specific to depressive symptoms or can be replicated with anxiety given high concurrence of these disorders</p>			<p>Pre-pregnancy BMI was mildly associated with IL-6 levels ($r = 0.23$, $p = 0.03$) in preliminary analysis but adjusting models for BMI did not alter the direction or significance of findings.</p> <p>Model 2: There was a <i>three-way interaction</i> among <u>prenatal Trp levels</u>, IL-6, and slopes of <u>time</u> on depression scores ($ps < 0.05$). \downarrow levels of <u>prenatal Trp</u> and \uparrow IL-6 were associated with \uparrow depressive symptoms in <u>late pregnancy</u> ($p = 0.04$) and with the change in depressive symptoms from <u>pregnancy to three postpartum</u> time points ($ps = 0.04$).</p> <p>Model 3: A <i>three-way interaction</i> among the KYN/TRP ratio, IL-6, and the depression scores trajectory from <u>pregnancy to 12 months postpartum</u>. \downarrow levels of <u>prenatal KYN/TRP ratio</u> and \uparrow levels of IL-6 were associated with \uparrow depressive scores at <u>delivery</u> ($p = 0.05$) and <u>12 months postpartum</u> ($p = 0.004$) and with a flatter trajectory of change in depressive symptoms from <u>pregnancy to 12 months postpartum</u> ($p = 0.048$). Conversely, at \uparrow levels of KYN/TRP ratio and \uparrow IL-6 levels were associated with a \downarrow in depressive scores from <u>pregnancy to 3</u> ($p = 0.03$) and <u>12 months</u> ($p = 0.014$) <u>postpartum</u>.</p>
<p>Garman² (2019) (N = 384) <i>South Africa</i></p>	<p>Identify trajectories of perinatal depressive symptoms and their predictors among low-income South African women who were already at risk of depression during pregnancy.</p>	<p>Prospective⁴</p>	<p>Bh, S, E</p>	<p>Food insecurity predicted classification of either <u>prenatal only depression</u> or <u>prenatal and postpartum depression</u>. The odds of being classified in the prenatal and postpartum depression trajectory was 2.5 greater (95% CI: 1.21-5.15; $p = 0.013$) among participants who reported being severely food insecure.</p> <p>Overall levels of social support at baseline \downarrow the odds of belonging to the <u>prenatal and postpartum depression class</u> (OR = 0.97, 95% CI: 0.95-0.99; $p = 0.011$). When looking at specific types of support, only a \uparrow level of family support (OR = 0.91, 95% CI: 0.86-0.96; $p = 0.001$) or \uparrow level of support from a significant other (OR = 0.94, 95% CI: 0.88-1.00; $p = 0.046$) \downarrow the odds of being classified into the <u>prenatal and postpartum depression class</u>.</p> <p>Those who reported IPV at baseline were 2.8 times \uparrow likely (95% CI: 1.23-6.52; $p = 0.014$) to belong to the <u>prenatal and postpartum depression class</u>.</p> <p>Odds of belonging to the <u>prenatal and postpartum depression class</u> were \uparrow among those who reported greater functional impairment (OR = 1.03, 95% CI: 1.02-1.06; $p = 0.002$), heavy drinking during pregnancy (OR = 2.12, 95% CI: 0.03-4.37; $p = 0.042$), had current (OR = 2.77, 95% CI: 1-32-5.80; $p = 0.007$) or lifetime diagnosis of depression (OR = 2.85, 95% CI: 1.38-5.87; $p = 0.004$), and high risk of suicide (OR = 2.58, 95% CI: 1.19- 5.61; $p = 0.017$).</p>
<p>Teshigawara (2019) (N = 132) <i>Japan</i></p>	<p>To determine whether cytokines and kynurenine metabolites can predict the development of</p>	<p>Prospective³</p>	<p>B</p>	<p>In the <u>non-depressed group</u>: TRP, KYN, 3HK, and KA were \uparrow <u>postpartum</u> compared to <u>pregnancy</u> (two-way repeated ANOVA, Trp: $F_{\text{group}}(3, 128) = 1.44$, $p = 0.234$, $F_{\text{period}}(1, 128) = 64.3$, $p < 0.0001$, $F_{\text{group} \times \text{period}}(3, 128) = 0.376$, $p = 0.771$; Kyn: $F_{\text{group}}(3, 128) = 0.927$, $p = 0.430$, $F_{\text{period}}(1, 128) = 96.4$, $p < 0.01$, $F_{\text{group} \times \text{period}}(3, 128) = 6.09$, p</p>

	depression in pregnancy.		<p>< 0.01; 3HK: $F_{\text{group}}(3, 128) = 0.0662$, $p = 0.978$, $F_{\text{period}}(1, 128) = 6.09$, $p < 0.05$, $F_{\text{group} \times \text{period}}(3, 128) = 1.98$, $p = 0.120$; KA: $F_{\text{group}}(3, 128) = 1.52$, $p = 0.213$, $F_{\text{period}}(1, 128) = 2.11$, $p = 0.149$, $F_{\text{group} \times \text{period}}(3, 128) = 5.32$, $p < 0.01$).</p> <p>In the <u>postpartum depressed group</u>: KYN and KA were \uparrow during <u>pregnancy</u>, but 3HAA during the <u>postpartum period</u> was \downarrow than that of the <u>non-depressed group</u>. No differences were noted in TRP or its metabolites between the <u>temporary gestational depressive group</u> or the <u>continuous depressive group</u> and the <u>non-depressive group</u>.</p> <p>The ratio of KYN in the <u>postpartum period</u> compared to that during <u>pregnancy</u> was significantly \downarrow in the <u>postpartum depressive group</u> compared to the <u>non-depressive group</u> (<i>one-way ANOVA</i>, $F(3, 128) = 5.27$, $p < 0.01$).</p> <p>In the <u>postpartum depressive group</u> KYN/TRP and KA/KYN ratio during <u>pregnancy</u> were \uparrow than those in the <u>non-depressive group</u>. KYN/TRP during <u>postpartum</u> to that during <u>pregnancy</u> was significantly \downarrow than the <u>non-depressive group</u> (<i>one-way ANOVA</i>, $F(3, 128) = 4.54$, $p < 0.01$).</p> <p>KYN, KA, and KYN/TRP, and KA/KYN ratio during <u>pregnancy</u> were \uparrow and 3HAA during <u>postpartum</u> was \downarrow in the <u>postpartum depressive group</u> compared to <u>non-depressive group</u>.</p> <p>KYN, KA, and KYN/TRP during <u>pregnancy</u> was correlated with depression scores during the <u>postpartum period</u> (<i>Pearson's correlation</i>: KYN: $r(77) = 0.330$, $p < 0.01$, KA: $r(77) = 0.278$, $p < 0.05$, KYN/TRP: $r(77) = 0.229$, $p < 0.05$, KA/KYN: $r(77) = 0.221$, $p = 0.05$). There was a <i>negative relationship</i> between 3HAA levels during <u>postpartum</u> period and depression scores (<i>Pearson's correlation</i>: $r(77) = -0.259$, $p < 0.05$).</p>
Vargas-Terrones (2017) (N = 124) Spain	Analyze trajectories of serotonin and tryptophan-related metabolites, bile acid metabolites, and microbial composition related to psychiatric history and current symptoms across the perinatal period.	Randomized control trial ³	<p>The percentage of depressed participants was \downarrow in the <u>intervention group</u> compared to the control group at <u>week 38</u> (18.6% vs. 35.6%) ($\chi^2 = 4.190$; $p = 0.041$) and at <u>6 weeks postpartum</u> (14.5% vs 29.8%) ($\chi^2 = 3.985$; $p = 0.046$).</p> <p>Significant differences were noted in the <i>multiple imputation analysis</i> at <u>38 weeks</u> (18.6% vs. 34.4%) ($\chi^2 = 4.085$; $p = 0.049$).</p> <p>A treatment effect was found in the per-protocol ($F_{2, 220} = 3.798$; $p = 0.024$) and in the <i>simple imputation</i> ($F_{2, 244} = 3.351$; $p = 0.037$) analyses. Differences were also found in the <i>group-time interaction</i> between gestational weeks 12-16 (baseline) and <u>6 weeks postpartum</u> ($p = 0.014$) in the per-protocol analysis.</p> <p>Differences were found in the group-time interaction between depression scores at <u>baseline</u> and <u>gestational week 38</u> ($p = 0.046$), and between <u>baseline</u> and <u>6 weeks postpartum</u> ($p = 0.025$), with a \downarrow depression score in the <u>intervention group</u> than in the <u>control group</u>.</p> <p>The participants considered to have excessive gestational weight gain, the <u>control group</u> had a \uparrow percentage of depression at <u>week 38</u> ($\chi^2 = 9.489$; $p = 0.002$) and at <u>6 weeks postpartum</u> ($\chi^2 = 5.202$; $p = 0.023$).</p>

				The percentage of depressed women was ↓ in the intervention group compared to the control group at week 38 for those with pre-pregnancy normal-weight BMI ($\chi^2 = 4.688; p = 0.030$).
<p>©Robertson Blackmore² (2016) (N = 171) US</p>	<p>Examine the relationship between exposure of intimate partner violence (IPV) and proinflammatory cytokine levels, a candidate mechanism accounting for poor psychiatric and obstetric outcomes, across the perinatal period</p>	<p>Prospective⁴</p>	<p>B, S</p>	<p>Lifetime exposure to IPV was associated with a range of psychiatric conditions, including generalized anxiety disorder, post-traumatic stress disorder, and depression. Further, IPV was associated with experiencing depression during both <u>pregnancy and postpartum</u>.</p> <p>Those with a history of IPV had ↑ levels of TNF-α ($z = -2.29, p < 0.05$) compared to those with <u>no IPV exposure</u>.</p> <p>After <i>controlling</i> for participants characteristics, a greater change in the levels of IL-6 during <u>pregnancy</u> compared to the <u>postpartum period</u> remained ($\beta = 0.21, p = 0.04$). This trend was different according to IPV status. Those who experienced violence had smaller changes in IL-6 across the time points compared to those <u>not exposed to violence</u> ($\beta = -0.36, p = 0.04$). From <u>6 weeks to 6-month PP</u>, those exposed to violence had a greater ↓ in IL-6 compared to those <u>without exposure</u> ($\beta = 0.36, p = 0.04$).</p> <p>The change in TNF-α levels at <u>32 weeks' gestation to 6 weeks PP</u> was ↑ than the change from <u>6 weeks to 6 months PP</u> ($\beta = 1.54, p < 0.01$).</p>
<p>Fasching (2012) (N = 361) Germany</p>	<p>Identify trajectories of perinatal depressive symptoms and their predictors among low-income South African women who were already at risk of depression during pregnancy.</p>	<p>Prospective³</p>	<p>B</p>	<p>Haplotype block analysis showed that 10 of the 14 haplotypes of the <i>THP2</i> gene were assembled in three haplotype blocks (B1-B3). SNPs rs6582071 and rs11178997 (haplotype A) were also analyzed given these SNPs are known to be of functional relevance.</p> <p>Genotype-phenotype association in haplotype Block A: The most common haplotype was GT (63.4% homozygous for this haplotype and 31.6% had one allele for <i>GT</i>). The extremely rare haplotype <i>GA</i> (only one carrier) was excluded.</p> <p>The <i>linear mixed model</i> indicated an effect for time ($p < 0.00001, F\text{-test}$) as well as haplotype GT ($p = 0.02, F\text{-test}$) and the interaction of time and haplotype GT ($p = 0.03, F\text{-test}$).</p> <p><i>Pairwise comparison</i> demonstrated ↑ depression scores at different timepoints: 1) time point 3 for those non-carriers of the GT haplotype compared to those carrying one copy of GT at time point 3 ($p < 0.01$). At timepoints 1 and 3, those non-carriers of the GT haplotype showed ↑ depression scores than those carrying two copies of the GT ($p = 0.01; p = 0.01$). ↑ depression scores were found at <u>timepoint 1</u> compared to <u>timepoint 2</u> in all three haplotype groups (0 GT: $p < 0.001$, 1 GT: $p < 0.01$, 2 GT: $p < 0.00001$). There was an ↑ in depression scores from <u>timepoint 2 to timepoint 3</u> for non-carriers of a GT haplotype ($p = 0.01$) and for carriers of two copies of GT ($p < 0.001$).</p>

				<p>Haplotype block B1: SNPs: rs6582071, rs11178997, rs1117899; Haplotypes: CAT, CGA, CGT, TAA</p> <p>Results are identical to those from haplotype block A described above.</p> <p>Haplotype block B3: Block B3 resulted in four haplotypes (GAA, TAA, TA, TTG) with the most common being TTA. 33% of those carrying two copies and 51.8%[^] carrying one copy.</p> <p><i>Linear mixed model:</i> Those carrying two copies of TAA (0.6%) were joined with the carriers of one copy of TAA (15.5%). An effect for time was shown ($p < 0.00001$, <i>F-test</i>) as well as the interaction between TAA and time ($p = 0.01$, <i>F-test</i>). Differences between the patient groups at time 1 were seen for TAA, and both genotype groups were different between all three time points ($p < 0.00001$, $p < 0.00001$, $p < 0.01$).</p> <p><i>Pairwise comparison:</i> Three timepoints showed ↑ depression scores at time 1 and time 2 for TAA (0 <i>TAA</i>: $p < 0.0001$, 1 + 2 <i>TAA</i>: $p < 0.0001$). At time 2 and 3, an ↑ in depression scores was seen in both groups (0 <i>TAA</i>: $p = 0.03$, 1 + 2 <i>TAA</i>: $p = 0.02$), and depression scores were lower at time 1 compared to time 3 (0 <i>TAA</i>: $p < 0.01$, 1 + 2 <i>TAA</i>: $p < 0.01$).</p> <p>SNPs outside of haplotype blocks: rs10879354 (T/T + T/C vs C/C) showed an effect for time ($p < 0.00001$) and SNP ($p = 0.04$) but not for interaction.</p> <p><i>Pairwise comparison</i> of the three timepoints showed ↑ depression scores at time 1 compared to time 2 ($p < 0.00001$); time 2 compared to time 3 indicated a depression score ↑ ($p < 0.001$); time 3 was ↑ than time 1 ($p < 0.01$).</p>
Lin ² (2009) (N = 200) <i>Taiwan</i>	To determine whether cytokines and kynurenine metabolites can predict the development of depression in pregnancy.	Cross-sectional ¹	B	<p>Six SNPs (T-703G, T-473A, A90G, C2755A, C10662T, G93329A) were noted from the <i>TPH2</i> gene.</p> <p>Two SNPs were found in the cases (T-473A, $p = 0.042$; A90G, $p = 0.038$) that were not found in <u>controls</u>.</p> <p><i>Risk analysis</i> showed that the “A” allele conferred a risk ($RR = 1.73$; 95% <i>CI</i>: 1.59-1.88) and demonstrated a dominant gene effect (A-allele carrier vs non-A allele carrier, <i>AC vs CC</i>; $p = 0.038$).</p> <p>A strong linkage disequilibrium in the 5’ region between SNPs -703A and A90G in both groups (<i>D’</i> ranged from 0.87 to 1) and the <i>D’</i> dropped as the distance between the pairs of markers ↑ (<i>D’</i> ranged from 0.50-0.76).</p> <p>The GTAA haplotype, which contains the risk 2755A allele, was different among <u>patients</u> and <u>controls</u> (<i>Fisher’s exact test</i>, $p = 0.044$); however, the significant in distribution of the GTAA haplotypes disappeared in a rigid permutation test ($p = 0.086$).</p>
Murakami ² (2008) (N = 865) <i>Japan</i>	To examine the association between dietary GI and glycemic load (GL)	Prospective ²	Bh	<p>Compared with dietary glycemic index (GI) in the <u>first quartile</u>, dietary GI in the <u>third quartile</u>, but not the <u>fourth</u> was associated with ↓ risk of <u>PP</u> depression. <i>Multivariate ORs</i> (95% <i>Cis</i>) for <u>PP</u> depression for each of the <u>four quartiles</u> were: 1.00 (reference), 0.68 (0.39-1.17), 0.56</p>

	and postpartum depression.			(0.32-0.995, $p = 0.048$), and 0.72 (0.41-1.26), respectively (p for trend = 0.18).
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171 Author² = secondary analysis; Design[#] = Design + Number of timepoints investigated; Domain of factors investigated in relation to depression: B =
172 Biological, Bh = Behavioral, E = Environmental, S = Social ; *Values (when provided)* = statistical values respective to analysis; Factors investigated in
173 relation to depression **bold**; Timeframe and/or groups investigated underlined.
174 ®Study reported race/ethnicity
175

176 Of the 25 articles included in the final review, 80% of the articles were published in 2011 or later
177 [30–49]. Though the US maternal mortality rates continue to markedly exceed that of other high-income
178 countries [50], over half (60%) of the studies [31–34, 36, 39–41, 45–48, 51–53] were conducted outside
179 of the US. Overall, sample sizes ranged from 16 to 3,252 (N = 9,481). Notably, sample sizes were much
180 lower in studies conducted in the US (n = 1,407, M = 141, SD = 127) [30, 35, 37, 38, 42–44, 49, 54, 55]
181 compared to non-US based studies (n = 8,074, M = 538, SD = 872.4) [31–34, 36, 39–41, 45–48, 51–53].
182 To determine if the difference was statistically significant, a Mann-Whitney U Test was performed using
183 the open-source software tool R v.2022.12.0+353 but did not demonstrate a statistically significant
184 difference (U = 50, $p = 0.1775$). However, the observable difference in sample sizes causes pause for
185 concern related to studies being sufficiently powered and potential limitations of existing evidence.
186 Thus, we deemed these findings to warrant further investigation to better understand implications and
187 possible explanations for the evident difference.

188 ***Upstream considerations for maternal mental health science***

189 A total of four [33, 42–44] of the 25 studies discuss conducting an *a priori* power analysis to
190 calculate the needed sample size with half of those being US based studies [37, 42]. However, of the two
191 US based studies reporting a power analysis, one [37] does not report the calculated sample size nor if
192 the study was sufficiently powered. Though power analysis was only reported in 16% of the 25 total
193 studies, over half (60%) [32, 34–38, 40, 41, 43, 46, 48, 49, 52, 53, 54] note a small sample size as a
194 study limitation. The percentage of US versus non-US based studies reporting sample size as a study
195 limitation was equal at 60% each. Given a majority of the studies do not discuss power and 60% of the

196 total included studies note a small sample size as a study limitation, all interpretations for subsequent
197 findings should be interpreted with caution.

198 We suspected secondary use of data from government or publicly available datasets with large
199 sample sizes would explain the difference in sample sizes between US versus non-US based studies.
200 Though nearly half of the studies were secondary analysis (48%) [38, 40, 41, 43–47, 49, 50, 53, 57], no
201 studies explicitly reported the use of government or publicly available datasets. Secondary analyses
202 accounted for 50% of the US based studies (50%) [40, 44, 47, 50, 57] versus 46.7% of non-US based
203 studies [38, 41, 43, 45, 46, 49, 53]. Given our secondary analysis assumption was false, we investigated
204 if differences in sources of research funding may account for differences in sample sizes as sources of
205 funding may impact study budgets. Of the 20 studies [33–35, 37, 38, 40–43, 45–54, 57] that reported
206 sources of funding, eight were from the US [33, 40, 42, 47, 50–52, 57] and 12 [34, 35, 37, 38, 41, 43,
207 45, 46, 48, 49, 53, 54] were non-US based studies. Of the eight in the US, seven studies [33, 40, 42, 47,
208 50, 52, 57] were federally funded whereas 9 non-US based studies [37, 41, 43, 45, 46, 48, 49, 53, 54]
209 reported support from federal funding. Such findings suggest that though non-US based funding is
210 slightly more diverse than US based funding sources, as expected, federal funding accounts for a
211 majority of US and non-US based research.

212 Since federal funding sources (e.g., National Institutes of Health [NIH]) are among the largest
213 sources of research funding, these findings prompted us to evaluate the scope of federal funding
214 allocated to maternal depression research. It is important to note that an in-depth analysis respective to
215 research funding budgets is beyond the scope of the present review and here we report the number of
216 publications coming from federally funded projects and the number of federally funded projects to date
217 on maternal depression. We used NIH RePORTER to approximate the number of publications funded
218 by NIH projects on “maternal depression” to compare US versus non-US based research

219 (reporter.nih.gov). Steps for this process can be seen in **Fig 2**. The initial search yielded 36,425
220 publications supported by 906 core projects (ranging from 1985 to 2023). Once duplicate publications
221 and publications not specific to maternal depression were removed (i.e., infant outcomes, other non-
222 perinatal population outcomes), only 136 (0.37%) US based publications under 93 (10.3%) core projects
223 (1991-2022) and 131 (0.36%) non-US based publications under 99 (10.9%) core projects (2002-2022)
224 remained from the initial search total of 36,425 publications and 906 core projects. These findings
225 suggest there is not a substantial difference by country in the number of publications or core projects
226 related to maternal depression, and that the amount of funding allocated to maternal depression research
227 may be overinflated once accounting for funding that does not have maternal outcomes as a primary
228 focus. For this reason, we also examined the project funding data from NIH RePORTER, irrespective of
229 country and publication, to understand how many maternal depression focused projects have been
230 federally funded to date. A total of 3,488 project results from 1985-2023 were returned for “maternal
231 depression.” However, similar to publications, once duplicate projects were accounted for and projects
232 with primary outcomes on persons other than perinatal persons were removed, only 158 projects (4.5%)
233 spanning over 38 years remained. Of the 158 projects, 92 (58.2%) were intervention studies. Further, a
234 number of southern states have some of the highest maternal mortality rates and/or poor maternal mental
235 health outcomes yet were among the lowest funded states for investigations on maternal depression
236 (e.g., Louisiana (0), Arkansas (0), Mississippi (0), New Mexico (0), Kentucky (1), Texas (4)) [1, 8, 58–
237 60].

238 **Fig 2. Steps for NIH RePORTER data acquisition**

239 These findings establish the first federally funded project in the US on perinatal depression
240 began 38 years ago indicating perinatal mental health is a relatively new area of investigation, yet
241 temporal trends in funding appear to be partial to intervention-based studies. Further, scientists appear to

242 be largely relying on secondary use of data to generate new knowledge which inevitably limits study
243 design and methodological decisions. Though further investigation is warranted, the use of secondary
244 data may be a product of budget limitations specific to maternal mental health focused research and
245 consequently result in inadequately powered studies that challenge advancements in maternal mental
246 health science and care. The rising maternal mortality and morbidity rates and evidence of perinatal
247 depression having short-term and long-term health consequences for the offspring and familial unit
248 positions maternal mental health as a public health issue. Given every person develops within a maternal
249 environment for up to 9.5 months, it is imperative that maternal mental health gains recognition as a
250 public health issue and sources of funding begin to prioritize maternal mental health science and care,
251 especially in those states with higher disease burden and mortality rates. Collectively, these findings
252 may partly explain why knowledge gaps persist and health disparity gaps continue to widen.

253 **Participant characteristics**

254 Of the 21 studies [33, 35–38, 40–45, 47–50] that reported sample age (88%), the mean age of
255 participants was 29.49 (2.71) years. Race and/or ethnicity was reported in nine [36, 40, 42, 44, 48, 50–
256 52, 57] of the 25 studies (36%), but only five studies [40, 44, 50, 51, 57] (20%) included race/ethnicity
257 in the analyses. Further, eight [36, 40, 42, 44 50–52, 57] of the nine studies that reported race/ethnicity
258 were studies conducted within the US and 66.7% of those studies [40, 42, 44, 51, 52, 57] had samples
259 comprised predominantly of Non-Hispanic White individuals. Meaning, existing knowledge on
260 determinants of perinatal depression may exclude minority populations which have the highest rates of
261 perinatal depression and maternal mortality and morbidity rates in the US [1,11, 58–60]. Of the 15
262 studies [35, 36, 40–42, 44–46, 48–53, 55, 57] that reported participant education, 80% [35, 40, 42, 44,
263 45, 49–53, 55, 57] had samples primarily comprised of individuals with at least some college education.
264 Nine studies [36, 38, 40, 41, 44, 45, 48, 49, 52] reported income and/or SES with 88.8% [36, 38, 40, 41,

265 44, 45, 49, 52] including a significant number (i.e., $\geq 50\%$ of total sample) of participants from low to
266 middle class. Nearly half (44%) of the studies [36, 38, 39, 45, 49–52, 55–57] reported parity with only
267 one study [49] specifically looking at first-time mothers.

268 These demographic factors are important to consider because current evidence suggests those
269 from lower SES and/or first-time mothers may be at increased risk of developing perinatal depression;
270 however, there is conflicting evidence for education being a risk factor versus a protective factor.
271 Demographic information is collected routinely at prenatal visits, and though largely un-modifiable, may
272 aid in detecting risk and providing evidence for clinical decisions on who warrants prenatal depression
273 screening to temporally monitor symptoms and the need for intervention. Therefore, future studies may
274 want to examine how different prenatal cohort demographics in clinical settings serve as predictors of
275 postpartum depression (PPD). Such investigations hold potential to leverage the use of existing data
276 with large sample sizes to inform how routinely collected clinical data can be aggregated and translated
277 into mechanisms for perinatal depression risk screening and provide evidence to inform clinical
278 decisions in who to screen during pregnancy.

279 The support of a partner is commonly suggested to be a protective factor for perinatal depression,
280 yet partner status was only reported in eight (32%) [33, 36, 44, 45, 49, 50, 52, 53] of the 25 studies.
281 Further, three studies [36, 50, 52] had at least half of the sample comprised of single individuals, and
282 five studies [44, 45, 50, 53] controlled for partner status in the analyses. Interestingly, only two studies
283 [38, 49] reported the mode of delivery (8%), and four studies (16%) [37, 38, 47, 56] reported
284 breastfeeding status. In the US, the overall cesarean delivery rate increased by 60% from 1996-2009
285 (20.7% to 32.9%), and then experienced a slight decline in 2019 (31.7%) before increasing again in
286 2020 (31.8%) and 2021 (32.1%) [61]. Though the COVID-19 pandemic may explain the most recent
287 increase in cesarean deliveries, growing evidence indicates there are psychological consequences

288 associated with cesarean deliveries, especially in the context of emergency cesarean deliveries [61] and
289 for Black/African American delivering persons [62]. Regarding breastfeeding status, the direction and
290 association of breastfeeding and perinatal depression has been controversial as some studies indicate
291 breastfeeding as a protective factor [63]. Conversely, it has been indicated that perinatal depression may
292 result in early cessation or that difficulties with breastfeeding may contribute to perinatal depression
293 symptoms. Thus, mode of delivery and breastfeeding status may be important variables to consider in
294 future investigations given the potential for psychological implications.

295 **Methodological factors**

296 There were 9 prospective cohort studies [39, 41, 46, 48, 50–52, 54, 57], eight cross-sectional
297 studies [34, 36, 38, 40, 43–45, 47], and six case-control studies [33, 35, 37, 49, 53, 56]. There was also
298 one pilot study [42] and one randomized control trial [55]. The most common types of analytic methods
299 applied were those looking at group differences (92%), correlations (52%), and regression (36%) while
300 more complex forms of analyses, such as, mixed effects modeling (8%) and path analysis (2%) were the
301 least common. All studies conducting biospecimen collection [33–40, 42, 43, 47–52, 54, 56, 57, 64]
302 provided methods for processing and analyzing of the samples, though the level of detail provided was
303 variable. All biospecimen samples were blood except for three studies that also collected either saliva
304 [48], fecal [42], or urine [57] samples in addition to blood samples. A total of six [33, 35, 36, 50, 52, 56]
305 studies reported the time of biospecimen collection, and one study reported requiring fasting (12 hours)
306 when collecting blood samples [35].

307 Though not unexpected, the Edinburgh Postnatal Depression Scale (EPDS) was the most used
308 instrument to measure depression (60%) [33, 35, 37–39, 42, 46–49, 51, 52, 54, 56, 57] followed by the
309 Center for Epidemiological Studies Depression (CES-D) (16%) [36, 40, 44, 55]. Only 20% of the

310 studies [41–43, 50, 53] utilized semi-structured interviews to measure depression for purposes other than
311 group allocation (i.e., depressive, control) and/or study eligibility. Of the 15 studies using EPDS to
312 measure depression, 40% did not report a specified cut-off score [39, 42, 47, 49, 51, 57]. The nine
313 studies [33, 35, 37, 38, 46, 48, 52, 54, 56] reporting EPDS cut-off scores varied between 9-13. The most
314 common cut-off score was 10 (33.3%) [38, 48, 56], which is lower than the current clinically
315 recommended cut-off score of ≥ 13 [66]. Of the seven studies [35, 37, 38, 46, 48, 54, 56] using an EPDS
316 cut-off score other than ≥ 13 , only three studies (28.6%) [35, 37, 46] provided scientifically supported
317 rationales for using an alternative cut-off score. The US Preventive Services Task Force indicated 10
318 and 13 as the most common cut-off scores used [10]. A recent individual participant data meta-analysis
319 suggested that using a cut-off score of ≥ 11 may be preferable due to combined sensitivity and
320 specificity being maximized [67, 68]. However, the current recommendation of ≥ 13 has remained
321 unchanged since it was developed by Cox and colleagues (1987) nearly four decades ago in a
322 postpartum sample in the United Kingdom.

323 As determined by quality appraisal assessments, concerns for risk of bias were noted or were
324 unclear related to the following types of bias: 13 (52%) selection bias, 3 (12%) recall bias, and 24 (96%)
325 measurement bias. **Fig 3.** A narrative description of risk of bias considerations for each included article
326 is detailed in **S1 Table**. Moderate level of risk was noted in six studies for selection bias [35, 40, 41, 43,
327 45, 47], one for recall bias [40], and zero for measurement bias, whereas high level of risk was noted in
328 two studies for selection bias [44, 46], two for recall bias [53, 57], and two for measurement bias [49,
329 53]. Further, a majority of the studies (88%) were indicated as having an unclear risk of bias for
330 measurement bias largely due to studies not providing sufficient information or references to support the
331 use of the measurement with respect to their sample characteristics and/or cut-off scores. For instance,
332 Sha and colleagues (2022) conducted a study in a non-Swedish sample (US based sample) but

333 referenced a study validating the Swedish version of the EPDS in pregnancy. Another example is that of
334 Miller and colleagues (2018) who used CESD to measure perinatal depression, and their supporting
335 reference was a study assessing the efficacy of the instrument for use as screener for depression in
336 community residing older adults (50-96 years of age).

337 **Fig 3. Summary of level of risk of bias per study.** ^aUS based study.

338

339 Further, it is important to note the items comprising the EPDS were adopted from existing scales
340 mainly developed in the United Kingdom (UK) in non-perinatal populations of variable age (16-65) [66,
341 69–71]. The sample characteristics described by Cox and colleagues (1987) are is incongruent with all
342 15 studies that reported using the EPDS. A total of 10 (66.7%) studies [33, 37, 41, 42, 46–51] cite Cox
343 and colleagues (1987) with 60% of these studies [33, 37, 42, 49–51] using this reference to substantiate
344 the validity and reliability of the instrument and/or cut-off score for use in their study though there are
345 notable differences in sample characteristics (i.e., country, mode of delivery, social class, relationship
346 status, language). Though the EPDS is currently considered “gold standard” for measuring perinatal
347 depression, increased inclusion of supporting references and/or scientifically supported rationales may
348 be particularly useful to aid in decreasing variability in cut-off scores by collectively establishing best
349 practices for determining cut-off scores respective to sample characteristics.

350 ***Methodological considerations***

351 As evidenced by the findings in this review, insufficient evidence is being provided for
352 instrument selection in measuring perinatal depression. Without robust measures for primary outcome or
353 group allocation variables, the risk of compromising the integrity of subsequent findings and the wider
354 body of evidence is high. Though the instrument has remained unchanged in nearly four decades, social
355 and political norms for child-bearing persons and marginalized groups have evolved since instrument

356 inception in the 1980's. Therefore, while it is common knowledge amongst maternal mental health
357 scientists that the EPDS or CESD are widely used to assess perinatal depression, it is important the
358 scientific community stay diligent in questioning the utility of instruments, especially when being used
359 in diverse samples. Thus, the psychometric properties of the instrument continually need to be critically
360 examined and it is important that supporting literature that is applicable to the present sample be
361 referenced as to generate evidence for instrument validity and reliability across diverse samples, to
362 establish best practices, and indicate when modifications and/or the development of new measures may
363 be warranted.

364 Given the variability in cut-off scores and evidence suggesting perinatal depression may
365 phenotypically differ between pregnancy and postpartum as well as from that of non-reproductive
366 depression [73, 74], it is important for future investigations to consider the utility of existing perinatal
367 depression measures for present day use. Such endeavors will aid in determining if and what
368 modifications may be warranted to improve the scientific and clinical utility of perinatal depression
369 measures. While we acknowledge the limitations of incorporating clinical interviews as a form of data
370 collection (e.g., time constraints, burdensome to participants/staff, training, internal validity concerns),
371 future investigations may be strengthened by conducting semi-structured interviews in addition to self-
372 report measures when measuring perinatal depression. Incorporating two forms of measurement that
373 yield two types of data (i.e., qualitative, quantitative) will not only strengthen any subsequent findings,
374 but may also be particularly useful to progress our understanding of depression symptoms exclusive to
375 perinatal populations and lead to advancements in life-stage informed measures that can increase
376 precision in detection and timely intervention.

377 The bioavailability of essential amino acids (e.g., tryptophan, competitor amino acids), the
378 precursors to a number of neurotransmitters commonly associated with psychiatric conditions, depends

379 on dietary intake. Thus, biospecimen collection respective to timing of food consumption is likely
380 important to consider in investigations including essential amino acids and its metabolites as levels may
381 significantly vary depending on when sample collection takes place. Yet no studies reported
382 biospecimen collection time in relation to timing of food consumption suggesting this is not common
383 practice. Free (non-albumin bound) tryptophan (TRP) is what can be transported across the blood-brain-
384 barrier (BBB) to make it available in the brain for serotonin synthesis [22]. Conversely, it has been
385 suggested that TRP has a higher affinity for the BBB than for albumin, and albumin bound TRP close to
386 the BBB may separate from albumin to then transport across the BBB. Meaning, measurement of both
387 free and total TRP is likely important in the study of psychiatric conditions, but only one study [34]
388 specified if free and/or total TRP was measured. For these reasons, it is important for future
389 investigations including essential amino acids to 1) consider biospecimen collection times in relation to
390 timing of food consumption to advance our understanding of tryptophan metabolism in the perinatal
391 period and 2) to clarify if free and/or total TRP is being measured as such considerations are essential
392 for making meaningful interpretations of the findings.

393 Lastly, each type of biospecimen and method for processing and analyzing of samples introduces
394 bias innate to the specified type and method [65]. Therefore, decisions on what type of biospecimen(s)
395 to collect and methods of analysis warrant thoughtful consideration. As evidenced by the articles
396 included in this review, there is a need for increased transparency in reporting of methods and rationales
397 to support such methods. Transparency is vital not only for the purposes of reproducibility but also to
398 collectively establish best practices for methods of biological sample selection, collection, processing,
399 and analysis. Overall, these findings suggest that methods of investigation in maternal mental health
400 science have room for improvement and can be strengthened with increased attention and reporting of
401 sufficiently supported methodological decisions and processes, such as those discussed in this review.

402 By strengthening the methods of investigation in maternal mental health science, we can progress
403 standards for best practices as well as mitigate the risk of generating conflicting findings that are a result
404 of unsound methods rather than true conflicting findings.

405 **Biological determinants**

406 A total of 20 studies [33–40, 42–44, 47–52, 54, 56, 57] investigated biological determinants of
407 perinatal depression. Inflammatory markers were investigated in 10 studies [33, 35, 36, 40, 44, 48, 50–
408 52, 57], tryptophan and/or tryptophan metabolites in seven studies [33, 34, 42, 49, 52, 54, 56], genetic
409 polymorphisms in three studies [37, 39, 43], micronutrient alterations in two studies [35, 38], and
410 neurological factors in one [47], respectively.

411 ***Inflammatory markers and oxidative stress***

412 TNF- α (pro-inflammatory cytokine) was positively correlated with prenatal depression and those
413 with prenatal depression had higher TNF- α levels compared to those without [35, 44]. Miller and
414 colleagues (2018) found that even when controlling for sociodemographic factors, those with prenatal
415 depression unresponsive to antidepressant treatment and those with untreated prenatal depression had
416 higher TNF- α levels compared to those with prenatal depression that responded to antidepressant
417 treatment. These findings suggest that TNF- α may be a useful biomarker for determining a subtype of
418 perinatal depression that is treatment resistant to antidepressants. However, it is important to note Miller
419 and colleagues (2018) do not specify specific antidepressants used for treatment nor the duration of
420 treatment. Additionally, intimate partner violence is commonly indicated as a risk factor for perinatal
421 depression. Robertson-Blackmore and colleagues (2016) found a history of intimate partner violence to
422 be positively associated with TNF- α . Also suggesting interpersonal relationships have potential to
423 induce inflammatory responses, Ross and colleagues (2018) found romantic partner relationships low in

424 both negative (e.g., conflict) and positive (e.g., support, intimacy) features to be associated with lower
425 anti-inflammatory cytokines (IL-10, IL-13) and higher pro-inflammatory profile (IL-6:IL-10 ratio).
426 Whereas Finy and colleagues (2018) found past (i.e., childhood abuse) and current adversities (i.e.,
427 lower SES) to be positively associated with elevations in inflammatory markers (i.e., CRP, IL-6).

428 A positive association among depression symptoms and IL-6 (involved in both immune response
429 and inflammation) was found [40, 48] and even when controlling for pre-pregnancy body mass index
430 (BMI), higher depression scores were positively associated with both IL-6 and TNF- α [36]. Similarly,
431 Achytes and colleagues (2020) found, even after adjusting for demographic factors and pharmacological
432 treatment, that postpartum individuals with elevated plasma levels of IL-6, IL-8 (pro-inflammatory
433 cytokine), and TNF- α (modest) had increased odds of PPD, while a decrease in IL-2 (pro-inflammatory
434 cytokine) increased the odds of PPD. Plasma IL-10 (anti-inflammatory cytokine) and IL-1 β (pro-
435 inflammatory cytokine) were not associated with increased risk for PPD. Results from Sha and
436 colleagues (2022) support the aforesaid findings specific to IL-6 but not for IL-1 β . Moreover, IL-1 β was
437 found to be negatively associated with depression scores across four-time points (i.e., three trimesters,
438 one postpartum time point). Findings from Sha and colleagues (2022) also suggest a potential second-
439 trimester biomarker panel (IL-6, TNF- α , quinolinic, and kynurenine) to predict PPD. Conversely,
440 Christian and colleagues (2009) found that depression scores were positively correlated with IL-2 and
441 IL-10, and Robertson-Blackmore and colleagues (2016) did not find depressive symptoms at 32 weeks'
442 gestation to be associated with IL-6 or TNF- α . Differences in perinatal timepoints assessed and
443 methodological decisions may explain conflicting results.

444 Across the pregnancy period depression was positively associated with oxidative stress, as
445 measured by 8-isoprostane (considered a stable biomarker of oxidative stress) in urine, and oxidative
446 stress mediated the relationship between prenatal depression and spontaneous preterm birth [57]. While

447 sources of oxidative stress vary, evidence suggests the sources are largely related to environmental and
448 lifestyle factors. Therefore, it may be meaningful to investigate factors that influence oxidative stress in
449 the perinatal period in relation to associated health outcomes (i.e., depression, spontaneous preterm
450 birth) to explore how such factors may be attenuated and leveraged for risk mitigation.

451 ***Tryptophan pathway, metabolites, and neurotransmitters***

452 Brain TRP availability was negatively associated with plasma competitor amino acid
453 concentrations during the postpartum period (+77% isoleucine, +55% leucine, +52% tyrosine) and the
454 intensity of postpartum “blues” [34]. It is important to note that though we acknowledge postpartum
455 blues as different than PPD, the difference is largely the duration of symptoms as postpartum blues is
456 considered transient. The timepoint investigated by Bailara and colleagues (2006) was three days
457 postpartum, meaning it is unknown if these symptoms were in fact transient or if symptoms continued
458 beyond study participation and were later considered PPD. Therefore, for transparency, we retained the
459 use of the term postpartum blues and decided to include these findings given the findings are consistent
460 with those in non-perinatal populations yet is understudied in perinatal populations [22, 79].

461 Plasma levels of serotonin and neuropeptide Y (stimulates food intake, particularly
462 carbohydrates) were lower in those with PPD [49]. Conversely, dopamine (role in movement,
463 motivation, pleasure) and norepinephrine (role in flight-or-fight response) were higher in those with
464 PPD compared to controls. Achytes and colleagues (2020) also found that lower plasma serotonin
465 increased the risk of PPD, whereas absolute plasma levels of TRP did not affect the risk of PPD. Though
466 not specific to depression, Achytes and colleagues (2020) also found that suicide, a distal outcome of
467 depression and a leading cause of maternal mortality, was associated with lower levels of plasma
468 serotonin and lower plasma serotonin increased the odds of a completed suicide attempt during

469 pregnancy even when adjusting for EPDS scores. Though such findings require further investigation,
470 serotonin may be significant biomarker of suicide risk in perinatal populations.

471 Prenatally, plasma levels of kynurenine (KYN) and kynurenic acid (KA) were significantly
472 higher in the depressed group compared to the non-depressed group. Postpartum, higher plasma levels of
473 KYN, KA, and KYN/TRP and KYN/KA ratios were observed in the PPD group compared to those in
474 the non-depressed group [54]. Sha and colleagues (2022) found quinolinic acid, a neurotoxic TRP
475 metabolite that gets synthesized via the KYN pathway, to be associated with depression in the third
476 trimester. Higher plasma levels of quinolinic acid were associated with both increased severity and risk
477 of falling into a category of clinically significant symptoms (i.e., EPDS ≥ 13). In non-perinatal
478 populations with depression, inflammation is suggested to play a role in the shunting of TRP down the
479 KYN pathway and KYN has become increasingly recognized as a potential link between inflammation
480 and depression [22, 80]. KYN has also been linked with sleep disturbances, a common depression
481 symptom, which is also commonly experienced perinatally [80, 81]. Poor sleep has also been widely
482 established as a risk factor for a number of chronic health conditions. For these reasons, it may be
483 beneficial for future research to explore such interactions and the directionality of said interactions as
484 they relate to perinatal depression onset, chronicity, and risk for comorbidities.

485 Conversely, Veen and colleagues (2016) found KYN to be significantly lower in patients with
486 perinatal depression compared to non-depressed controls. Similarly, findings from Nazzari and
487 colleagues (2020) suggest a negative association among prenatal KYN levels and depression symptoms
488 in late pregnancy and postpartum after adjusting for maternal age. No differences were found in the
489 plasma levels of TRP or its metabolites among perinatal depressed groups compared to non-depressed
490 controls [54, 56]. Kimmel and colleagues (2022) found no significant associations among TRP/serotonin
491 related metabolites or bile acids and depression. While three studies [42, 48, 56] provided conflicting

492 results related to KYN levels, differences in the timepoints assessed, the country where the study took
493 place, and differences in methodological decisions may explain the conflicting results as lifestyle
494 choices and psychosocial and environmental factors are likely quite different between countries. Two of
495 the three studies [42, 56] were also likely underpowered as one was a pilot study with a sample size of
496 30 and the second had a sample size of 42, with 23 being cases of PPD while the remaining were
497 controls. Lastly, as previously discussed, sleep disturbances have been linked to the KYN pathway and
498 depression, and inflammation is suggested to increase the shunting of TRP down the kynurenine
499 pathway. However, five of the seven studies examining TRP did not consider inflammation as a variable
500 in their study nor did any of the seven studies assess sleep. Inflammation and sleep disturbances are both
501 commonly experienced perinatally which may explain why these factors have been overlooked;
502 however, for the reasons discussed, they are important factors to consider in the context of perinatal
503 depression.

504 ***Genetic Polymorphisms***

505 Catechol-O-methyltransferase (*COMT*) is a gene that provides instruction for the metabolism
506 of catecholamine neurotransmitters (i.e., epinephrine, norepinephrine, dopamine). A common functional
507 polymorphism studied in relation to psychiatric conditions is the *COMT* variant, *Val¹⁵⁸Met* (rs4680),
508 where an amino acid change of valine [val] to methionine [met] is suggested to reduce the activity of the
509 *COMT* enzyme that metabolizes the aforesaid neurotransmitters [82–84]. This polymorphism is
510 suggested to influence cognition and behavior in psychiatric conditions, such as depression. Though the
511 *COMT* variant is minimally explored in perinatal depression, Comasco and colleagues (2011) found an
512 association among the polymorphism (*COMT-Val¹⁵⁸Met*) and PPD symptoms at 6 weeks but not at 6
513 months. Additionally, genetic variation in the Monoamine oxidase A (*MAOA*) gene is suggested to
514 contribute to depression, specifically when *MAOA* activity is high. Higher gene activity occurs when

515 there is a polymorphism in rs1137070 where a C allele replaces a T. Higher *MAOA* activity induced by
516 this polymorphism may result in rapid catalyzation of the neurotransmitters serotonin and
517 norepinephrine [85]. However, a meta-analysis suggests the T variant is associated with major
518 depression in non-pregnant populations [86]. With regard to gene-gene interactions, Comasco and
519 colleagues (2011) found *COMT-MAOA* interactions to be significantly associated with PPD symptoms.
520 For instance, among low *MAOA* carriers (T allele), the *Met* variant of the *COMT* gene was related to
521 PPD symptoms; whereas the high *MAOA* variant (C allele) was related to PPD symptoms only when
522 combined with the *Met* allele of *COMT*. In terms of gene-environment interactions, *COMT-Val¹⁵⁸Met*
523 was also associated with PPD symptoms when psychiatric history and stress were present. This
524 interaction effect may explain why studies have reported significant associations of both *MAOA*
525 polymorphisms with depression.

526 Two studies explored polymorphisms of tryptophan hydroxylase 2 (*TPH2*), the rate limiting
527 enzyme of serotonin biosynthesis, in those with perinatal depression [39, 43]. The *TPH2* gene plays a
528 major role in the regulation of the neurotransmitter serotonin, and genetic variants of *TPH2* are
529 suggested to play a significant role in both susceptibility to depression and response to a commonly
530 prescribed treatment, selective serotonin reuptake inhibitors (SSRIs) [87, 88]. Lin and colleagues (2009)
531 found that the *TPH2 C2755A* polymorphism occurred only in those with perinatal depression and/or an
532 anxiety disorder. Further, though significance faded after Bonferroni correction, a risk analysis
533 demonstrated that the *TPH2 C2755A* polymorphism increased risk of perinatal depression and exhibited
534 a dominant gene effect. However, it is important to note the reported study is specific to a Han Chinese
535 population, and the authors position this polymorphism as a potential population specific indicator of
536 depression risk based these findings and current evidence in Han Chinese populations. Also exploring
537 *TPH2* polymorphisms, Fasching and colleagues (2012) found the single-nucleotide polymorphism

538 (SNP) in intron 8 (rs10879354) to be the only SNP to show consistent effects across all time points (\geq
539 31 weeks gestation, 48-72 hours postpartum, 6-8 months postpartum) in a German population. Since
540 *TPH2* polymorphisms influence the activity of neurotransmitters commonly associated with depression
541 in non-perinatal and perinatal populations [87, 88], it would be beneficial for future investigations to
542 further examine potential genetic biomarkers and their influence on relevant metabolic pathways.
543 Progressing this area of inquiry will not only improve the odds of discovering a genetic biomarker for
544 perinatal depression risk but may also advance our understanding of population specific biomarkers
545 which could drastically increase precision in early detection and intervention.

546 ***Micronutrient alterations***

547 A negative association among vitamin B12, cobalamine deficiency (cB12), and serotonin were
548 observed with probable PPD [38]. Adequate amounts of B12 are suggested to be particularly important
549 in pregnancy for both the pregnant person as well as the offspring given its role in nervous system health
550 [89, 90]. Concurrent with folate, B12 aids in DNA synthesis as well as red blood cell production.
551 Interestingly, dietary sources considered high in B12 (i.e., animal-based proteins) are also sources high
552 in TRP, the precursor to serotonin [91]. In the same study [38], a positive association was found among
553 Methylmalonic acid (MMA) (suggested marker of functional deficiency of vitamin B12), homocysteine
554 (hcy) (broken down by B12 and folic acid; elevated levels suggest vitamin deficiency), and 5
555 methyltetrahydrofolic acid (5-methyl THF) (suggested marker of a folate/methyl trap due to existing
556 B12 deficiency) and depression symptoms. Further, elevated MMA and 5-methyl THF were found to be
557 significant predictors of probable PPD, and MMA was suggested to be a potential mediator of PPD.

558 Other micronutrient alterations that were associated with prenatal depression were total n-3
559 polyunsaturated fatty acids (n-3 PUFA), eicosapentaenoic acid (EPA), and docosahexaenoic acid

560 (DHA). EPA and DHA are two notably important fatty acids given they are critical for the development
561 and function of the central nervous system in both perinatal persons and the developing fetus and have
562 anti-inflammatory properties [92]. Chang and colleagues (2018) found that those with prenatal
563 depression had lower levels of total n-3 PUFA, EPA, and DHA compared to those without prenatal
564 depression. Prenatal depression duration was negatively correlated with total n-3 PUFA, EPA, and
565 DHA. These findings indicate micronutrient deficiencies, either due to low dietary consumption and/or
566 an existing functional deficiency, may be useful measures for detecting perinatal depression risk or early
567 symptom onset. Though supplementation of B12 has provided conflicting results, reviews and meta-
568 analyses of RCTs have shown the fatty acids discussed can improve depression symptoms in perinatal
569 and non-perinatal populations and may be useful as an independent or adjuvant treatment modality
570 depending on the individual [92–94]. This is particularly important to note for perinatal populations as
571 pharmacological interventions are not highly desired in pregnant or breastfeeding persons due to
572 concerns for potential implications on the developing offspring [95, 96]. Thus, though future research is
573 needed, micronutrient supplementation may be desirable option for those at risk or those exhibiting mild
574 depressive symptoms during pregnancy to serve as form of risk mitigation and indirect health promotion
575 strategy for the developing offspring.

576 *Neurological alterations*

577 Brain serotonin-1A (5HT1A) receptor binding potential, as measured by positron emission
578 tomography (PET), suggested a 20-28% reduction in postsynaptic 5HT1A receptor binding in those
579 experiencing PPD [47]. The most significant reductions were found to be in the anterior cingulate
580 (related functions - emotional expression, attention, mood regulation) and mesiotemporal cortices which
581 includes the amygdala (input and processing of emotion) and hippocampus (episodic memory). Likely
582 due to methods of data acquisition and the unknown risks for perinatal individuals and their offspring,

583 investigations into neuroanatomical features and their respective roles in perinatal specific depression
584 are sparse. While there are some conflicting findings, the present findings are consistent with some
585 literature on depression and/or anxiety in non-perinatal populations [98, 99].

586 **Behavioral determinants**

587 Six studies [33, 38, 41, 45, 46, 55] investigated behavioral determinants of perinatal depression.
588 Dietary intake was investigated in three studies [38, 45, 46] whereas suicide (i.e., attempts, ideation, risk)
589 was explored in two [33, 41]. Physical activity [55] and functional impairment [41] were each explored in
590 one.

591 Though specific to the third quartile (ascending quartiles per glycemic index/load), Murakami and
592 colleagues (2008) found higher dietary glycemic index (GI) decreased the risk of PPD, while no
593 associations were found between PPD and dietary glycemic load (GL). Lower milk, meat, and egg
594 consumption during the postpartum period was associated with probable PPD [38]. Further, even after
595 adjusting for potential dietary and non-dietary confounding factors, higher tryptophan intake was
596 independently negatively associated with depressive symptoms in pregnancy [45]. TRP, the precursor to
597 the neurotransmitter serotonin that is commonly associated with depression, is an essential amino acid.
598 Essential amino acids, such as TRP, are only made available through dietary intake as they are not
599 independently produced by the body [22]. Though Dhiman and colleagues (2021) did not specifically
600 examine TRP, animal and plant-based proteins (i.e., milk, meat, eggs, spirulina, nuts and seeds) are among
601 some of the highest sources of TRP. Thus, together these findings indicate lower dietary consumption of
602 TTRP in the perinatal period may contribute to increased risk of depression onset which is consistent with
603 findings from animal and human studies in non-perinatal populations [19, 22, 73, 74]. Additionally,
604 though not a variable noted in any of the included studies, nausea and vomiting due to “morning sickness”

605 or hyperemesis gravidarum (severe type of morning sickness) occurs in roughly 70% of pregnancies.
606 Thus, these variables may be particularly important to consider in investigations of TRP metabolism
607 perinatally as these variables are likely to increase risk for depletion of essential nutrients vital for maternal
608 and fetal health.

609 Two studies independently demonstrated alcohol consumption [41] during pregnancy or a high
610 risk of suicide (i.e., current and past attempts and ideation) [33, 41] increased the odds of being classified
611 into the perinatal depression group. Those endorsing higher functional impairment had increased odds of
612 being classified in the perinatal depression group [41] whereas a single randomized control trial (RCT)
613 [55] demonstrated a prenatal physical exercise program to decrease the risk of PPD. The RCT consisted
614 of 60-minute sessions three times per week starting at 12-16 weeks gestation and found the percentage of
615 people reporting depression was lower in the intervention group than in the control group at both 38 weeks
616 gestation and 6 weeks' postpartum. The findings related to substance abuse, history of suicide attempts or
617 current suicidal ideation, and exercise are consistent with existing literature. Conversely, functional
618 impairment is a less commonly studied factor [75]. Functional impairment is a marked feature of clinical
619 depression yet is not routinely assessed, if at all, during the perinatal period. Exploring the implications
620 of functional impairment in the perinatal period may be particularly useful to clinically monitor for
621 declines from baseline functioning for those with and without pre-existing disabilities or functional
622 impairments. Further research in this area may help advance detection strategies for life-stage specific
623 onset or exacerbations of pre-existing functional impairment that may not otherwise be visible to clinicians
624 and provide evidence for identifying individuals in need of increased support. While we understand these
625 behavioral factors may increase the risk of PPD and behavioral interventions targeting such factors may
626 aid in mitigating risk, it is important to consider who is disproportionately impacted by perinatal

627 depression and the broader contextual factors that serve as potential barriers and are beyond the immediate
628 control of the individual (e.g., social determinants of health).

629 **Social and environmental determinants**

630 A total of seven studies [36, 37, 40, 41, 50, 51, 53] investigated social and environmental
631 determinants of perinatal depression. Five studies investigated significant life events (e.g., trauma,
632 intimate partner violence, history of childhood abuse) [37, 40, 41, 50, 53] and social support [36, 37, 40,
633 41, 51]. Perceived stress was investigated in two studies [36, 37] and unhappiness with pregnancy [37]
634 and food insecurity [41] were investigated in one study.

635 Two commonly suggested risk factors of perinatal depression, psychiatric history [37] and
636 significant life events [37, 40, 41, 50, 53], were positively associated with perinatal depression [76, 77].
637 Even after adjusting for sociodemographic factors, personal history of depression, and timing of
638 depression onset, those reporting a history of childhood trauma were at higher risk of PPD, anxiety, and
639 suicide attempts than those without [53]. A dose effect was present between the number of childhood
640 trauma types and risk of PPD. Robertson-Blackmore and colleagues (2016) examined lifetime exposure
641 to intimate partner violence and found lifetime intimate partner violence to increase the likelihood of
642 experiencing perinatal depression. For those currently endorsing frequent hostile and insensitive social
643 interactions experienced an increase in prenatal depressive symptoms [36]. Further, there was a negative
644 relationship among social support and depression symptoms, and low social support served as a
645 significant predictor of perinatal depressive symptoms [36, 41, 51]. Relatedly, higher negative qualities
646 in one's interpersonal relationships were associated with greater depressed mood, perceived stress, and
647 pregnancy distress [51]. Collectively, these findings indicate the level of past exposure, type of
648 exposure, and current appraisal of interpersonal relationships may moderate one's level of risk for PPD.

649 Consistent with current evidence, perceived stress was positively correlated with perinatal
650 depression [36, 37, 40, 51]. Being unhappy about one’s pregnancy was also positively correlated with
651 perinatal depression [36]. Such findings are particularly important to note for US based research given
652 the current political and social climate related to child-bearing age person’s rights and abortion access.
653 Irrespective of one’s personal views on the matter, the recent changes in federal and state level
654 regulations are likely to increase rates of perinatal depression and subsequently result in a surge of
655 negative health outcomes in both perinatal persons and the offspring. Fox and Brod (2021) investigated
656 the cost of perinatal complications in the US for all 2019 births from conception to age 5 and found such
657 complications to result in \$32.2 billion in societal costs (i.e., healthcare expenses, loss of productivity,
658 social support services) [78]. It was also suggested these estimates likely underrepresent the totality of
659 the financial burden. This analysis was conducted prior to federal and state level changes on abortion
660 access and a global pandemic. Despite spending more on healthcare than any other developed country,
661 the US and its healthcare system have yet to gain control over the rising maternal mortality and
662 morbidity rates. Meaning the US is likely not prepared to manage a surge in perinatal health
663 complications, especially so soon after a global pandemic. Therefore, advancements in maternal mental
664 health care are vital for individual and systemic health. Future investigations to further examine
665 unhappiness with pregnancy as a potential risk factor as well as diligent monitoring of trends in
666 incidence since the change in regulations are necessary to generate evidence for increased resources and
667 support.

668 One study [41] found food insecurity to predict perinatal depression in two groups (i.e., prenatal
669 only depression, prenatal and postpartum depression) and the odds of experiencing depression both
670 prenatally and in the postpartum was 2.5 greater in the presence of food insecurity. Interestingly, non-
671 perinatal specific research that began examining the impact of COVID-19 on food insecurity found food

672 insecurity to disproportionately impact racial and ethnic groups, and the states with the highest projected
673 food insecurity rates based on overall population occurred in states that also have some of the highest
674 maternal mortality rates (i.e., Louisiana, Texas) [76]. These findings suggest food insecurity as a
675 potential predictor of PPD and demonstrates the importance of post-pandemic science to consider the
676 remnant effects of global pandemics on perinatal health.

677 **Prospective interactions**

678 The specific factors explored across the four domains were highly variable. Therefore, this
679 review does not claim to present an exhaustive description of all potential interactions that can be
680 interpreted from findings of the aggregated factors. Due to patterns in which interactions with TRP and
681 its metabolites emerged, we specifically chose to focus on these interactions as they may suggest a
682 potential role in perinatal depression risk and onset.

683 Although minimally explored in perinatal populations, disruption in serotonin or the serotonergic
684 system is widely considered to contribute to depression onset, maintenance, and response to treatment
685 (i.e., SSRIs) in non-perinatal populations [88, 98, 99]. Some evidence suggests the disruption of the
686 serotonergic system is more prominent in biologically born females compared to males, and that the
687 dysregulation of serotonin may partly explain why biologically born females experience depression at
688 two times the rate of biologically born males. Given TRP is the precursor to serotonin, brain TRP
689 availability is vital for adequate production of the neurotransmitter serotonin. Other essential amino
690 acids (e.g., isoleucine, leucine, phenylalanine) compete with TRP to cross the BBB and are the
691 precursors to several other neurotransmitters (e.g., dopamine, norepinephrine) that are implicated in
692 psychiatric conditions [79, 100]. Consistent with current evidence indicating TRP competes with other
693 essential amino acids to cross the BBB, Bailara and colleagues (2016) found a negative association

694 among brain TRP availability and competitor amino acid concentrations, notably one of which was
695 tyrosine, a precursor of dopamine and norepinephrine. Since essential amino acids (i.e., TRP, isoleucine,
696 leucine, phenylalanine) are not independently produced by the body and depend on dietary intake for
697 availability, dietary habits, food accessibility, and other factors that may influence changes in metabolic
698 activity (e.g., genetic polymorphisms, morning sickness, breastfeeding, comorbid conditions) are
699 particularly important to consider in this area of inquiry. A majority of the studies in this review
700 examining TRP and its metabolites did not concurrently examine or control for dietary habits,
701 micronutrients, and/or food accessibility; however, a majority of the studies that did examine such
702 factors independent of TRP found associations with PPD [35, 38, 41, 46].

703 The mechanisms underlying the increased uptake of TRP in the brain are not fully understood,
704 but some evidence suggests higher dietary carbohydrate intake can promote the uptake of TRP in the
705 brain resulting in increased serotonin [100, 101]. Interestingly, Rihua and colleagues (2018) found
706 plasma levels of serotonin and neuropeptide Y (stimulates food intake, particularly carbohydrates) [102,
707 103] to both be lower in those with PPD. Achytes and colleagues (2020) also found lower levels of
708 plasma serotonin to increase risk of PPD but did not denote increased risk of PPD related to plasma
709 TRP. However, they did note an elevated KYN/serotonin ratio was associated with an increased risk of
710 PPD. TRP degradation into KYN is suggested to increase in response to immune and inflammatory
711 activation in non-perinatal populations experiencing depression [19, 22, 104, 105]. Since pregnancy
712 naturally induces immune and inflammatory responses in the pregnant individual to accommodate the
713 developing fetus, TRP degradation into KYN may occur more often during this life-stage and increase
714 one's risk for depression. Veen and colleagues (2016) did not explore the aforesaid in the pregnancy
715 period, but they did find this to be the case in the physiological postpartum period.

716 Though the life-stage itself induces a unique immune and inflammatory response, additional
717 factors throughout the perinatal period, such as the social, environmental, and behavioral factors
718 discussed in this review (e.g., stress, social support, intimate partner violence) may further promote
719 immune and inflammatory responses and increased TRP degradation down the KYN pathway
720 predisposing one to depression onset. Further, sleep disturbances are common perinatally and are often
721 attributed to “normal” pregnancy and postpartum symptoms, but sleep disturbances also happen to be a
722 common symptom of depression and/or anxiety in non-perinatal populations. Though sleep disturbances
723 are linked to the TRP and KYN pathways, they are not considered in any study in this review yet may
724 serve as a moderating factor that perpetuates a negative feedback loop which contributes to chronicity or
725 a risk for symptom relapse, notably in the postpartum period due to poor quality of sleep as a result of
726 child rearing responsibilities. Meaning, certain biochemical pathways may account for specific
727 depression symptoms and indicate subtypes of perinatal depression that can be leveraged to increase
728 precision in detection and intervention.

729 In the context of PPD, these findings may indicate when dietary intake of tryptophan or
730 tryptophan uptake promoting foods are limited amid immune and inflammatory responses, competitor
731 amino acids are being prioritized for transport across the BBB and/or TRP may be shunted towards the
732 KYN pathway. Moreover, both pathways may result in decreased production of the neurotransmitter
733 serotonin and explain the risk for and onset of PPD, and the level of risk would be further increased for
734 those with a genetic predisposition (i.e., genetic polymorphisms) or those experiencing the other
735 biopsychosocial or behavioral factors discussed in this review. Thus, future investigations are needed to
736 further explore these prospective interactions as these interactions may serve as significant risk factors
737 of PPD that can be detected and intervened upon during pregnancy.

738 **Conclusion**

739 The factors discussed in this review have been independently indicated as probable determinants
740 of PPD risk and onset. However, what is not evident in independent investigations but is demonstrated
741 in this review is that various interactions among diverse determinants and TRP metabolism may provide
742 a deeper understanding of what contributes to the pathophysiology of perinatal depression or perinatal
743 depression risk. Future investigations are needed to address methodological issues in maternal mental
744 health science and care as well as explore these prospective interactions as these interactions hold
745 potential to evolve as a PPD risk phenotype (observable characteristics). Such a phenotype can serve as
746 a robust foundation for the development of clinically efficient yet meaningful mechanisms for risk
747 detection and inform patient centered risk mitigation strategies. Further, the present review establishes
748 the value of integrative approaches in the investigation of perinatal depression and suggests the
749 application of team science principles (e.g., collaboration, diverse expertise) may be particularly useful
750 to this area of inquiry to expedite the discovery of clinically relevant findings and strengthen scientific
751 methods.

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1048 **Supporting information**

1049 **S1 Table. Description of risk of bias considerations.** Author² indicates the study was a secondary
1050 analysis. ®Study reported race and/or ethnicity.

1051 **S1 Checklist. PRISMA 2020 Checklist.**

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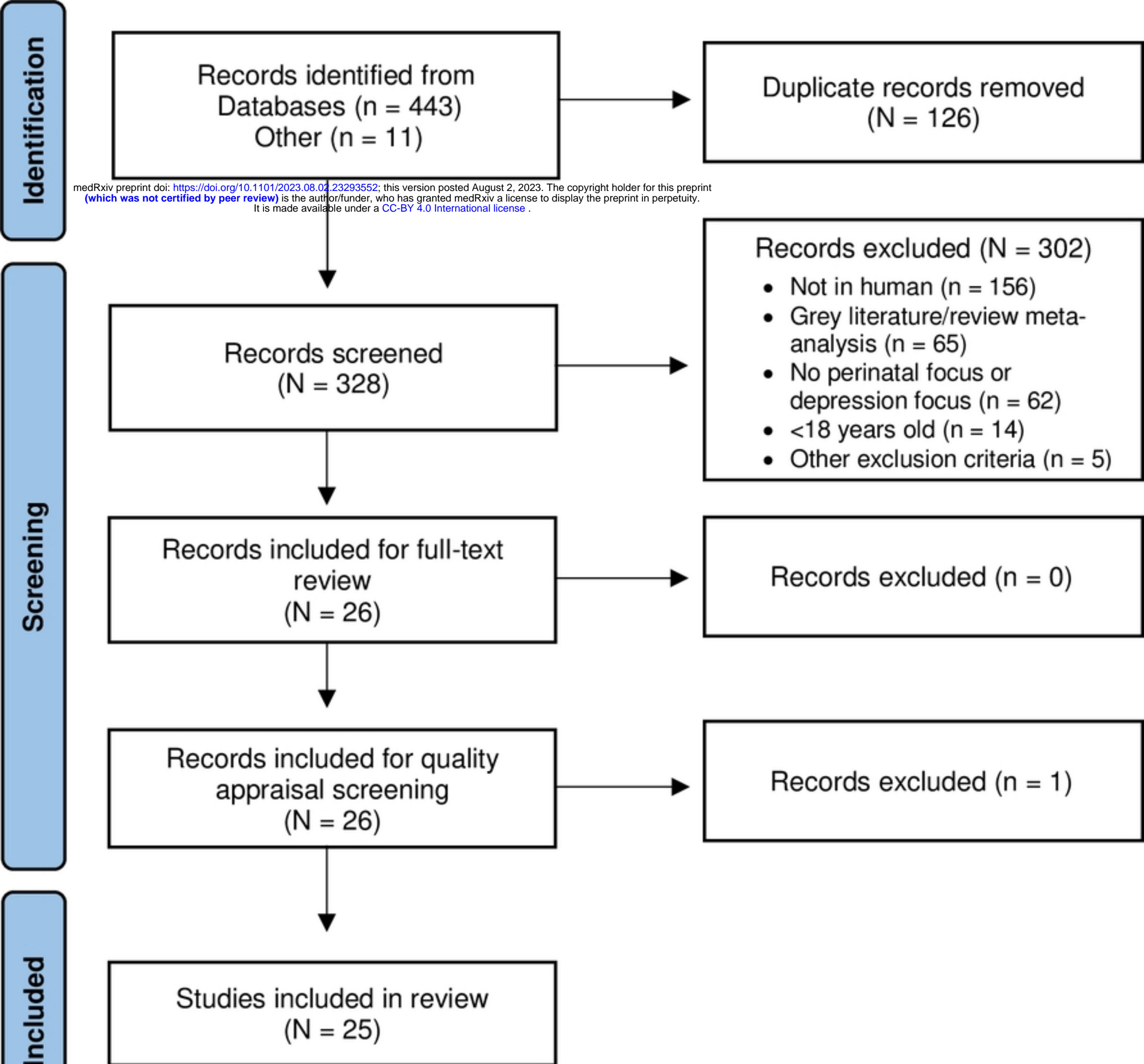


Fig 1

NIH RePORTER

(Publications)

Step 1

Search "maternal depression"

Step 2

Publications (N = 36,425)
Projects (N = 906)

Step 3

Remove duplicates, publications not specific to perinatal persons

Publications (N = 267)
Projects (N = 192)

Step 4

Separate US vs. Non-US studies

Step 5

Publications

US (n = 136); Non-US (n = 131)

Projects

US (n = 93); Non-US (n = 99)

Timeframes

1991-2022; 2002-2022

NIH RePORTER

(Projects)

Step 1

Search "maternal depression"

Step 2

Export data
Projects (N = 3,488)

Step 3

Remove duplicates, publications not specific to perinatal persons

Projects (N = 158)

Step 4

Organize data by state column

At the state level, projects were then quantified to assess funding in states with some of the highest maternal mortality and/or maternal mental health rates

Louisiana (n = 0)

Arkansas (n = 0)

Texas (n = 3)

Step 5

Quantify intervention studies

(N = 92)

*Keywords searched (intervention, treatment, therapy, therapeutic)

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Study	Domain	Perinatal period	Selection bias	Recall bias	Measurement bias
^a Achytes et al. (2022)	B, Bh	PP			
^a Kimmel et al. (2022)	B	PN			
^a Sha et al. (2022)	B	PN			
Dhiman et al. (2021)	B	PP			
Teshigawara et al. (2021)	B	PN			
Nazzari et al. (2020)	B	PN			
^a Ross et al. (2017)	B, S	P			
Vargas – Terrones et al. (2017)	Bh	PN			
^a Robertson-Blackmore et al. (2016)	B, S	PN			
Fasching et al. (2012)	B	PN			
Comasco et al. (2011)	B, S	PP			
^a Christian et al. (2009)	B, E	P			
^a Moses-Kolko et al. (2008)	B	PP			
Miyake et al. (2022)	Bh	P			
Garman et al. (2019)	Bh,S,E	PN			
Chang et al. (2018)	B	P			
Lin et al. (2009)	B	PN			
^a Finy et al. (2018)	B, S	P			
^a Miller et al. (2018)	B	P			
Murakami et al. (2008)	Bh	PN			
Rihua et al. (2018)	B	PP			
Veen et al. (2016)	B	PP			
Bailara et al. (2006)	B	PP			
Tebeka et al. (2021)	S	PP			
^a Venkatesh et al. (2019)	B	P			

Key:

- Low risk
- High risk
- Moderate risk
- Unclear risk

- P Pregnancy
- PP Postpartum
- PN Perinatal

- B Biological
- Bh Behavioral
- E Environmental
- S Social

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Fig3