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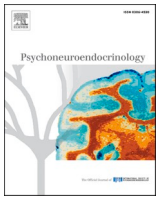

Associations between prenatal inflammation and dimensions of depressive symptoms across the perinatal period

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ABSTRACT

Objective: The perinatal period is characterized by physiological changes, including fluctuations in inflammation, and an increased risk for depression. However, the timing and cytokine-specific relations to depressive symptoms during and after pregnancy are unclear. In this study, we examined the relationships between four cytokines (IL-6, IL-8, IL-10, and TNF-α) and depression at multiple time points throughout the perinatal period and investigated the role of different dimensions of depressive symptoms in these associations.

Method: We used longitudinal data from 314 mothers (M_{age} = 29.25, M_{INR} = 2.78, 56.6 % Black/African American) in the Early Life Adversity and Biological Embedding Study from the first trimester of pregnancy to the early postnatal period. Multiple linear regressions examined the relationships between cytokines and maternal depressive symptoms. Specifically, we investigated these relationships throughout pregnancy, using cytokine slopes, third-trimester levels, and changes late in pregnancy, from the second to third trimester. Then, we investigated whether cytokines levels predicted depressive symptoms at future time points, including postnatally. Analyses with the same model structure, looking at different symptom dimensions, were adjusted using multiple comparison procedures (Bonferroni).

Results: Cytokine levels were not associated with total depression scores at any time point. IL-6 levels and anhedonia symptoms were positively associated in the third trimester (β = 0.13, p = 0.01, q = 0.04). More positive IL-6 and TNF-α slopes across pregnancy, indicating increasing levels of TNF-α over time, were associated with greater average prenatal anhedonia symptoms (β = 0.91, p = 0.01, q = 0.04 and β = 0.92, p = 0.01, q = 0.03, respectively). Increases in IL-6 from the second to third trimester predicted less postnatal anxiety (β = −0.15, p = 0.01, q = 0.02), whereas increases in TNF-α from the second to third trimester predicted greater third-trimester anxiety and sad mood (β = 0.08, p = 0.03, q = 0.05, β = 0.09, p = 0.01, q = 0.03). None of the depressive symptoms were associated with IL-8 or IL-10 at any time point (ps = 0.05–0.96).

Conclusions: Findings provide additional evidence for the role of IL-6 and TNF-α in perinatal depressive symptoms. Anhedonia symptoms and third-trimester inflammation may be particularly important. Future work focusing on dimensions of depressive symptoms and inflammatory processes across the perinatal period is key to elucidating specific temporal associations. Further investigation of how changes in inflammation across pregnancy relate to specific types of depressive symptoms could inform and improve perinatal care and intervention.

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1. Introduction

Depression is a biopsychosocial disorder and has consistently been linked with dysregulated immune processes and higher inflammation (Zunszain et al., 2013). Broadly, inflammation is a response to bodily threats, such as injury, infection, and stress, that assists in recovery but can disrupt energy, mood, and physiological processes when excessive or prolonged (Oronsky et al., 2022; Straub, 2017). Studies show that inflammation has depressogenic effects, with higher levels of pro-inflammatory cytokines associated with worse depressive symptoms (Leff-Gelman et al., 2016) and, conversely, depression has been associated with immune dysfunction (Harrison et al., 2009; Irwin and Miller, 2007). The bidirectional relationships between physiological factors, like inflammation, and depression during the perinatal period, when the body rapidly changes, physically and hormonally (Mor et al., 2017), are particularly relevant yet unclear. Thus, the current study aims to investigate associations between cytokines and dimensions of depressive symptoms across pregnancy to (1) identify periods of increased vulnerability to depression in the perinatal period and (2) clarify the role of each cytokine and symptom in the larger relationship between inflammation and depression.

The perinatal period, defined by pregnancy and the first-year postbirth, is a particularly salient time to investigate the relations between inflammation and depression because immune activity fluctuates across pregnancy (Mor et al., 2017). In healthy pregnancies, the first trimester is characterized by heightened inflammation as immune cells facilitate placentation. This process is reflected in elevated circulating levels of pro-inflammatory cytokines, including IL-6, IL-8, and TNF-α. Inflammation typically declines across the second trimester, as levels of these biomarkers decline, and expression of anti-inflammatory cytokines, like IL-10, rise (Mor et al., 2017). Another spike in inflammation occurs closer to delivery, facilitating parturition (Mor et al., 2017). This late-pregnancy rise in inflammation (Kendall-Tackett, 2007) may leave women particularly vulnerable to developing depression in the third trimester and postpartum (Leff-Gelman et al., 2016; McCormack et al., 2023; Robinson and Klein, 2012).

Pregnancy is a period of unique stress and physical and emotional demands with an increased risk for developing depression (Soares and Zitek, 2008). An epidemiological study found that depression was the only disorder with higher prevalence among pregnant and postpartum women, compared to non-pregnant women, after controlling for stress and sociodemographic factors (Vesga-Lopez et al., 2008). Increased risk for depression occurs throughout pregnancy as well as the postpartum period and has been associated with inflammatory changes. However, the changes, timing, and effects of inflammation across pregnancy that may contribute to this heightened risk for depression remain largely unexplored.

Several biomarkers of inflammation are associated with depression, including the pro-inflammatory cytokines IL-6 and TNF-α (Osimo et al., 2020), though such elevations are not uniformly observed in depressed patients. There is some evidence that IL-10, an anti-inflammatory cytokine, is also elevated in depression (Himmerich et al., 2019; Zuo et al., 2024), which may reflect a 'sickness' response in which the body counteracts pro-inflammatory cytokines (Lasselin, 2021). Notably, the presence of IL-10 in depression corresponds to shorter, milder episodes, which may be attributed to its anti-inflammatory properties (Gazal et al., 2015; Mesquita et al., 2008). In prenatal depression, higher levels of IL-6, IL-10, and TNF-α are also observed (Sawyer, 2021). IL-8, a pro-inflammatory cytokine involved in chemotaxis, has been associated with bipolar disorders more than depressive disorders (Shkundin and Halaris, 2024). However, a few studies have found associations between depression and lower IL-8 levels (Zhu et al., 2022; Zou et al., 2018). While one study found heightened IL-8 in pregnant women with remitted depression (Osborne et al., 2022), to our knowledge, no studies have investigated relations between IL-8 and depressive symptoms across pregnancy.

IL-6 levels increase during delivery, and pro-inflammatory cytokines broadly increase as the body begins immune recovery after giving birth (Bränn et al., 2017; Groer et al., 2005). During this time, anti-inflammatory cytokines initially decrease, with inflammatory activity returning to equilibrium in the following weeks (Bränn et al., 2017). However, associations between prenatal cytokines and postnatal depression are inconsistent. For instance, some studies find positive associations between postnatal depression and prenatal IL-6 (e.g., Sha et al., 2022; Simpson et al., 2016) and TNF-α (e.g., Christian et al., 2018), whereas others do not (e.g., Achtyes et al., 2020; Buglione--Corbett et al., 2018; Corwin et al., 2008; Simpson et al., 2016). Inflammation in mothers at birth, measured by IL-6 and CRP levels, predicted postpartum depressive symptoms (Liu et al., 2016; Roomruangwong et al., 2017). However, much of the extant literature focuses solely on third-trimester and postpartum depression and well-studied cytokines, such as IL-6 and TNF-α (e.g., Bränn et al., 2017; Liu et al., 2016; Roomruangwong et al., 2017). Our study aims to reproduce and extend findings on prenatal IL-6 and TNF-α predicting postnatal depression, explore associations in lesser-studied cytokines (IL-8 and IL-10), and elucidate potential trimester-specific relations to specific postnatal depressive symptoms.

Depressive symptom heterogeneity has been linked to differences in neural circuitry (e.g., reward sensitivity, vigilance to threat) and biological pathways, including inflammation (Majd et al., 2020; Milaneschi et al., 2020; Nusslock et al., 2024). Therefore, it is important to examine associations between cytokines and specific dimensions of depressive symptoms, such as anhedonia, anxiety, and sad mood. Anhedonia, the inability to experience enjoyment from previously rewarding activities, is a core dimension of depression that is associated with treatment resistance and recurrence (Khazanov et al., 2020; Shankman et al., 2014) and has strong neurobiological underpinnings (Gorwood, 2008). Among the dimensions of depressive symptoms, anhedonia is the most consistently and strongly linked to inflammation, specifically IL-6 and TNF-α (Swardfager et al., 2016). Pro-inflammatory cytokine modulation of neural reward circuitry is one well-supported explanation for this observed relationship between anhedonia and inflammation (Nusslock et al., 2024). Another dimension of depressive symptoms is sad mood (e.g., hopelessness, restricted affect). One study on the relations between inflammation and depressive symptoms did not find significant associations between inflammation and sadness (Foley et al., 2021). However, there is some evidence that inflammation is associated with sickness behaviors, influencing mood, sleep, and appetite (Dantzer, 2009; Kaster et al., 2012). Lastly, anxiety is often co-morbid with depression (Rao, 2009). Inflammation in anxiety is less studied and straightforward than in depression, however, there is evidence that cytokines influence individual responses to threat (e.g., sensitivity to threat, vigilance, social perceptions), which are related to anxiety symptoms (Nusslock et al., 2024). Prior work has investigated relationships between IL-6 and anxiety symptoms: some studies found that IL-6 was positively associated with anxiety symptoms, in addition to depression (Lee, 2020; O'Donovan et al., 2010), and one study found that IL-6 levels did not prospectively predict anxiety symptoms (Lee, 2020), like in depression (Bränn et al., 2017; Leff-Gelman et al., 2016). While there is evidence for associations between inflammation and various dimensions of depressive symptoms, most strongly with anhedonia, prior studies primarily investigated these relationships in clinical samples, outside of pregnancy. Our study examines these relationships throughout pregnancy in a community sample.

Few studies have examined perinatal relations between cytokines and depressive symptoms, and many findings involving the same cytokines have not replicated (Osborne and Monk, 2013; Simpson et al., 2016), including in perinatal samples (Silva-Fernandes et al., 2024). No studies, to our knowledge, have examined how inflammation relates to dimensions of depressive symptoms across the perinatal period, a time of potentially unique vulnerability due to normative cytokine fluctuations. Thus, the goals of the current study are to investigate the

relationships between depressive symptom dimensions (anxiety, sad mood, and anhedonia) and each cytokine prenatally, how these relationships may change across the perinatal period, and determine when inflammation and symptom associations may be strongest. We assessed contemporaneous associations between each symptom dimension and cytokine, first using average prenatal values and then third-trimester values only. Leveraging our longitudinal dataset, we also investigated whether prenatal cytokines predicted early postnatal symptoms. To investigate dynamic associations, we assessed whether cytokine changes from the second to third trimester were associated with third-trimester and postnatal symptoms.

We preregistered the following hypotheses about total prenatal depressive symptoms (https://osf.io/gpkqa). Based on prior work (Osimo et al., 2020), for total prenatal depressive symptoms (combining all dimensions), we hypothesized positive relationships with IL-6 and TNF-α, in particular, but also potentially with IL-10. We did not have a hypothesis about the relationship between IL-8 and prenatal total depression, given the limited prior literature (Shkundin and Halaris, 2024). We also expected that greater prenatal inflammation (IL-6, IL-8, and TNF-α) would be associated with greater total postnatal depressive symptoms, though not as strongly as with prenatal depressive symptoms, with the strongest relations for IL-6 and TNF-α. Due to the anti-inflammatory properties of IL-10, we hypothesized that higher prenatal IL-10 levels would be associated with fewer postnatal depressive symptoms. In the dynamic association analyses, we hypothesized that increases in pro-inflammatory cytokines (IL-6, IL-8, and TNF-α) across pregnancy would predict greater total depressive symptoms in the late prenatal and early postnatal periods, consistent with prior work (Bränn et al., 2017; Leff-Gelman et al., 2016). Inversely, we expected that, based on its anti-inflammatory nature, increases in IL-10 would predict decreased depressive symptoms in the third trimester and early postpartum. Additionally, we used the factor structure from a previous study (Lautarescu et al., 2022) to examine dimensions of depressive symptoms and tested the following non-preregistered hypotheses: (1) compared to anxiety and sad mood, we expected greater anhedonia to be associated with higher inflammation levels, and (2) anhedonia would be most strongly associated with IL-6 and TNF-α.

2. Methods

2.1. Study design and participants

Data were collected as part of the Early Life Adversity and Biological Embedding (eLABE) Study, a multi-wave, longitudinal study designed to investigate the impacts of early psychosocial adversity on neural, cognitive, and emotional development. The study originally enrolled 395 pregnant women and their singleton offspring, exceeding the recruitment goal of 350, and stopping due to the COVID-19 pandemic. Participants were oversampled for exposure to socioeconomic adversity (e.g., poverty, access to healthcare) and recruited in two obstetric clinics: one community clinic and one private insurance clinic. Exclusion criteria included multiple gestations, substance use during pregnancy (except for alcohol, marijuana, or tobacco), known pregnancy complications, and fetal congenital anomalies. Prenatal assessments were conducted during each trimester of pregnancy. Mothers were assessed shortly after birth and at 4-months postpartum. Data collection at these time points is complete and is ongoing at subsequent waves. Written informed consent was obtained from mothers after describing study protocols and prior to participation, and all protocols were approved by the Institutional Review Board at Washington University in St. Louis.

Current analyses included all participants with at least two trimesters of inflammation and depression data (controlling for gestational age to retain maximal data) and excluded those with conditions or taking medications associated with aberrant inflammation (e.g., preeclampsia, taking steroids) (N = 314). In our sample, 114 participants had complete data (every cytokine at every time point) and for those with missing data, 90 participants were missing data from the first trimester only, 79 were missing data from the second trimester only, 22 were missing the third trimester only, and 9 participants had data for all trimesters, but were missing cytokine-specific data at one time point (e.g., missing IL-6 in the first trimester). At times, cytokine data were not collected on the same date that the EPDS was administered. The proportion of these instances differed by trimester, ranging from approximately 10–64 % of the sample with data on different dates (median days between collection ranged from 25 to 29 days apart; more details available in Supplemental Table S1). Follow-up analyses determined that collection date differences, both binarized (0 = same day, 1 = different days) and continuous (absolute number of days between collections), were not related to cytokines or EPDS scores and analyses were re-run accounting for days between data collection and did not change significant results (see Supplemental Tables S2–5).

2.2. Measures

2.2.1. Demographics

Demographic data, including family income, child sex, maternal pre-pregnancy BMI, maternal age, maternal race and ethnicity, and gestational age, were collected via maternal self-report and medical records. Alcohol, tobacco, and marijuana use during pregnancy are reported in Table 1, and substance use was added as a covariate in significant findings. Income-to-needs ratio (INR) was measured by dividing a family's total income by the federal poverty guidelines of needs based on family size. We used INR to create a threshold score for above or below the poverty line (threshold of 2) to control for economic adversity. Threshold scores were used based on evidence that prenatal inflammation is associated with socioeconomic disadvantage, specifically with an income-to-needs ratio that is less than 2 (Sanders et al., 2024).

2.2.2. Maternal depression

Depressive symptoms during pregnancy were measured each trimester using the Edinburgh Postnatal Depression Scale (EPDS; Cox et al., 1987). Average prenatal depression was calculated with mean scores of trimester data (breakdown of descriptive statistics for trimester-specific and prenatal average scores, including proportions of participants above the EPDS clinical cut-off (EPDS < 12; Kendall-Tackett, 2024), are available in Table 1). Postnatal maternal depressive symptoms were measured at 4-months post-delivery using the EPDS (see Table 1). The EPDS is the recommended measure of perinatal depression due to its distinction between depressive symptoms and normative physical pregnancy symptoms (Siu et al., 2016). Initial analyses used total EPDS scores, and a set of follow-up analyses examined relations between perinatal inflammation and dimensions of depressive symptoms. Specifically, we distinguished between anxiety, sad mood, and anhedonia symptoms, using a three-factor model (validated by Lautarescu et al., 2022), rather than using the single composite EPDS score, and re-ran all analyses. We averaged scores within each factor to account for the different number of items in each symptom dimension (see Supplemental Materials and Table S6 for specific EPDS item breakdown). Information on relations within and between subscales across the pre- and post-natal periods is available in the results section.

2.2.3. Maternal inflammation

Maternal cytokines were measured using antecubital blood samples during each trimester of pregnancy and at birth. Blood samples were refrigerated at 4 °C, centrifuged for 5 min at 1620 x g within 12 h of collection, and serum and plasma were stored at −80 °C. Following the same approach as Sanders et al., (2024), we measured the serum levels of four inflammatory biomarkers: IL-6, IL-8, IL-10, and TNF-α. These cytokines were measured in triplicate using a multiplex immunoassay protocol on an automated microfluidic platform, Simple Plex assay (Aldo et al., 2016). Cytokine outliers, 3 or more standard deviations outside of the mean, were excluded from analyses. Lower limits of

Table 1
Descriptive statistics for current sample.

Variable	Observed Range	Mean (*SD*) or %
Maternal Age at Delivery (years)	18.58–41.83	29.25 (5.39)
Child Sex (% female)		43 %
Maternal Race (self-reported)		
White		37.9 %
Black/African American		56.6 %
Asian		1.3 %
Other (Mixed race, Middle Eastern, Asian Indian, and Hispanic/Latino)		2.2 %
Ethnicity (% Hispanic/Latinx)		2.2 %
Income-to-needs threshold (% below)		61.5 %
Income-to-needs (raw data)	0.35–12.04	2.78 (2.83)
Pre-pregnancy Body Mass Index (BMI)	16.14–57.52	28.68 (7.95)
Gestational Age (days)	206–291	269.92 (10.88)
Prenatal Substance Use (% any endorsed)		23.2 %
Alcohol Use		6 %
Tobacco Use		12.1 %
Marijuana Use		11.5 %
Total Depressive Symptoms (prenatal average)	0–24	4.89 (4.34)
8 % above EPDS clinical cut-off		
Anxiety Symptoms (prenatal average)	0–2.89	0.73 (0.61)
Sad Mood Symptoms (prenatal average)	0–2.3	0.44 (0.45)
Anhedonia Symptoms (prenatal average)	0–2.5	0.25 (0.41)
Total Depressive Symptoms (1st trimester)	0–25	5.17 (5.01)
12 % above EPDS clinical cut-off		
Total Depressive Symptoms (2nd trimester)	0–26	4.86 (4.88)
11 % above EPDS clinical cut-off		
Total Depressive Symptoms (3rd trimester)	0–25	4.32 (4.72)
8 % above EPDS clinical cut-off		
4-month Postnatal Depressive Symptoms (average)	0–26	6.16 (5.48)
16 % above EPDS clinical cut-off		
Depressive Symptoms at Year 2 (BDI)	0–42	7.43 (8.08)
Depressive Symptoms at Year 3 (BDI)	0–52	6.29 (7.13)
Interleukin 6 (IL−6) (averaged across trimesters)	0.01–1636.06	11.25 (96.36)
Interleukin 8 (IL−8) (averaged across trimesters)	0.01–761.40	11.31 (63.85)
Interleukin 10 (IL−10) (averaged across trimesters)	0.01–172.27	4.57 (14.37)
Tumor necrosis factor alpha (TNF-α) (averaged across trimesters)	0–436.29	6.97 (35.48)
IL−6 Slope (across trimesters)	0.43–2.13	1.02 (0.15)
IL−8 Slope (across trimesters)	0.56–2.02	1.03 (0.17)
IL−10 Slope (across trimesters)	0.62–1.81	0.98 (0.14)
TNF-α Slope (across trimesters)	0.41–2.49	1.04 (0.17)

Note: Cytokine levels are reported in raw form (pg/mL) and $\log_{10}$ transformation form was used for analyses. Alcohol, marijuana, and tobacco use across pregnancy were binary measures and percentages reflect the proportion of mothers who endorsed use of any kind at any point during pregnancy. Detailed breakdown of BMI by category is available in the Supplement (Table S9).

detection range from 0.08 pg/mL (IL-8) to 0.28 pg/mL (TNF-α). Across runs, the average intra-assay coefficients of variation (CVs) for triplicate samples were 3.6 % (IL-6), 2.1 % (IL-8), 2.4 % (IL-10), and 3.8 % (TNF-α). The corresponding inter-assay coefficients of variation (CVs) were 3.6 %, 3.2 %, 4.5 %, and 1.3 %, respectively. Cytokine measurements were reliable across runs according to ideal CV cut-offs (CVs < 5 %; Aldo et al., 2016). Trimester-specific cytokine levels are shown in Supplemental Table S7.

2.3. Data analysis

Average concentrations were calculated across gestational blood draws for each cytokine. Given the increase in cytokines during the third trimester (Kendall-Tackett, 2007), we expanded upon these analyses by looking at relationships between depressive dimensions and inflammation during the third trimester. Slopes were calculated using simple linear regression models to assess the rate of change in cytokine levels across pregnancy. Slope calculations required at least two trimesters of cytokine data, which was an inclusion criterion for the present analyses. Cytokine data were normalized with $\log_{10}$ transformations to account for skewed and kurtotic distributions. The first trimester was defined as the first 14 weeks of pregnancy, the second trimester spanned from 14 to 27 weeks, and the third trimester was from 27 weeks onward. Information on relations within and between cytokines across pregnancy is available in the results section.

Multiple linear regressions examined the relationships between cytokines at various time points and maternal depressive symptoms (total versus anhedonia, sad mood, and anxiety). Cytokines were measured using: a) prenatal averages (to assess relations with overall prenatal cytokine levels), b) third-trimester values (which may be most predictive of postnatal symptoms), c) slopes across all three trimesters (to assess changes across pregnancy), and d) difference scores from the second to third trimester (to determine if an increase in cytokines specifically in the third trimester predict antenatal or postnatal depressive symptoms). Analyses were conducted using the stats 4.3.1 package in R. Relationships between depressive symptom dimensions and inflammation were assessed with each biomarker independently. Multiple comparison procedures (Bonferroni) were applied to all analyses with the same model structure (same time point and cytokine with different dimension outcomes), and adjusted significance values (q) are reported. To isolate timing effects, for models that predicted outcomes at future time points (e.g., prenatal inflammation to postnatal symptoms), we used residualization and accounted for symptoms that were concurrent with the predictor variables.

3. Results

The analyzed sample included 314 women and was well-powered. Based on effect sizes from a recent meta-analysis on associations between cytokines and depression (Osimo et al., 2020), the minimum sample size to achieve adequate power for our analyses is 105 participants (power = 0.95, α = 0.01, two-tailed test). We ran power analyses for each of the cytokines of interest and reported the most conservative sample size based on the cytokine with the lowest effect size in the meta-analysis (IL-10, $f^2 = 0.31$) and based on the model with the most predictors (n = 8). Power analyses were conducted in G*Power 3.1. The necessary sample size for 95 % power is 206, if we conservatively estimate an effect size 50 % smaller ($f^2 = 0.15$) and 304 for an effect size roughly 66 % smaller ($f^2 = 0.10$). The means, ranges, and standard deviations for relevant demographic variables, covariates, predictors, and outcomes are shown in Table 1. Demographics in this sample (maternal race, child sex, maternal pre-pregnancy BMI, and INR) were representative of the demographics of the entire sample (see Supplemental Table S8 for whole sample demographic information).

3.1. Relations within and between inflammatory cytokines across trimesters

IL-6 levels were moderately correlated between the first trimester and other trimesters and were strongly correlated between the second and third trimesters (Supplemental Figure S1). IL-8 and IL-10 levels showed similar patterns in that they were weakly correlated between the first trimester and other trimesters and were moderately correlated between the second and third trimester. TNF-α levels were moderately correlated across all trimesters. The second and third trimesters were most strongly correlated across all cytokine types, except for TNF-α (Supplemental Figure S1). Between cytokines, IL-6 and TNF-α levels were most strongly correlated across all trimesters (Supplemental Figure S2). While all cytokines were positively correlated, IL-8 was the least strongly correlated with the other three cytokines across all trimesters (Supplemental Figure S2).

Within each participant, cytokine levels across trimesters were

plotted, with aggregate trajectories in red (Supplemental Figure S3). On average, IL-6 and IL-8 levels significantly increased from the second to third trimester. On the other hand, IL-10 levels remained relatively stable from the first to second trimester, with a significant decrease in the third trimester. TNF-α levels significantly increased across each subsequent trimester.

3.2. Relations with total EPDS scores

All of the inflammation analyses accounted for maternal pre-pregnancy body mass index, child sex, gestational age, and income-to-needs. The pre-registered analyses with the total EPDS scores were all non-significant and are included in the supplement (denoted with T-S#). The analyses presented here focus on non-pre-registered analyses of EPDS dimension scores, with Bonferroni correction for multiple comparisons. Findings with prenatal averages of dimension scores were non-significant and are reported in the supplement (Tables S10-13).

3.3. EPDS dimension scores interrelationships

Anxiety and sad mood symptoms were most strongly correlated, both prenatally and postnatally (Supplemental Figures S2 and S4). Sad mood and anhedonia symptoms were also strongly correlated prenatally and postnatally (Supplemental Figures S2 and S4). The anxiety and anhedonia dimensions were moderately correlated prenatally and postnatally (Supplemental Figures S2 and S4). Prenatal and postnatal dimension scores were all moderately correlated (*rs* = 0.43–0.57, see Supplement for more detail). Across trimesters, all three dimension scores remained stable, on average, with relatively flat trajectories (Supplemental Figure S5). Anxiety scores from the first to third trimester significantly decreased, which was the only significant change observed across the dimensions.

3.4. IL-6 and EPDS dimension scores

Greater levels of IL-6 in the third trimester were associated with greater levels of anhedonia symptoms in the third trimester and remained significant after accounting for anhedonia scores in the second trimester (Table 2, Supplemental Figure S6). IL-6 levels in the third trimester were not associated with anxiety or sad mood symptoms in the third trimester (Supplemental Table S14) or with any postnatal symptoms (Supplemental Table S15). Low INR (below the poverty line) was associated with greater sad mood and anhedonia symptoms in the third trimester. Increases in IL-6 from the second to third trimester were associated with fewer anxiety symptoms at 4-months postpartum after accounting for prenatal anxiety scores (Table 3, Supplemental Figure S7), but were not associated with third-trimester symptoms or other 4-month postnatal symptoms (Supplemental Tables S16 and S17). IL-6 slopes across pregnancy, indicating increasing levels of IL-6 across pregnancy, were associated with greater prenatal anhedonia (Table 4, Figure S8), but not prenatal anxiety or sad mood symptoms (Supplemental Table S18). In summary, third-trimester IL-6 was related to third-trimester anhedonia, IL-6 slopes were associated with greater average prenatal anhedonia, and increases in IL-6 from the second to third trimester were associated with fewer anxiety symptoms 4-months postpartum.

Table 2
Third-trimester IL-6 predicting third-trimester anhedonia symptoms (n = 208).

Outcome Variable: Anhedonia (T3)					
Predictor	**B**	**SE**	**t**	**p (q)**	**95 % CI**
Intercept	−1.25	0.99	−1.26	0.21	[−3.21, 0.71]
IL−6 (T3)	**0.13**	**0.05**	**2.55**	**0.01 (0.04)**	**[0.03, 0.22]**
Anhedonia (T2)	**0.49**	**0.07**	**6.57**	**<0.001 (< 0.001)**	**[0.34, 0.64]**
Child Sex (Male)	−0.02	0.06	−0.38	0.71	[−0.15, 0.10]
Pre-pregnancy BMI	−0.01	0.004	−1.30	0.19	[−0.01, 0.003]
Maternal Age (years)	0.01	0.01	0.82	0.41	[−0.01, 0.02]
Gestational Age (total days)	0.01	0.004	1.37	0.17	[−0.002, 0.01]
INR (Above threshold)	−0.02	0.08	−0.20	0.84	[−0.18, 0.14]
Substance Use (Endorsed)	0.10	0.08	1.18	0.24	[−0.06, 0.26]

Note: Bold indicates predictors that passed Bonferroni correction. Substance use includes endorsements of alcohol, tobacco, and/or marijuana in any trimester. BMI = Body Mass Index; IL = Interleukin; INR = income-to-needs ratio; T2 = s trimester; T3 = Third trimester.

3.5. TNF-α and EPDS dimension scores

More positive TNF-α slopes across pregnancy, indicating increasing levels of TNF-α over time, were associated with greater average prenatal anhedonia (Table 4, Supplemental Figure S9), but not anxiety or sad mood symptoms (Supplemental Table S19). Increases in TNF-α from the second to third trimester were significantly associated with greater sad mood and anxiety symptoms in the third trimester, but not anhedonia, after controlling for symptoms in the second trimester (Table 5, Supplemental Figures S10a and S10b). TNF-α levels in the third trimester were not associated with symptoms in the third trimester (Supplemental Table S20) or 4-months postnatal (Supplemental Table S21). In summary, TNF-α slopes were related to greater average prenatal anhedonia, and increases in TNF-α from the second to third trimester significantly

Table 3
Changes in IL-6 from the second to third trimester predicting postnatal anxiety symptoms (n = 139).

Outcome Variable: Postnatal Anxiety Score Model I					
Predictor	**B**	**SE**	**t**	**p (q)**	**95 % CI**
Intercept	2.01	1.55	1.30	0.20	[−1.07, 5.08]
IL−6 Change (T2 to T3)	−0.14	0.07	−2.08	0.04 (0.11)	[−0.27, −0.01]
Child Sex (Male)	−0.12	0.12	−1.00	0.32	[−0.35, 0.12]
Pre-pregnancy BMI	−0.01	0.01	−1.02	0.31	[−0.02, 0.01]
Maternal Age (years)	**−0.03**	**0.01**	**−2.42**	**0.02 (0.05)**	**[−0.06, −0.01]**
Gestational Age (total days)	0.0002	0.01	0.04	0.97	[−0.01, 0.01]
INR (Above threshold)	0.03	0.15	0.20	0.84	[−0.26, 0.32]
Substance Use (Endorsed)	0.03	0.14	0.18	0.86	[−0.26, 0.31]
Model II (controlling for prenatal anxiety)					
Intercept	1.82	1.32	1.38	0.17	[−0.80, 4.43]
IL−6 Change (T2 to T3)	**−0.15**	**0.06**	**−2.71**	**0.01 (0.02)**	**[−0.26, −0.04]**
Prenatal Anxiety (mean)	**0.64**	**0.09**	**7.17**	**<0.001 (< 0.001)**	**[0.46, 0.82]**
Child Sex (Male)	−0.06	0.10	−0.61	0.55	[−0.26, 0.14]
Pre-pregnancy BMI	−0.01	0.01	−1.06	0.29	[−0.02, 0.01]
Maternal Age (years)	−0.02	0.01	−1.48	0.14	[−0.04, 0.01]
Gestational Age (total days)	−0.002	0.01	−0.52	0.61	[−0.01, 0.01]
INR (Above threshold)	0.02	0.13	0.16	0.88	[−0.23, 0.27]
Substance Use (Endorsed)	0.03	0.12	0.22	0.82	[−0.21, 0.27]

Note: Bold indicates predictors that passed Bonferroni correction. Substance use includes endorsements of alcohol, tobacco, and/or marijuana in any trimester. BMI = Body Mass Index; IL = Interleukin; INR = income-to-needs ratio; T2 = s trimester; T3 = Third trimester.

Table 4
Cytokine slopes predicting prenatal anhedonia symptoms (averaged across trimester).

Outcome Variable: Prenatal Anhedonia Symptoms (average)																				
Predictor	**IL-6** (n = 251)					**IL-8** (n = 251)					**IL-10** (n = 250)					**TNF-α** (n = 250)				
	B	**SE**	**t**	**p (q)**	**95 % CI**	***B***	**SE**	**t**	**p (q)**	**95 % CI**	***B***	**SE**	**t**	**p (q)**	**95 % CI**	***B***	**SE**	**t**	**p (q)**	**95 % CI**
Intercept	0.02	0.63	0.03	0.98	[−1.22, 1.26]	−0.06	0.65	−0.10	0.92	[−1.34, 1.21]	0.13	0.64	0.21	0.84	[−1.13, 1.39]	−0.11	0.64	−0.18	0.86	[−1.37, 1.14]
Slope	**0.91**	**0.37**	**2.47**	**0.01 (0.04)**	**[0.18, 1.63]**	0.58	0.35	1.66	0.10	[−0.11, 1.27]	0.31	0.40	0.78	0.43	[−0.47, 1.09]	**0.92**	**0.35**	**2.62**	**0.01 (0.03)**	**[0.23, 1.59]**
Child Sex (Male)	−0.003	0.05	−0.06	0.95	[−0.10, 0.09]	−0.01	0.05	−0.31	0.76	[−0.11, 0.08]	−0.02	0.05	−0.43	0.67	[−0.12, 0.07]	−0.01	0.05	−0.13	0.90	[−0.10, 0.09]
Pre-pregnancy BMI	**0.01**	**0.003**	**2.93**	**0.004 (0.01)**	**[0.003, 0.01]**	**0.01**	**0.003**	**2.56**	**0.01 (0.03)**	**[0.002, 0.01]**	**0.01**	**0.003**	**2.72**	**0.01 (0.01)**	**[0.002, 0.01]**	**0.01**	**0.003**	**2.84**	**0.01 (0.01)**	**[0.003, 0.01]**
Maternal Age (years)	−0.01	0.01	−1.72	0.09	[−0.02, 0.001]	−0.01	0.01	−1.45	0.15	[−0.02, 0.003]	−0.01	0.01	−1.55	0.12	[−0.02, 0.002]	−0.01	0.01	−1.69	0.09	[−0.02, 0.001]
Gestational Age (total days)	0.001	0.002	0.43	0.67	[−0.003, 0.01]	0.001	0.002	0.57	0.57	[−0.003, 0.01]	0.001	0.002	0.26	0.79	[−0.004, 0.01]	0.001	0.002	0.63	0.53	[−0.003, 0.01]
INR (Above Threshold)	**−0.13**	**0.06**	**−2.26**	**0.03 (0.04)**	**[−0.25, −0.02]**	**−0.14**	**0.06**	**−2.38**	**0.02 (0.03)**	**[−0.25, −0.02]**	**−0.13**	**0.06**	**−2.28**	**0.02 (0.04)**	**[−0.25, −0.02]**	−0.12	0.06	−2.00	0.05 (0.07)	[−0.23, −0.002]
Substance Use (Endorsed)	0.10	0.06	1.71	0.09	[−0.02, 0.21]	0.08	0.06	1.43	0.16	[−0.03, 0.20]	0.09	0.06	1.56	0.12	[−0.02, 0.21]	0.10	0.06	1.78	0.08	[−0.01, 0.22]

Note: Bold indicates predictors that passed Bonferroni correction. Substance use includes endorsements of alcohol, tobacco, and/or marijuana in any trimester. BMI = Body Mass Index; IL = Interleukin; INR = income-to-needs ratio; TNF = Tumor Necrosis Factor.

Table 5
Changes in TNF-α predicting T3 symptoms, controlling for T2 symptoms (n = 140).

Outcome Variable: Anxiety (T3)					
Predictor	**B**	**SE**	**t**	**p (q)**	**95 % CI**
Intercept	−0.97	1.35	−0.72	0.47	[−3.64, 1.71]
TNF-α Change (T2 to T3)	**0.09**	**0.04**	**2.23**	**0.03 (0.05)**	**[0.01, 0.17]**
Anxiety (T2)	**0.61**	**0.07**	**8.89**	**<0.001 (< 0.001)**	**[0.47, 0.74]**
Child Sex (Male)	−0.04	0.09	−0.48	0.63	[−0.22, 0.13]
Pre-pregnancy BMI	0.003	0.01	0.63	0.53	[−0.01, 0.01]
Maternal Age (years)	0.0004	0.01	0.05	0.96	[−0.02, 0.02]
Gestational Age (total days)	0.004	0.01	0.76	0.45	[−0.01, 0.01]
INR (Above threshold)	0.14	0.11	1.29	0.20	[−0.08, 0.35]
Substance Use (Endorsed)	0.05	0.11	0.45	0.65	[−0.16, 0.26]
Outcome Variable: Sad Mood (T3)					
Intercept	−0.50	1.16	−0.44	0.66	[−2.79, 1.78]
TNF-α Change (T2 to T3)	**0.08**	**0.04**	**2.17**	**0.03 (0.05)**	**[0.01, 0.14]**
Sad Mood (T2)	**0.47**	**0.07**	**6.26**	**<0.001 (< 0.001)**	**[0.32, 0.62]**
Child Sex (Male)	−0.06	0.08	−0.73	0.47	[−0.20, 0.09]
Pre-pregnancy BMI	0.01	0.004	1.02	0.31	[−0.004, 0.01]
Maternal Age (years)	0.001	0.01	0.14	0.89	[−0.01, 0.02]
Gestational Age (total days)	0.002	0.004	0.47	0.64	[−0.01, 0.01]
INR (Above threshold)	−0.03	0.09	−0.35	0.73	[−0.22, 0.15]
Substance Use (Endorsed)	0.04	0.09	0.44	0.66	[−0.14, 0.22]
Outcome Variable: Anhedonia (T3)					
Intercept	−0.54	1.15	−0.47	0.64	[−2.81, 1.74]
TNF-α Change (T2 to T3)	0.06	0.03	1.81	0.07	[−0.01, 0.13]
Anhedonia (T2)	**0.52**	**0.08**	**6.50**	**<0.001 (< 0.001)**	**[0.36, 0.68]**
Child Sex (Male)	−0.05	0.07	−0.63	0.53	[−0.19, 0.10]
Pre-pregnancy BMI	−0.01	0.004	−1.02	0.31	[−0.01, 0.004]
Maternal Age (years)	0.01	0.01	1.34	0.63	[−0.01, 0.02]
Gestational Age (total days)	0.002	0.004	0.48	0.63	[−0.01, 0.01]
INR (Above threshold)	−0.11	0.09	−1.19	0.24	[−0.29, 0.07]
Substance Use (Endorsed)	−0.05	0.09	−0.54	0.59	[−0.23, 0.13]

Note: Bold indicates predictors that passed Bonferroni correction. Substance use includes endorsements of alcohol, tobacco, and/or marijuana in any trimester. BMI = Body Mass Index; INR = income-to-needs ratio; TNF = Tumor Necrosis Factor; T2 = s trimester; T3 = Third trimester.

predicted greater depression and anxiety in the third trimester.

3.6. Exploratory cytokines (IL-8 and IL-10) and EPDS dimension scores

IL-8 and IL-10 measures were not significantly associated with any dimension of maternal depressive symptoms: not in the third trimester (Supplemental Tables S22 and S23), using slopes (Tables S24 and S25),

or predicting postnatal symptoms (Tables S26 and S27). However, increases in IL-8 from the second to third trimester were associated with greater sad mood and anhedonia symptoms in the third trimester ($\beta = 0.08$, $p = 0.03$, $q = 0.05$ and $\beta = 0.09$, $p = 0.01$, $q = 0.04$, respectively), but not anxiety symptoms (Supplemental Table S28). However, after accounting for symptoms in the second trimester and adjusting for multiple comparisons, these relationships became non-significant (Supplemental Table S29). After adjusting for multiple comparisons, changes in IL-10 from the second to third trimester were not associated with symptoms in the third trimester (Supplemental Table S30).

4. Discussion

As previously outlined, there is a heightened vulnerability to depression in the perinatal period, yet the mechanisms underlying this vulnerability are unclear. Cytokine levels fluctuate significantly between trimesters of pregnancy, and inflammation tends to be greater, on average, during pregnancy than outside of pregnancy (Bränn et al., 2017). Prior work has broadly and robustly shown that greater inflammation is bidirectionally associated with greater depressive symptoms (e.g., Osimo et al., 2020), however the timing of these relations perinatally are less clear. Thus, some work has begun to investigate how inflammation during pregnancy may confer risk for depression, and vice versa, in the perinatal period. It is crucial to better understand these relations contemporaneously and dynamically within the perinatal period and identify inflammatory markers associated with depressive symptoms to inform and refine treatment targets. To address the gaps in the literature, the current study explored temporal associations between depressive symptoms and inflammation, examining slopes across pregnancy, third-trimester specific effects, and inflammation changes from the second to third trimester to determine times of particular risk. We did not find any significant relations between total pre- or postnatal depression symptoms and cytokine levels. However, our follow-up analyses focused on dimensions of depressive symptoms to parse apart independent relationships between inflammation and distinct symptoms of depression: anxiety, sad mood, and anhedonia. We found evidence for associations between perinatal depressive symptoms and both IL-6 and TNF-α. Notably, IL-6 and anhedonia were associated in the third trimester, and both IL-6 and TNF-α slopes across pregnancy were significantly associated with average prenatal anhedonia. While based on exploratory analyses, these findings suggest there is utility in assessing specific dimensions of depressive symptoms and measuring inflammation longitudinally, across pregnancy, to elucidate temporal relationships.

As noted above, when using depression composite scores, there were no significant associations between cytokines and depressive symptoms at any time point. However, in many of the single depression score and dimensional symptom models, greater socioeconomic disadvantage (measured as INR) was associated with higher depressive symptoms. These results demonstrate socioeconomic disparities in mental health that should be considered in future research. Although the composite depression and cytokine results do not replicate some prior work (McCormack et al., 2023), this may be attributable to different samples (e.g., clinical vs. non-clinical) and methodological differences (e.g., the timing of cytokine and depression measurement, measures used) between studies. It is possible that our results would have aligned with past findings if we had sampled for clinical depression and had a larger proportion of participants with severe depressive symptoms. Differences in findings across studies may also be attributable to the use of diverse depression instruments in the literature, including the Diagnostic and Statistical Manual of Mental Disorders, the Center for Epidemiological Studies-Depression, the Hamilton Depression Rating Scale, and the Patient Health Questionnaire (McCormack et al., 2023). We assessed depressive symptoms with the EPDS, which is recommended for measuring perinatal symptoms according to the U.S. Preventive Services Task Force (Siu et al., 2016). To address the mixed results on the relationships between prenatal inflammation and depression, future work may benefit from including measures of depression used in studies outside of the perinatal period in studies of pregnancy to better compare relations between inflammation and depression across contexts.

Consistent with past research on the relevance of inflammation in the third trimester (Kendall-Tackett, 2007; Leff-Gelman et al., 2016; McCormack et al., 2023; Robinson and Klein, 2012), we found that greater third-trimester IL-6 was associated with greater third-trimester anhedonia symptoms. This finding aligns with hypotheses and neuroimmune network models that suggest that inflammation may blunt reward sensitivity and contribute to anhedonia (Nusslock et al., 2024). In our study, higher levels of third-trimester inflammatory cytokines, like IL-6, may contribute to depression vulnerability in late pregnancy and early postpartum. The relationship between IL-6 and anhedonia in the third trimester highlights a crucial time for holistic clinical intervention, targeting inflammation and anhedonia symptoms. Our finding on the association between IL-6 slopes and prenatal anhedonia further emphasizes the potential relevance of anhedonia symptoms, specifically, in the study of perinatal mood and inflammation.

Surprisingly, we also found that increases in IL-6 from the second to third trimester predicted less anxiety at 4-months postpartum. It is difficult to theorize potential reasons for this relationship due to the lack of research on dimensional depressive symptoms and changes in depressive symptoms during the perinatal period. More broadly, the literature on IL-6 and anxiety is mixed and relatively limited, with one study finding no association between third-trimester IL-6 and increased postnatal anxiety (Furtado et al., 2019) and another concluding that higher IL-6 was associated with greater anxiety in the late prenatal and early postnatal periods (Osborne et al., 2019). Importantly, these studies measured anxiety separately from mood symptoms, using the Hamilton Anxiety Rating Scale and State-Trait Anxiety Inventory, rather than measuring depressive symptoms dimensionally, using the EPDS. Thus, our study may have detected relations between somewhat different constructs than those examined in prior studies. Additionally, some studies have considered biological and inflammatory influences on changes in depressive symptoms (e.g., IL-6 predicting changes in depression across pregnancy) (Silva-Fernandes et al., 2024), but very few have examined the effects of perinatal cytokine changes like ours, which may explain different results. It is also possible that postnatal anxiety is associated with postnatal inflammation, which was not measured in our sample. Nonetheless, further research comparing measures of anxiety is needed to clarify the directional nature of the association between prenatal IL-6 and postnatal anxiety symptoms, which may aid early risk identification and postpartum mental healthcare resources.

We also observed that TNF-α slopes were associated with average prenatal anhedonia symptoms, which supports prior findings that TNF-α is associated with perinatal depressive symptoms (Miller et al., 2009; Osimo et al., 2020). Several studies have found that greater TNF-α levels were associated with greater anhedonia symptoms (Rengasamy et al., 2021; Swardfager et al., 2016) and established that treating inflammation subsequently reduces anhedonia (Eyre et al., 2015; Felger et al., 2020; Howren et al., 2013; Jones et al., 2020). However, these studies did not examine these relationships during the perinatal period. Interestingly, we also found that increases in TNF-α from the second to third trimester were associated with greater anxiety and sad mood in the third trimester. While we expected to find significant associations between increased TNF-α and anhedonia, rather than anxiety or sad mood, these results are still consistent with prior work on TNF-α and depression more broadly, as measured by composite scores and clinical diagnoses (Sawyer, 2021). Further, increases in TNF-α predicting greater anxiety symptoms may also be indirectly explained by the influence of pro-inflammatory cytokines, including TNF-α, on threat-related sensitivity and circuitry in cortico-amygdala regions (Nusslock et al., 2024). We did not, however, find associations between TNF-α and postnatal symptoms, which contrasts three prior studies that reported higher

TNF-α was associated with fewer postnatal symptoms (Silva-Fernandes et al., 2024). The different relationships observed between symptoms and IL-6 and TNF-α (e.g., TNF-α related to sad mood, but not IL-6) may also be related to each cytokine's role in mechanistic pathways that potentially contribute to inflammation-related depressive symptoms (Eisenberger et al., 2017). For instance, TNF-α has been shown to induce sickness behaviors (e.g., disruptions in sleep and appetite, worsened mood) in animal models (Dantzer, 2009; Kaster et al., 2012) and is implicated in serotonin modulation (Bortolato et al., 2015), which regulates mood, appetite, and sleep. Our results provide some preliminary evidence for distinct relationships between TNF-α and dimensions of depressive symptoms and add to the growing literature on the influence of TNF-α, among other cytokines, on perinatal mental health.

Overall, we did not find evidence for associations between IL-8 at any point during pregnancy and dimensions of depressive symptoms. A few studies found relationships between greater IL-8 and fewer depressive symptoms. However, these included clinical samples outside of pregnancy, which may explain the differing results. IL-8 is not commonly included in studies on perinatal inflammation and depression and was exploratory in our analyses. IL-8 has been associated with several forms of psychopathology, including bipolar disorder and schizophrenia, whereas IL-6 and TNF-α are more specifically associated with depression (Tsai, 2021). Similarly, we did not find any significant relationships between IL-10 and depressive symptom dimensions. This contrasts several previous findings that greater IL-10 was associated with greater depression, but shorter, milder episodes (Gazal et al., 2015; Mesquita et al., 2008). As discussed above, our analyses examining symptom changes differed from prior results because of differences in samples (animal models and clinical samples versus community sample) and measures (semi-structured interview versus EDPS). Given the uncertainty about the role of prenatal IL-8 and IL-10 in depressive symptoms, future studies should continue to include these cytokines, particularly in perinatal studies with greater levels of depression than in the current study. This will improve the current understanding of inflammatory mechanisms in perinatal depression.

The longitudinal nature of the current study allowed us to address gaps in the literature by investigating inflammation and depressive symptoms across each trimester of pregnancy, as well as postnatally, and assessing inflammatory predictors of changes in depression to clarify the nature and timing of these relationships. Distinguishing dimensions of depressive symptoms advances this body of research by revealing that prenatal inflammation may be most strongly associated with dimensions of depressive symptoms later in pregnancy and offers a new approach to examining relationships between inflammation and depression. Of note, the direction of these associations cannot be inferred from these findings. Assuming the relationship is causal, there are three potential scenarios: inflammation could provoke depression, depression could provoke inflammation, or there could be bidirectional effects. Sorting out these possibilities will require multi-wave studies, which have been done in non-pregnant samples, and favor the bidirectional scenario, at least among those who have experienced childhood adversity (Miller and Cole, 2012). Our findings also remained after accounting for prenatal substance use (alcohol, marijuana, and tobacco), which has been associated with greater perinatal depression and anxiety (Pentecost et al., 2021) and dysregulated immune functioning (Ashford et al., 2019; Horn et al., 2018), including lower levels of first-trimester TNF-α in co-users of tobacco and cannabis (Ashford et al., 2019) and greater levels of IL-6 in the second and third trimesters in tobacco smokers (Ashford et al., 2013). Rates of substance use in our sample are comparable to national surveys of prenatal substance use (Chang, 2020), and distinguishing potential substance-related effects from associations between cytokines and symptom dimensions provides stronger evidence for these relationships in the perinatal period. Our sample composition is another notable strength: our sample size is well-powered and fairly large compared to other similar studies (e.g., O'Donovan et al., 2010; Simpson et al., 2016; Zuo et al., 2024), and it is relatively racially diverse and representative of the local St. Louis community ("U.S. Census Bureau QuickFacts," n.d.). Moreover, unlike some prior work (e.g., Foley et al., 2021; Simpson et al., 2016), we use a non-clinical, community sample that was not recruited or oversampled for depression. While sample differences prevent us from directly comparing results to other work, our findings provide preliminary evidence for relationships between inflammation and sub-clinical depressive symptoms. This preliminary evidence could allow for broader generalizability of results beyond clinical contexts and psychiatric diagnoses. Associations between dimensions of perinatal depressive symptoms and IL-6 and TNF-α suggest that future work should continue to examine the influences of inflammation in non-clinical populations, as it may be relevant for preventive healthcare and psychoeducation during the perinatal period.

Future work should also address limitations in the current study. First, due to variability in blood collection each trimester, some participants only had one or two trimesters of cytokine data. This variability limited our sample size because slope calculations required at least two trimesters of cytokine data, and some analyses required third-trimester data. However, our sample size was the largest in the third trimester which circumvented additional sample inclusion restrictions. We did not use multiple imputation to account for missing data due to natural cytokine variation between trimesters and a lack of evidence-based predictors of inflammation to use for imputation (Mor and Cardenas, 2010). Compared to the entire sample (N = 395), our sample subset (N = 314) did not differ significantly in demographics or depressive symptoms (see Supplemental Table S8). Second, our study only collected four inflammatory markers: IL-6, IL-8, IL-10, and TNF-α. This data allowed us to assess theory-driven hypotheses with well-studied cytokines in depression (IL-6 and TNF-α) and explore the potential role of less-studied cytokines in depression (IL-8 and IL-10). However, we were unable to examine the role of other inflammatory markers that are frequently associated with depressive symptoms, like C-reactive protein (CRP) and IL-1β (Osimo et al., 2020; Shelton et al., 2015; Silva-Fernandes et al., 2024), so future work should include a more comprehensive cytokine panel. Our study also did not measure hormones, which are related to inflammation throughout pregnancy, and may be an important addition to studies on perinatal depression (Robinson and Klein, 2012). Third, as mentioned previously, prior work has found bidirectional associations between inflammation and depression (Silva-Fernandes et al., 2024), and while our findings delineate the timing of associations between specific cytokines and depressive symptoms, they do not establish directionality. These associations should be interpreted in the context of our study, oversampled for mothers experiencing socioeconomic disadvantage, which has been associated with heightened stress (Daalderop et al., 2023), inflammation (Muscatell et al., 2020), and depression (Nagy et al., 2022). Future research may benefit from assessing the role of perinatal stress in psychoimmune functioning. Finally, our use of the factor structure in the EPDS allowed for distinguishing between types of symptoms. Still, future work should consider assessing these dimensions more fully, with measures designed to target specific constructs. Follow-up work that includes deliberate measures of anxiety, sad mood, and anhedonia could compare differences in relationships with cytokines based on operationalizations of these dimensions and build upon the current findings.

4.1. Conclusions

In sum, our study examined relationships between several cytokines and depressive symptoms and aimed to identify when these associations may be strongest throughout the perinatal period and how inflammation may relate to dimensions of depressive symptoms differently. Notably, anhedonia was associated with IL-6 in the third trimester and TNF-α trajectory across pregnancy. These findings highlight the importance of considering dimensional symptoms of depression and extend prior work by including time points across the perinatal period and investigating

the influence of inflammatory changes on depressive symptoms. Measuring inflammation and depression longitudinally suggested that third-trimester inflammation may be particularly relevant when studying perinatal depression risk. Although some results on the specific symptom associations with changes in inflammation differ from prior studies, it is clear that inflammatory changes from the second to third trimester warrant further investigation and may provide a key opportunity for intervention to prevent the development or progression of depressive symptoms in late pregnancy and early postnatal period.

CRediT authorship contribution statement

Margaret McPhee Redic: Writing – original draft, Visualization, Formal analysis, Conceptualization. **J. Philip Miller:** Writing – review & editing, Software, Resources, Project administration, Methodology, Data curation. **Mary Kimmel:** Writing – review & editing, Methodology, Conceptualization. **Joan Luby:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Tara Smyser:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Cynthia E. Rogers:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Barbara B. Warner:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Christopher D. Smyser:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Deanna M. Barch:** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Gregory E. Miller:** Writing – review & editing, Software, Resources, Methodology, Investigation, Data curation, Conceptualization. **Edith Chen:** Writing – review & editing, Resources, Methodology, Investigation, Conceptualization.

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Declaration of Competing Interest

Deanna M. Barch consults for Janssen & Janssen and Boehringer Ingelheim. The other authors have no financial disclosures or potential conflicts of interest.

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Appendix A. Supporting information

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