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The Association of Inflammatory Biomarkers with Perinatal Depressive Symptoms: A
Systematic Review and Meta-Analysis

THESIS

submitted in partial satisfaction of the requirements
for the degree of

MASTER OF ARTS

in Social Ecology

by

Zoe E. Eng

Thesis Committee:
Professor Ilona S. Yim, Chair
Assistant Professor Amy L. Dent
Professor Jodi Quas

2021

DEDICATION

To

my family and friends

in recognition of their love and support

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ABSTRACT OF THE THESIS

The Association of Inflammatory Biomarkers with Perinatal Depressive Symptoms: A Systematic Review and Meta-Analysis

by

Zoe E. Eng

Master of Arts in Social Ecology

University of California, Irvine, 2021

Professor Ilona S. Yim, Chair

This meta-analysis set out to integrate and reconcile the disparate research on inflammatory biomarkers and perinatal depressive symptoms, in order to better understand the role of inflammation and depressive symptoms surrounding pregnancy. Overall, a small positive effect with a trending p-value emerged. Small statistically significant effects emerged between several biomarkers indicative of inflammation and depressive symptoms, depending on which markers were included and when during pregnancy or post partum those biomarkers were collected.

INTRODUCTION

Perinatal depression, a major or minor depressive episode occurring during pregnancy through the first twelve months after delivery, is a severe and debilitating mental health disorder, not only for mothers but for their babies and entire families, all of whom may suffer when mothers cannot bond with or care for their infant (Murray & Stein, 1989; Dubber, Reck, Müller, & Gawlik, 2015). Approximately 20% of pregnant women experience depression during pregnancy and 10 to 20% of women experience depression after delivery (Bowen & Muhajarine, 2006; Lee & Chung, 2007).

Perinatal depression is defined by onset of mood symptoms with various cutoffs, according to the particular authority. The American Psychiatric Association's *Diagnostic and Statistical Manual* describes depressive symptoms with peripartum onset as beginning "during pregnancy or in the 4 weeks following delivery" (APA, 2013). This is often thought to be the main authority as psychiatrists diagnose cases of depression, but medical fields do not always use the same cut-off for onset. The International Classification of Diseases (ICD)-10, the medical guidelines set forth by the World Health Organization and often used for billing purposes in medical practices, suggest an onset "within six weeks of delivery" (WHO, 2016). This standard was upheld in the recent 2018 update, the ICD-11, although the exact cut-off point allows for some flexibility given the inclusion of the word *about*— "within about 6 weeks after delivery" in its definition (WHO, 2018). Most researchers, though, use the timeline provided by the American College of Obstetricians and Gynecologists (ACOG). ACOG defines perinatal depression as a major or minor depressive episode "during pregnancy or in the first 12 months after delivery" (ACOG, 2015). There is some evidence to suggest that the postpartum immune system recovery back to pre-

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pregnant levels can be gradual (Watanabe et al., 1996). As such, ACOG's longer timeframe for onset of perinatal depressive symptoms was retained for this meta-analysis.

The risk factors for perinatal depression are complex and span the biopsychosocial framework. Documented, psychosocial risk factors include low social support, especially from partner; marital status; stressful life events; childcare stress and infant temperament; socioeconomic status; and unplanned/unwanted pregnancy (O'Hara & Swain, 1996; Beck, 2001; Lancaster et al., 2010). Known biological risk factors for perinatal depression include HPA axis dysregulation (especially CRH trajectories, Yim et al., 2015), sleep (Ross et al., 2005), obesity (Molyneaux et al., 2014), and previous depression history (Beck, 2001). Another possible biological risk factor for perinatal depression could be inflammation (Osborne & Monk, 2013). Not only does it vary normatively during the course of pregnancy, but it has been shown to be linked to depression in non-pregnant populations (Dowlati et al., 2010).

In pregnancy, there is a heightened state of inflammation due to the body's adaptations in order to not reject the fetus while maintaining maternal health, a state that also fluctuates some across pregnancy (Mor, 2007). These ongoing changes, which occur during normative pregnancy cycles, complicate efforts to understanding the precise biological contributions to the disorder's etiology. Early in pregnancy, for instance, the immune system is characterized by increased Type 1 T helper cell activity (Th1) and an increase in M1 macrophages while the placenta is developed and the blastocyst implants (Mor & Cardenas, 2010; Edvinsson et al., 2017). The period of implantation and placentation during the first and early second trimester have been described as similar to "an open wound" that naturally creates a pro-inflammatory environment (Mor & Cardenas,

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2010). Once the placenta has developed, there is a shift toward M2 macrophages to help prevent the fetus from being rejected prematurely before childbirth (Edvinsson et al., 2017). The mother, placenta, and fetus are then able to live and grow symbiotically in an anti-inflammatory environment (Brann et al., 2017; Mor & Cardenas). This period of pregnancy, during the second trimester, is characterized by an increase in Type 2 T helper cells (Th2; Morelli et al., 2015). The pro-M2 macrophage environment continues into the third trimester at which time there is a final shift back to M1 macrophages and Th1 to prepare for childbirth with an increase of immune cells in the myometrium (Edvinsson et al., 2017; Morelli et al., 2015; Brann et al., 2017). This helps prepare the body for the contraction of the uterus, the delivery of the baby, and the rejection of the placenta (Mor & Cardenas, 2010).

After childbirth, the body must heal and physiologically adapt to care for the baby, which can be affected by a woman's choice to breastfeed or bottle feed—bottle feeding would lead to mammary involution (Brann et al., 2017; Corwin et al., 2015). This early postpartum period is thought to be predominantly characterized by Th1 (Morelli et al., 2015).

Researchers have gradually directed more attention toward how deviations in these normative patterns of changes during pregnancy relate to depressive symptoms. Results, however appear mixed. Some studies have uncovered positive correlations between markers of inflammation while others have reported negative relations and still others have seen statistically nonsignificant results (Osborne & Monk, 2013). Yet, the complicated nature of the normative course of changes, combined with variations in the specific inflammatory marker being studied, make direct comparisons between individual studies

difficult. Moreover sample characteristics (e.g., racial and ethnic group, health history) also vary and theoretically may also have implications for inflammation and perinatal depression (Osborne & Monk, 2013).

A more integrated and holistic way of integrating findings, therefore, is needed. Meta-analysis provides such an approach. The overarching purpose of the present study was to explore the relation between inflammatory biomarkers and perinatal depressive symptoms, specifically framed by moderators of theoretical and methodological importance.

Theoretical Moderators

Specific inflammatory biomarkers. Various inflammatory biomarkers reflect their varying roles in the immune system. Some inflammatory biomarkers are generally pro-inflammatory, promoting inflammation, while others are inhibitory, decreasing the inflammatory response. As the immune system changes throughout the normative course of pregnancy, certain specific inflammatory biomarkers are more predominant during particular phases in normative pregnancy (e.g., some specific inflammatory biomarkers are produced by Th1 or Th2 cells; Osborne & Monk, 2013). This variability in inflammatory biomarkers may also affect the association between inflammatory biomarkers and perinatal depressive symptoms. If a particular inflammatory biomarker is assessed when it is normatively more predominant, it may be difficult to see the association above the heightened levels of the biomarker. It is possible that certain inflammatory biomarkers may provide different kinds of insight into the association between inflammation and perinatal depressive symptoms. As the different biomarkers act according to their different

roles in the immune system, only assessing one or a small number of different biomarkers would not help see those differences.

Hypothesis. Interleukin (IL)-6 was one of the earlier inflammatory biomarkers available to researchers for assays, so it is widely used in non-pregnant and pregnancy research (Tanaka et al., 2014). But its common inclusion as a measure does not necessarily stem from a strong theoretical foundation compared to other biomarkers, whose actions in the immune system may merit greater attention. Other inflammatory biomarkers may play more important roles in health (Song & Kellum, 2005). C-Reactive Protein (CRP) was also discovered early, but it has been more studied in the context of cardiovascular disease than depression (Ridker, 2009). A meta-analysis examining IL-6 and CRP and depressive symptoms in longitudinal studies of nonpregnant samples actually found a stronger effect in CRP (Valkanova, Ebmeier, & Allan, 2013). Another meta-analysis showed that IL-6 had a similar effect size to IL-1 receptor antagonist (IL-1ra) in non-pregnant samples and that IL-1 had a larger association with major depressive symptoms (Howren et al., 2009). Given these trends, CRP and IL-1 may simply be more strongly associated with perinatal depressive symptoms than IL-6.

Time of assessment of inflammatory biomarkers. Due to the changes that occur throughout pregnancy and the postpartum period, the association between inflammatory biomarkers and depressive symptoms likely changes based on the time at which the inflammatory biomarkers are assessed. As discussed next, there may be specific windows during shifts in inflammatory status are stronger rather than weaker predictors of depressive symptoms.

Hypotheses. Research on the etiology of other morbidities of pregnancy suggest that changes in the immune environment throughout pregnancy could be implicated. For instance, the degradation of the placenta linked with the development of preeclampsia appears to be associated with a shift from Th2 to Th1, a pattern opposite to that seen in normative pregnancy (Ahn et al., 2011). Preterm birth has also been associated with increased local inflammation earlier in pregnancy than would be expected to prepare for parturition (Wei et al., 2010). Gestational diabetes can create a pro-inflammatory environment related to insulin resistance, even during normally anti-inflammatory phases of pregnancy (Osborne & Monk, 2013). Inflammation that varies from the timing of normative pregnancy (e.g., too early in preterm birth) could also be an indicator of perinatal depressive symptoms. Stated another way, it may generally be easier to detect the association between inflammatory biomarkers and perinatal depressive symptoms at times of lower inflammation, like during mid-pregnancy. It may also be the case, though, that, during these same times, women could be more vulnerable to the psychosocial risk factors for perinatal depression, like perceived stress or low partner support.

Alternatively, it is possible that the association between inflammatory biomarkers and perinatal depressive symptoms could be easier to detect at states of higher inflammation, closer to implantation and closer to the time of parturition. During these heightened pro-inflammatory states, the immune system is already being stressed by the placenta and fetus, so it is possible that the body may be more susceptible to becoming overwhelmed and succumbing to disease due to the cumulative burden of chronic stress (McEwen, 1998).

Methodological Moderators

Specimen type. Most studies of inflammatory biomarkers rely on either serum or plasma blood but there are alternate specimen types by which to assess these biomarkers. How biomarkers are collected could influence their association with perinatal depressive symptoms.

Hypothesis. Saliva is a less invasive, newer method of assessing inflammatory biomarkers. Some studies have found that saliva is not highly correlated with assays from circulating blood (Fernandez-Botran et al., 2011, Cullen et al., 2015), suggesting saliva may be a less accurate way to study inflammatory biomarkers than measures derived from blood samples. Saliva can also be easily confounded by infections in the mouth, such as gingivitis (which would produce inflammatory biomarkers at the site of the infection), leading to less certainty about what is actually being assessed (i.e., oral health or circulating levels of inflammation; Johannsen et al., 2006). As such, the association between inflammatory biomarkers and depressive symptoms will likely be weaker when assessed in saliva relative to other methods.

Time of assessment of depressive symptoms. Perinatal depression encompasses a wide span of time, including an onset during pregnancy through the full year post partum. Given that inflammation varies significantly across pregnancy and afterward, it is crucial to consider when markers of inflammation and symptoms are measured when evaluating their associations.

Hypotheses. It is possible that the heightened state of inflammation during pregnancy may make the relation easier to detect, but it is also possible that the relation could be attenuated when inflammation is already so heightened due to the normative immune processes of pregnancy. Depression during and shortly after pregnancy is thought

to be related to different inflammatory phenomena and thus associations may vary

between these (Osborne & Monk, 2013). Depression during pregnancy is the greatest risk

factor for postpartum depression so it can be difficult to disentangle the two, but

depression during pregnancy is still considered a distinct disorder (Wisner et al., 2013).

Why Meta-Analysis and Why Now?

As mentioned, findings from extant research vary significantly as to whether or not

(and when) inflammatory biomarkers are related to depressive symptoms in pregnant and

postnatal women (e.g., Ahn & Corwin, 2015; Brann et al., 2017; Chang et al., 2018).

Methodological and sample variations make it difficult to integrate findings. Moreover,

such studies are time and labor intensive, often leading to relatively small sample sizes,

which further limit generalizability. By combining studies into a single meta-analysis, the

limitations inherent in individual studies can be minimized and more comprehensive

insight into trends can be gained. Given the prevalence of perinatal depression and its

debilitating effects on mothers, children, and families, it is imperative to understand more

fully the role that inflammation plays in its occurrence. Such an understanding can lay the

foundation for earlier identification and intervention.

<center>**CHAPTER 1: Method**</center>

Strategy for Searching the Literature

CINAHL, MEDLINE, PsycINFO, and PubMed were searched on November 20,

2018for studies with no limits on study languages or date of publication. Abstracts were

searched for combinations of keywords for inflammatory markers (e.g., *cytokine*,

interleukin, *inflammat**) and perinatal depression (e.g.,*"postpartum depress*"*, *"puerperal*

depress*", *"depress* in pregnan*"*), see Table 1.1 for full search parameters. Both general

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terms for inflammation (e.g., inflammat* and immunolog*) were used. Specific biomarkers were also (e.g., IL-6, TNF-a) included given that some authors likely included the specific biomarkers of inters in their titles and abstracts, rather than broader terms, such as inflammatory biomarkers. Multiple terms for perinatal depression were also included in order to encompass the different time points encompassed in perinatal depression (e.g., postpartum depress* referring to depressive symptoms, antenatal depress* referring to symptoms before birth). These two terms also reflect the differences in regional phrasing (postpartum depression being more commonly used in the US, while antenatal depression is more commonly used in the UK and Australia).

This search retrieved 345 documents across the four electronic databases. After 187 duplicates were removed, 158 remained for screening.

Criteria for Including Studies

Inclusion criteria. The main inclusion criteria were the measurement of both inflammatory biomarkers and depressive symptoms around pregnancy. Any type of inflammatory biomarker could have been assessed.[1] While many biological markers act within the immune system or could be considered inflammatory in nature, the following definition was followed here: proteins that are related to inflammatory diseases and biological processes. Depressive symptoms included perinatal, postpartum, antenatal, postnatal, puerperal, or pregnancy depression. Depression or depressive symptoms could have been measured with either clinical interviews or with self-report inventories.

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[1] After full-text screening, the above tighter definition of inflammatory biomarkers was created which excluded a number of non-protein immune biomarkers, like CD4 cell counts, HIV viral load, and immunoglobulin A (some of which were included in the initial literature search terms).

Participants could have been studied at any gestational age through one year post partum, the is the cutoff point for perinatal depression according to ACOG.

Studies could be longitudinal over the course of a pregnancy, cross-sectional or case control in design. As the effect of inflammatory biomarkers on perinatal depression risk likely impacts women around the world similarly, all locales and reporting languages were included.

Exclusion criteria. Nonhuman animal studies were excluded. Studies of depression following pregnancy loss were excluded, as these pregnancies would be expected to differ biologically from term pregnancies. Studies with non-pregnant/non-maternal samples were excluded, although studies with both non-depressed pregnant and non-depressed non-pregnant comparison samples were included. (Only the non-depressed pregnant comparison sample was retained for the calculation of the effect size.)

Intervention studies were excluded, as the focus of this meta-analysis is on the observation of the natural progression of a woman's changing inflammatory biomarkers and her associated risk of developing perinatal depression. All single case studies were excluded. Review papers' references were searched for suitable studies to include but reviews themselves were excluded.

This resulted in a total of 48 articles eligible for potential inclusion in the final meta-analysis, see Figure 1.1. The current report contains 19 of these studies, all of which contained all information necessary to calculate effect sizes.

Procedure for Gathering Information about Studies

Information coded in research reports. Six types of information were coded from each study to enable moderator analyses: (1) report characteristics, (2) setting

characteristics, (3) participant characteristics, (4) inflammatory biomarker variable characteristics, (5) perinatal depression variable characteristics, and (6) study variable characteristics. Report characteristics include the first author's name and the year of publication. The setting characteristics include the country and region in which the study was conducted. Participant characteristics include demographics such as maternal age, gestational age, and ethnicity of the sample. Inflammatory biomarker characteristics include the specific inflammatory biomarker and the specimen type in which it was assessed. Perinatal depression characteristics include the specific measure used to assess perinatal depressive symptoms and the gestational age or time post partum at which it was assessed. Study variable characteristics reflect the larger research design, for instance, if the study assessed other constructs besides inflammatory biomarkers and perinatal depressive symptoms, was longitudinal or not, etc. Table 1.2 provides a complete list of the information coded from each study.

Coding procedure. Most information was documented verbatim as the study authors reported (e.g., inflammatory biomarker name). For the time of assessment (for both inflammatory biomarkers and depressive symptoms), the exact time of assessment was documented. From this documentation, codes were created for the moderator variables to create relevant categories for analysis. Some codes reflected predefined categories. Specimen type was coded separately with both blood versus non-blood products (e.g., urine) and specific components of blood (e.g., plasma, serum) as well as non-blood products. Likewise, gestational age was recoded into trimesters from exact weeks.

Method of Data Integration

Effect size estimation. Pearson's product-moment correlation coefficient were used as the effect size of choice. Most studies assessed and reported depressive symptoms on a continuous scale, and inflammatory biomarkers are also measured on a continuous scale. This also allows for an understanding of the severity of depressive symptoms. The correlation would suggest an association between an *amount* of an inflammatory biomarker with *severity* of depressive symptoms. For those studies that did not report correlation matrices, correlations were calculated from the reported means, standard deviations, and subgroup sizes using the Campbell Collaboration Practical Meta-Analysis Effect Size Calculator (Wilson, n.d.). Depressed or depressive symptom groups were used as the "treatment" group, while non-depressed groups were used as the "control" group. In these cases, correlations represent associations between an *amount* of an inflammatory biomarker with the *presence* of depression. All studies except for one reported zero-order correlations. Shelton et al., 2015 used gestational age as a covariate as the study included participants from 16-26 weeks' gestational age.

Calculating mean effect sizes. Each mean correlation was weighted for both the overall analysis and the moderator analyses (Borenstein et al., 2013). These adjustments give greater weight to the studies with larger sample sizes, as they provide a more precise estimate of the true effect. These more precise estimates thus should be given greater weight in the mean correlations. Ninety-five percent confidence intervals were calculated around each mean correlation (for each study, as well as for the overall and moderator analyses). When the 95% confidence interval did not overlap with zero, the standard interpretation is that there is no association between the two variables and the null

hypothesis is rejected. Analyses were conducted using Comprehensive Meta-Analysis, which calculates all weighted mean correlations (Borenstein et al., 2013).

Identifying independent hypothesis tests. A shifting unit of analysis approach was used for this meta-analysis (Cooper 2010). Within each study, different correlations were coded as individual, separate estimates of the association between inflammatory biomarkers and perinatal depressive symptoms (e.g., if a study assessed multiple biomarkers). The samples' individual correlations were then averaged together to create a study mean correlation before assessing the association between inflammatory biomarkers and perinatal depressive symptoms overall. This allows each individual study and sample to contribute only one correlation to the overall mean.

In the moderator analyses to follow, correlations from the same sample were not averaged together if they were from different categories of the moderator. For example, if a study assessed IL-6 and IL-10, that study would contribute one mean correlation for the overall analysis between inflammatory biomarkers and perinatal depressive symptoms. However, in the moderator analysis examining specific biomarkers, there would be separate correlations for IL-6 and IL-10 from that study.

This shifting unit of analysis approach allowed the retention of the information that can be gained from the multiple correlations from each study, while also ensuring that violations of the assumption that statistical tests are independent were minimized (Cooper 2010). Additionally, because each study would contribute only one weighted correlation, studies with small samples that have several correlations did not have excessive influence on a mean compared to a study with a larger sample and fewer correlations.

Testing for moderators. In order to determine whether the moderators described above affect the association between inflammatory biomarkers and perinatal depressive symptoms, homogeneity analyses were conducted. This was assessed with a within-group goodness-of-fit statistic (Q_w), which can detect if there is more variation in the correlations of the meta-analysis than would be expected from sampling error alone. If this Q_w shows significantly more variation than sampling error can explain, moderator analyses were run. These analyses assessed if the magnitude of the correlations varied systematically due to the moderators. A significant Q_w gives an empirical reason to test for moderators, as it would suggest that there is systemic variation in the correlations of the studies in the meta-analysis (Cooper et al., 2009).

In the moderator analyses, a between-groups goodness-of-fit statistic was used (Q_b). A significant Q_b indicates more variability among the mean correlations for the moderator categories than sampling error alone can explain. In practice, a significant Q_b means that the mean correlation between inflammatory biomarkers and perinatal depressive symptoms differs by the moderator category tested. Thus, for example, in the specimen type moderator analysis, the association is expected to differ depending on whether the inflammatory biomarkers were assessed in plasma, serum, or urine. A significant overall Q_b, which simply shows whether there is a difference within the moderator category, would be followed by pairwise comparisons to identify which among the three possible specimen types differs from the others. The pairwise comparisons interpretation, if significant, suggests that two of the mean correlations differ significantly from each other (Cooper et al., 2009).

Modeling error. Due to both the wide variability in the methodology of studies and the expected variation in individuals due to theoretical reasons (e.g., ethnicity, differences in health status), overall and moderator analyses were conducted with a random-effects model. The model was additionally assessed with the fixed-effect model for a sensitivity analysis. A sensitivity analysis allows us to see if the assumptions underlying the different models of error affect the results of the meta-analysis (Greenhouse and Iyengar, 1994). The random-effects model assumes that the true effect varies across studies (and thus would vary in the population of interest), whereas the fixed-effect model assumes that the true effect is unchanging and does not vary in the population or due to study differences. In the latter model, the only reason that parameter estimates differ would be due to sampling error. The fixed-effect model thus gives even greater weight to studies with large samples, assuming that each study is assessing the same effect. The random-effects model does still give greater weight to larger samples but not to the same extent, as it assumes that multiple effects exist in the population and their magnitude may vary.

CHAPTER 2: Results

Overall Correlation

Correlations within each independent sample were first averaged together, producing 19 correlations that contributed to the overall association between inflammatory biomarkers and perinatal depressive symptoms. This mean weighted correlation was statistically significant under the fixed-effect model of error [$r = -0.09$, 95% CI (-0.10, -0.08), $p < 0.001$] and not statistically significant for the random-effects model of error [$r = 0.07$, 95% CI (-0.01, 0.15), $p = 0.07$], indicating that there is a small positive correlation with a trending p-value under the random-effects model of error. Additionally,

there was statistically significantly more variation around each weighted mean than can be explained by sampling error alone [Q_w(18) = 1380.36, $p < 0.001$]. This significant Q_w statistic indicates that there is systematic variation among the 19 mean correlations that allowed for investigation of the moderators that might explain this variation.

The four moderator analyses were then conducted using a shifting unit of analysis approach to test whether variables of theoretical and methodological interest can explain this variation. Random effects model results are presented in full in Table 2.1 and are described below.

Theoretical Moderators

Specific inflammatory biomarkers. When the overall Q statistic was examined, the model was significant, suggesting that there is more variability than sampling error alone explains which can instead be explained by the specific inflammatory biomarker included [Q_b(32) = 74.01, $p < 0.001$].[2] Comparisons were then conducted between all possible pairings of biomarkers: CRP, IFN-y, IL-1B, IL-6, IL-8, and IL-10 (see Tables 2.2a and 2.2b). Of note, IL-6 was positively correlated with depressive symptoms [$r = 0.09$, 95% CI (0.03, 0.15), $k = 13$], while IFN-y was negatively correlated with depressive symptoms [$r = -0.07$, 95% CI (-0.16, 0.03), $k = 6$]. IL-10 showed a similar pattern [$r = -0.02$, 95% CI (-0.12, 0.08), $k = 8$], with a negative association with depressive symptoms, compared to IL-6's positive association [Q_b(1) = 3.46, $p = 0.06$]. These patterns suggest, in combination, that generally pro-inflammatory biomarkers, like IL-6, have positive associations with perinatal depressive symptoms, while predominantly anti-inflammatory biomarkers, like IFN-y and

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[2] The overall analysis and all other moderator analyses included all 94 inflammatory biomarkers that were included in the meta-analysis. This moderator analysis only incorporates those 33 specific inflammatory biomarkers which were assessed in three or more studies.

IL-10, have negative associations with perinatal depressive symptoms. Additionally, CRP was positively associated with depressive symptoms [r = 0.09, 95% CI (-0.04, 0.21), k = 5], while IFN-y remained negatively associated with depressive symptoms [$Q_b(1)$ = 3.60, p = 0.06]. CRP has demonstrated effect sizes in the same positive direction as IL-6 in previous meta-analyses on major depression in non-pregnant samples (Howren et al., 2009; Valkanova et al., 2013).

      Time of assessment of inflammatory biomarkers. Time of assessment was significant only during pregnancy, but not before/during/after labor or in the postpartum period, see full results in Table 2.3, likely due to the number of studies. No differences exist between associations based on time of assessment of inflammatory biomarker when categorized as before, during, or after labor [$Q_b(3)$ = 2.76, p = 0.43]. This Q statistic remained statistically not significant when excluding the moderator category for right after labor, $Q_b(2)$ = 1.17, p = 0.56 (but retaining the general postpartum period/after labor). The moderator category for right after labor could have been an artifact of one specimen type— umbilical cord serum is only able to be collected right after labor when umbilical cords are clamped and cut. Umbilical cord serum was only assessed in one study (Fransson, 2012).

      Differences did emerge, however, when comparisons were made among the trimesters, [$Q_b(2)$ = 22.13, p < 0.001]. When assessed during the first trimester [r = 0.27, 95% CI (0.18, 0.36), k = 1], the association between inflammation and depressive symptoms was stronger than when biomarkers were assessed during the second trimester [r = 0.04, 95% CI (-0.09, 0.17), k = 5; $Q_b(1)$ = 8.60, p = 0.003]. A similar difference (i.e., the association is stronger) emerged comparing the first [r = 0.27, 95% CI (0.18, 0.36), k = 1] and third trimesters [r = -0.03, 95% CI (-0.12, 0.06), k = 6; $Q_b(1)$ = 21.24, p < 0.001].

Interestingly, the association becomes negative during the third trimester, although there was no significant difference between the positive association in the second trimester and the negative association in the third trimester [$Q_b(1) = 0.75$, $p = 0.39$]. This change in directionality could reflect the change from an anti-inflammatory state where mother, placenta, and fetus are able to thrive together during late second trimester to the pro-inflammatory state prior to parturition when there is an increase of immune cells in the myometrium, helping to promote the contraction of the uterus, delivery of the baby, and rejection of the placenta (Mor & Cardenas, 2010).

Statistically significant differences did not exist based on time of assessment during the postpartum period across the categories, [$Q_b(2) = 0.88$, $p = 0.64$].

Methodological Moderators

Specimen type. Different specimen types were differently associated with depressive symptoms [$Q_b(3) = 29.27$, $p < 0.001$], see Table 2.4 for full results.[3] Plasma and serum blood were differently associated [$Q_b(1) = 4.24$, $p = 0.04$], with plasma being negatively correlated with depressive symptoms [$r = -0.01$, 95% CI (-0.12, 0.09), $k = 10$] and serum being positively correlated [$r = 0.13$, 95% CI (0.04, 0.21), $k = 8$]. Serum is more strongly (and positively) associated with perinatal depressive symptoms than plasma, suggesting that assessing inflammatory biomarkers in serum may be more helpful to detect the association with perinatal depressive symptoms. Plasma [$r = -0.01$, 95% CI (-0.12, 0.09), $k = 10$] and umbilical cord serum also significantly differed [$Q_b(1) = 4.51$, $p = 0.03$], with inflammation markers according to umbilical cord serum [$r = 0.15$, 95% CI (0.04,

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[3] The initial specimen type moderator analysis included urine and three types of blood, but results remained statistically significant when urine was removed [$Q_b(2) = 5.83$, $p = 0.05$].

0.26), $k = 1$] were positively associated (again, unlike plasma, for which biomarkers were negatively associated) with perinatal depressive symptoms. Thus, inflammation levels according to umbilical cord serum seemed to function, at least in terms of their links to depression, much like those in serum. As might be expected, given that both blood serum and umbilical cord serum index serum levels, it is unsurprising that the links between inflammatory makers in serum [$r = 0.13$, 95% CI (0.04, 0.21), $k = 8$] and umbilical cord serum [$r = 0.15$, 95% CI (0.04, 0.26), $k = 1$] and depressive symptoms did not differ from one another [$Q_b(1) = 0.13$, $p = 0.72$].

Time of assessment of depressive symptoms. The association did not vary significantly based on time of assessment of depressive symptoms, dichotomized to before or after giving birth [$Q_b(1) = 0.30$, $p = 0.59$], see Table 2.5 for full results. This could indicate that women who were assessed positively during pregnancy are not functionally different from women with postpartum symptoms, as they just went on to continue to have postpartum depressive symptoms, as depressive symptoms during pregnancy are an important predictor of postpartum depressive symptoms.

CHAPTER 3: Discussion

This meta-analysis set out to integrate and reconcile the disparate research on inflammatory biomarkers and perinatal depressive symptoms, in order to better understand the role of inflammation and depressive symptoms surrounding pregnancy. Overall, a small positive effect with a trending p-value emerged. Small statistically significant effects emerged between several biomarkers indicative of inflammation and depressive symptoms, depending on which markers were included and when during pregnancy or post partum those biomarkers were collected. If these findings continue to

hold as more studies are added, results have import implications for identification and possibly earlier intervention for women at risk for postpartum depression.

First, the present study suggested that all inflammatory biomarkers are not identical. Instead, the direction of their association with depressive symptoms varies in alignment with the biomarkers' tendencies towards pro- or anti-inflammatory functions. Most notably, IL-6, IFN-y, IL-10, and CRP were all related to depressive symptoms. High inflammation is thought to be associated with depression, as the immune system activates similar to in cases with an acute wound or illness (Dowlati et al., 2010). By better understanding this association, not only can we have a better grasp of the etiology of perinatal depression overall, but eventually this knowledge could lead to better treatment options that help to target the specific aspects of the immune system that underpin the disorder. Anti-inflammatory medications have already been suggested for major depression, but they may not be as helpful against an already heightened anti-inflammatory state during pregnancy.

Second, turning to sample type, plasma and serum are often used interchangeably when assessing inflammatory biomarkers. Here, however, the two types of sampling procedures produced different results, with serum being a more robust correlate than plasma. Serum is more stable once separated and thus can be stored for longer, while plasma may generally be a better representation of circulating blood (WHO, 2002; Bowen et al., 2010). Umbilical cord serum was no more useful in understanding the association between inflammatory biomarkers and perinatal depressive symptoms than serum, and umbilical cord serum must be collected right after labor. As such, umbilical cord serum does not appear to be an important method for future research related to perinatal

depression. The main hypothesis for specimen type was related to saliva, but no studies were found that assessed salivary inflammatory biomarkers and perinatal depressive symptoms. As salivary assays become more reliable, it will be important to assess their value in this aiding in understanding of the links between inflammation in pregnancy and depressive symptoms as well. Noninvasive methods could be especially valuable with difficult to reach populations, if their value can be demonstrated.

Third, in terms of timing, the first trimester appears most important in terms of when to assess inflammatory biomarkers as predictors of subsequent depressive symptoms. Indeed, the association between inflammation and depressive symptoms was far more robust than during the latter trimesters. The heightened state of inflammation around time of implantation could be key to understanding perinatal depression, but, given the difficulty identifying and recruiting women in this window (during which many may not know they are pregnant), novel tactics to recruit and retain participants will be important in subsequent research. In fact, in the present meta-analysis, only one studyconducted by Haeri (2013) included women in this trimester (they were on average at 12.7 weeks' gestational age). Haeri accessed the records of women who had previously given blood for genetic screening and was able to achieve a large sample through this method. There were no significant differences based on postpartum assessment time points of inflammatory biomarkers. More research is needed to better understand the normative changes in inflammation and the immune system functioning during the first year post partum, in order to give a better indication for cut-off points. This could also be due to the fact that immune system changes tend to be less extreme post partum, aside from those directly after childbirth.

And fourth, across the studies included in the meta-analysis and in contrast to the importance of timing of the assessment of inflammatory makers, the timing of assessment of depressive symptoms (during pregnancy or post partum) was unrelated to the links between inflammation and depression. Depressive symptoms during pregnancy are a likely predictor of postpartum depressive symptoms (Josefsson et al., 2001). Thus, it is possible that assessing symptoms during pregnancy is a strong indicator of who will eventually develop postpartum depression. Yet, the two are not identical. Brann et al. (2018) did not find that pregnancy onset depression predicted postpartum depression, and others have noted the importance of distinguishing the two (Osborne & Monk, 2013). In order to help better understand if this continuation of symptoms is the case, more longitudinal and ideally prospective studies are needed.

Despite the unique and exciting findings reported here, limitations are also important to note. First, only 19 published studies with full reporting are included. In order to improve this meta-analysis, an important next step is to search the grey literature. This could include relevant yet unpublished research, collected for example, by posting announcements on the listservs of the relevant organizations (e.g., American Psychosomatic Society). In addition, researchers who have authored at least two publications on immune function and depressive symptoms around pregnancy will be emailed individually. Subsequent analyses will also assess whether the literature search missed studies (via Duval and Tweedie's trim-and-fill procedure) and a moderator analysis to test for publication bias.

Second, the present study data were only coded by a single coder. In the future, studies need to be independently double-coded. Discrepancies need to be resolved to ensure that all studies are properly and reliably coded and interpreted.

Third, though not a limitation, further moderator analyses should be conducted in the future. One is whether a clinical diagnosis or the use of a clinical interview impacts the strength of the relation, or whether cutoff points on measures of depressive symptoms affect the evident association. Certainly clinical interview is considered the gold standard for diagnosis but these are expensive, time consuming , and not scalable as a screening or early identification index. Analyses, though, could also study depressive *symptoms* in more depth and contrast those findings with analyses of actual depression diagnoses. And finally, time during the day during which biomarkers were assessed should be examined. There is some evidence to suggest diurnal patterns of inflammatory biomarkers exist which could impact evident associations (Vgontzas et al., 2005). Likewise, other potential moderators, such as circulating (e.g., basal) vs. reactive response tendencies (Carpenter et al., 2010), infant gender (Myers & Johns, 2019), or mother's ethnicity, and maternal age, all of which should be investigated in a more rigorous and systematic manner.

In closing, by studying via meta-analysis variability in the association between inflammatory biomarkers and perinatal depressive symptoms, the present research will help further solidify our understanding of the complex etiology of perinatal depression. This understanding could also help support the development of novel anti-inflammatory treatment strategies and highlight important directions for future research.

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APPENDIX A: Tables and Figures

Table 1.1 Full Search Parameters

Search Terms	Search Parameters	Electronic Databases	Documents Retrieved
cytokine or interleukin or chemokine or inflammat* or proinflammat* or pro-inflammat* or anti-inflammat* or interferon or immunolog* or lymphocyte or "natural killer cell" or "NK cell" or T-cell or B-cell or T-helper or "T helper" or macrophage or "tumor necrosis factor" or neutrophil or granulocyte or monocyte or leukocyte or "nuclear factor" or "tumor growth factor" or "acute phase protein" or "inflammatory marker" or "inflammatory biomarker" or "immune marker" or "immune biomarker" or T-suppressor or IL6 or IL-6 or TNF-alpha or TNF-a or IL1B or IL1beta or IL-1B or IL-1beta or IFNy or IFNgamma or IFN-gamma or IFN-y or IL10 or IL-10 or IL6R or IL-6R or IL1RA or IL-1RA or "C-reactive protein" or CRP or IL2 or IL-2 or IL4 or IL-4 or IL1 or IL-1 or IL8 or IL-8 or IL12 or IL-12 or IL5 or IL-5 or IL13 or IL-13 or IFNa or IFNalpha or IFN-alpha or IFN-a or IL1a or IL-1a or IL1alpha or IL-1alpha or NF-kappaB or "kappa B" or NF-KB or NFKB or NFkappaB or IL18 or IL-18 or TGF-B or TGFB or TGF-beta or TGFbeta or IL17 or IL-17 or "granulocyte colony stimulating factor" or G-CSF or GCSF or CD4+ or CD8+ or IL22 or IL-22 or IL21	The *abstract* of documents was searched using the PsycINFO, MEDLINE, and CINAHL search engines. The *title/abstract* of documents was searched using the PubMed search engine.	*Through ProQuest:* PsycINFO *Through NLM Catalog:* MEDLINE PubMed *Through EBSCO:* CINAHL	*PsycINFO:* **69** records retrieved *MEDLINE:* **105** records retrieved *CINAHL:* **43** records retrieved *PubMed:* **128** records retrieved TOTAL: **158** records retrieved after duplicates removed

or IL-21 or IL23 or IL-23 or MIP-1beta or MIP1beta or MIP1B or MIP-1B *AND* "postpartum depress*" or "post-partum depress*" or "post partum depress*" or "antenatal depress*" or "perinatal depress*" or "postnatal depress*" or "post natal depress*" or "post-natal depress*" or "depress* in the puerperium" or "puerperal depress*" or "depress* in pregnan*"			

Figure 1.1 Flow Diagram of Study Selection

```
┌─────────────────────────────┐      ┌─────────────────────────────┐
│  Records identified through  │      │  Additional records identified│
│     database searching       │      │ through reference lists search│
│       CINAHL (n = 43)        │      │                               │
│      MEDLINE (n = 105)       │      │          (n = 11)             │
│      PsycINFO (n = 69)       │      │                               │
│      PubMed (n = 128)        │      │                               │
└─────────────────────────────┘      └─────────────────────────────┘
                │                                    │
                └──────────────┬─────────────────────┘
                               ▼
              ┌─────────────────────────────┐
              │ Records after duplicates     │
              │ removed                      │
              │ (n = 164)                    │
              └─────────────────────────────┘
                               │
                               ▼
              ┌─────────────────────────────┐      ┌─────────────────────────────┐
              │   Abstracts screened         │─────▶│   Records excluded           │
              │   (n = 164)                  │      │   (n = 54)                   │
              └─────────────────────────────┘      └─────────────────────────────┘
                               │
                               ▼
              ┌─────────────────────────────┐      ┌─────────────────────────────┐
              │   Full-text articles         │      │ Full-text articles excluded: │
              │   assessed for eligibility   │─────▶│   Animal study (n = 1)       │
              │   (n = 110)                  │      │   Child sample (n = 1)       │
              └─────────────────────────────┘      │ No depression measure (n = 3)│
                               │                    │ No immune marker (n = 17)    │
                               ▼                    │   Review paper (n = 38)      │
              ┌─────────────────────────────┐      │ Sample not pregnant (n = 2)  │
              │   Studies included in        │      └─────────────────────────────┘
              │   qualitative synthesis      │
              │   (n = 48)                   │
              └─────────────────────────────┘
                               │
                               ▼
              ┌─────────────────────────────┐
              │   Studies included in        │
              │   preliminary meta-          │
              │   analysis                   │
              │   (n = 19)                   │
              └─────────────────────────────┘
```
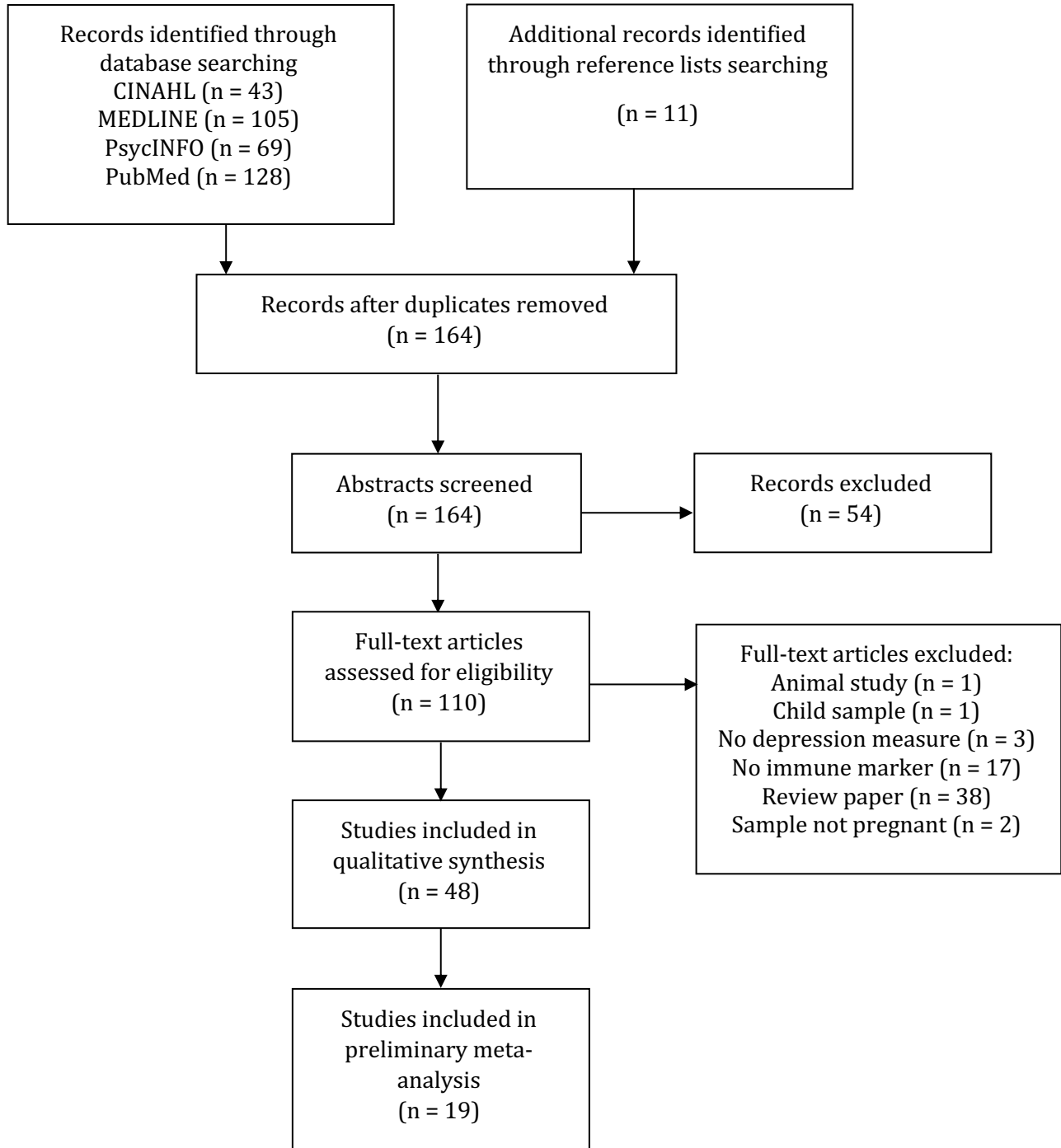
Table 1.2. Complete list of information coded

Report characteristics
1. Author names
2. Year
3. Report type (e.g., journal article, conference paper, dissertation)
Setting characteristics
1. Country
2. State/region
3. Institution/recruitment setting (e.g., clinic, hospital)
Participant characteristics
1. Defining characteristics of overall sample (e.g., marital status, education)
2. Health defining characteristics of overall sample (e.g., history of depression, BMI)
3. Sample size
4. Characteristic defining sample subgroups (e.g., preterm vs. term)
5. Subgroup size
6. Socioeconomic characteristics of the sample
7. Average age
8. Standard deviation of average age
9. Median age
10. Age range of mothers
11. Average gestational age
12. Median gestational age
13. Gestational age range
14. Race/ethnicity breakdown
15. Annual income
16. Proportion living in poverty
Inflammatory biomarker (IB) variable
1. Author label of IB
2. IB units of measurements
3. Specimen type
4. Blood component
5. Reliability of assay
6. Average gestational age/time postpartum at assessment
7. Standard deviation of average gestational age
8. Range of gestational age
9. Was time of day the sample was taken reported?
10. If so, how?

11. Did the study assess circulating levels of IB or in response to a stressor?

12. If a stressor, describe the stressor

Perinatal depression (PND) variable

1. PND measure name

2. Was the measure created or adapted?

3. If so, how was the measure created or adapted?

4. Reliability of the PND measure

5. Were the analyses conducted with depressive symptoms as a continuous variable?

6. Describe how the participants were categorized into depressed/non-depressed groups

7. Average gestational age/time post partum at assessment

8. Standard deviation of average gestational age

9. Was this an assessment of postpartum or pregnancy depression?

Study variable characteristics

1. Did the study report the gender of the infants?

2. If so, describe for the whole study

3. Were other study constructs included in the main study?

4. If so, describe the other study constructs

5. Were IB and PND assessed concurrently?

Table 2.1. Overall and Individual Study Effects

	r	95% CI Lower	95% CI Upper	z value	p value
Ahn 2015	0.04	-0.14	0.22	0.43	0.67
Albacar 2010	0.00	-0.06	0.06	0.02	0.99
Brann 2017	-0.11	-0.12	-0.10	-16.10	<0.001
Brann 2018	0.12	0.10	0.14	13.28	<0.001
Chang 2018	0.10	-0.03	0.22	1.55	0.12
Cheng 2014	0.15	0.01	0.27	2.16	0.03
Corwin 2008	0.81	0.61	0.91	5.31	<0.001
Edvinsson 2017	-0.22	-0.24	-0.21	-35.87	<0.001
Fransson 2012	0.18	0.10	0.26	4.53	<0.001
Groer 2006	-0.13	-0.22	-0.05	-3.11	0.002
Haeri 2013	0.27	0.18	0.36	5.58	<0.001
Karlsson 2017	0.14	0.09	0.19	5.30	<0.001
Liu 2016	0.23	0.16	0.31	5.75	<0.001
Okun 2013	-0.01	-0.06	0.05	-0.31	0.76
Osborne 2018	0.13	0.06	0.19	3.90	<0.001
Roomruangwong 2017[4]	0.17	-0.12	0.43	1.13	0.26
Ruyak 2014	0.06	-0.08	0.19	0.83	0.41
Shelton 2015	-0.15	-0.21	-0.10	-5.33	<0.001
Skalkidou 2009	0.02	-0.09	0.12	0.29	0.78
Overall, Fixed-Effect	-0.09	-0.10	-0.08	-23.36	<0.001
Overall, Random-Effects	0.07	-0.01	0.15	1.83	0.07

[4] The authors published six manuscripts from this study with identical samples. It was abstracted only once and counted as a single study.

Table 2.2a. Results for Moderator Analysis for Specific Inflammatory Biomarkers

		95% CI			
	r	Lower	Upper	k	p
Specific Inflammatory Biomarker					
ADA	-0.11	-0.31	0.09	3	0.28
AXIN1*	-0.17	-0.26	-0.09	3	<0.001
CCL11	-0.15	-0.29	0.00	3	0.06
CD244	-0.13	-0.28	0.04	3	0.13
CD40	-0.13	-0.29	0.05	3	0.16
CD5	-0.04	-0.29	0.22	3	0.77
CRP	0.09	-0.04	0.21	5	0.17
CSF1	-0.05	-0.31	0.21	3	0.71
CST5*	-0.19	-0.32	-0.06	3	0.01
CX3CL1	-0.11	-0.29	0.08	3	0.26
DNER	0.00	-0.33	0.34	3	0.99
hGDNF	-0.11	-0.23	0.01	3	0.08
IFN-y	-0.07	-0.16	0.03	6	0.19
IL-10	-0.02	-0.12	0.08	8	0.69
IL10RB*	-0.14	-0.25	-0.02	3	0.02
IL-13	0.09	-0.11	0.28	3	0.38
IL15RA	-0.14	-0.30	0.04	3	0.12
IL17C	-0.12	-0.26	0.03	3	0.11
IL-18	0.18	-0.03	0.37	3	0.10
IL-1Beta	0.20	-0.23	0.57	4	0.37
IL-5	0.10	-0.18	0.37	3	0.48
IL-6*	0.09	0.03	0.15	13	0.003
IL-7	0.03	-0.20	0.26	4	0.80
IL-8	0.09	-0.06	0.23	6	0.25
MCP-1	0.17	-0.09	0.41	4	0.21
SLAMF1	-0.11	-0.25	0.04	3	0.16
STAMPB*	-0.18	-0.29	-0.06	3	0.004
TNFalpha	0.10	-0.09	0.29	7	0.28
TNFB	-0.04	-0.26	0.20	3	0.76
TNFRSF9	-0.08	-0.22	0.07	3	0.31
TRAIL	0.12	-0.30	0.50	3	0.58
uPA*	-0.14	-0.24	-0.03	3	0.01
VEGFA	0.01	-0.31	0.34	3	0.93
Overall correlation*	-0.05	-0.07	-0.02	129	<0.001

* p < 0.05

Table 2.2b. Probability values for differences between average correlations for each specific inflammatory biomarker

Specific Inflammatory Biomarker	r	CRP	IFN-y	IL-1B	IL-6	IL-8	IL-10
CRP	0.09						
IFN-y	-0.07	**0.06**					
IL-1B	0.20	0.62	0.24				
IL-6*	0.09	0.95	*0.01*	0.62			
IL-8	0.09	0.98	**0.09**	0.62	0.93		
IL-10	-0.02	0.19	0.54	0.33	**0.06**	0.24	
TNF-a	0.10	0.88	0.12	0.69	0.90	0.87	0.25

* p < 0.05

Table 2.3. Time of Assessment of Inflammatory Biomarkers

		95% CI			
	r	Lower	Upper	k	p
Overall Comparison					
Pregnancy	0.04	-0.04	0.12	11	0.34
Labor	0.11	-0.08	0.29	2	0.25
Right After Labor*	0.15	0.04	0.26	1	0.01
Postpartum	0.11	0.00	0.22	7	0.06
During Pregnancy					
First Trimester*	0.27	0.18	0.36	1	<0.001
Second Trimester	0.04	-0.09	0.17	5	0.55
Third Trimester	-0.03	-0.12	0.06	6	0.50
During Postpartum Period					
During labor - 5 days postpartum	0.11	-0.01	0.23	4	0.08
5 days - 3 months postpartum	0.17	-0.05	0.38	4	0.12
3 months - 1 year postpartum	0.04	-0.14	0.22	1	0.67

* p < 0.05

Table 2.4. Results for Moderator Analysis by Specimen Type

		95% CI			
	r	Lower	Upper	k	p
Plasma	-0.01	-0.12	0.09	10	0.79
Serum*	0.13	0.04	0.21	8	0.004
Umbilical cord serum*	0.15	0.04	0.26	1	0.01
Urine*	0.81	0.61	0.91	1	<0.001

* p < 0.05

Table 2.5. Results for Moderator Analysis by Time of Assessment of Depressive Symptoms

	r	95% CI		k	p
		Lower	Upper		
Postpartum	0.10	-0.002	0.20	11	0.06
Pregnancy	0.05	-0.09	0.19	9	0.48