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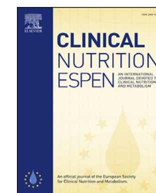

Original article

Bioactive metabolites of OMEGA-6 and OMEGA-3 fatty acids are associated with inflammatory cytokine concentrations in maternal and infant plasma at the time of delivery

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SUMMARY

Background & aims: Inflammation is necessary for a healthy pregnancy. However, unregulated or excessive inflammation during pregnancy is associated with severe maternal and infant morbidities, such as pre-eclampsia, abnormal infant neurodevelopment, or preterm birth. Inflammation is regulated in part by the bioactive metabolites of omega-6 (n-6) and omega-3 (n-3) fatty acids (FAs). N-6 FAs have been shown to promote pro-inflammatory cytokine environments in adults, while n-3 FAs have been shown to contribute to the resolution of inflammation; however, how these metabolites affect maternal and infant inflammation is still uncertain. The objective of this study was to predict the influence of n-6 and n-3 FA metabolites on inflammatory biomarkers in maternal and umbilical cord plasma at the time of delivery.

Methods: Inflammatory biomarkers (IL-1β, IL-2, IL-6, IL-8, IL-10, and TNFα) for maternal and umbilical cord plasma samples in 39 maternal-infant dyads were analyzed via multi-analyte bead array. Metabolites of n-6 FAs (arachidonic acid and linoleic acid) and n-3 FAs (eicosapentaenoic acid and docosahexaenoic acid) were assayed via liquid chromatography-mass spectrometry. Linear regression models assessed relationships between maternal and infant inflammatory markers and metabolite plasma concentrations.

Results: Increased plasma concentrations of maternal n-6 metabolites were predictive of elevated pro-inflammatory cytokine concentrations in mothers; similarly, higher plasma concentrations of umbilical cord n-6 FA metabolites were predictive of elevated pro-inflammatory cytokine concentrations in infants. Higher plasma concentrations of maternal n-6 FA metabolites were also predictive of elevated pro-inflammatory cytokines in infants, suggesting that maternal n-6 FA status has an intergenerational impact on the inflammatory status of the infant. In contrast, maternal and cord plasma concentrations of n-3 FA metabolites had a mixed effect on inflammatory status in mothers and infants, which may be due to the inadequate maternal dietary intake of n-3 FAs in our study population.

Conclusions: Our results reveal that maternal FA status may have an intergenerational impact on the inflammatory status of the infant. Additional research is needed to identify how dietary interventions

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that modify maternal FA intake prior to or during pregnancy may impact maternal and infant inflammatory status and associated long-term health outcomes.

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Abbreviations

AA	arachidonic acid
COX	cyclooxygenase
DHA	docosahexaenoic acid
DiHOME	dihydroxy-octadecenoic acid
DiHDPA	dihydroxydocosapentaenoic acid
DiHET	dihydroxy-eicosatrienoic acid
DiHETE	dihydroxy-eicosatetraenoic acid
EET	epoxyeicosatrienoic acid
EPA	eicosapentaenoic acid
EpDPA	epoxydocosapentaenoic acid
EpETE	epoxyeicosatetraenoic acid
EpOME	epoxyoctadecenoic acid
EPOX	cytochrome-P450 epoxygenase
HDHA	hydroxydocosahexaneoic acid
HEPE	hydroxyeicosapentaenoic acid
HETE	hydroxyeicosatetraenoic acid
HETrE	hydroxy-eicosatrienoic acid
HODE	hydroxy-octadecadienoic acid
HOTrE	hydroxy-octadecatrienoic acid
IL	interleukin
KODE	keto-octadecadienoic acid
LA	linoleic acid
LOX	lipoxygenase
LXA4	lipoxin A4
FA	fatty acid
n-3 FA(s)	omega-3 fatty acid(s)
n-6 FA(s)	omega-6 fatty acid(s)
nM	nanomolar
PGD_2	prostaglandin D_2
PGE_2	prostaglandin E_2
$PGF_2\alpha$	prostaglandin $F_2\alpha$
TNFα	tumor necrosis factor α
TXB2	thromboxane B23

1. Introduction

Inflammation plays a key role during pregnancy [1], with excessive systemic inflammation potentially increasing the risk of both maternal and neonatal morbidity. In pregnant women, inflammation contributes to the development of complications, such as hypertensive disorders of pregnancy [2,3], peripartum cardiomyopathy [4,5], and gestational diabetes [3]. In infants, exposure to excessive *in utero* inflammation is associated with abnormal birth outcomes, such as preterm birth [6], altered neurodevelopment [7–9], diminished lung function [10,11], failed newborn hearing screens [12], and decreased birth weight [13,14]. Exposure to elevated inflammation *in utero* is also associated with an increased risk for developing chronic diseases such as asthma [15,16], cerebral palsy [7], or schizophrenia [17].

Several cytokines and chemokines have emerged as valuable markers of inflammation during pregnancy (Fig. 1) [18]. Tumor necrosis factor alpha (TNFα), interleukin 1-beta (IL-1β), and interleukin 8 (IL-8) are considered pro-inflammatory cytokines. TNFα plays an important role in stimulating immune cells to produce reactive oxygen species [19] and promotes embryo implantation into the uterus [20]. IL-1β promotes antibody production and facilitates T cell differentiation [21]. IL-8 regulates immune cell activation [22] and promotes placental cell invasion into the maternal uterus [23]. However, excess levels of TNFα and IL-8 are associated with pregnancy loss, pre-eclampsia, and other poor pregnancy outcomes [20,23]. In contrast, interleukin 10 (IL-10) is an anti-inflammatory cytokine known for inhibiting pro-inflammatory cytokine production and immune cell proliferation [24]. Decreased maternal IL-10 levels are associated with pregnancy complications such as preterm birth, intrauterine growth restriction, and pre-eclampsia [25]. Interleukin 2 (IL-2) and interleukin 6 (IL-6) have pleiotropic inflammatory effects. IL-2 promotes inflammation by increasing effector T cell differentiation and growth; however, it also simultaneously promotes the resolution of inflammation by activating regulatory T (T_{reg}) cells [26]. Similarly, IL-6 induces synthesis of some inflammatory acute phase proteins while simultaneously inhibiting the production for other acute phase proteins [27]. IL-6 is also involved in regulating embryo implantation and placental development during pregnancy [23].

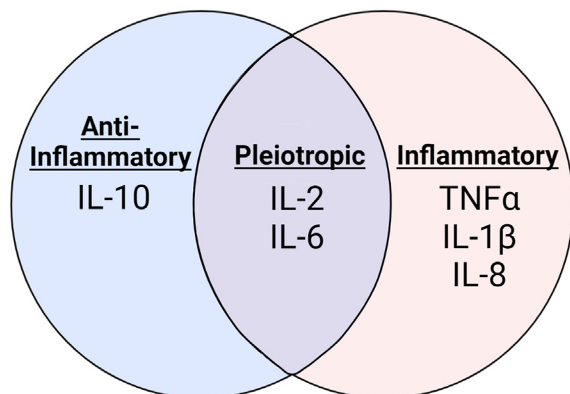

Fig. 1. Primary inflammatory properties of cytokines assessed in this study.

The metabolism of dietary fatty acids (FAs) – which is tightly regulated during pregnancy – plays an important role in modulating inflammation [28]. Figures 2 and 3 show the metabolism of the polyunsaturated omega (n)-6 and (n)-3 FAs via the lipoxygenase (LOX), cyclooxygenase (COX), and cytochrome-P450 epoxygenase (EPOX) enzymatic pathways into biologically active metabolites [29]. Metabolites produced from n-6 FAs such as arachidonic acid (AA) and linoleic acid (LA) generally promote inflammation by stimulating immune cell activation and migration [30,31]. However, several n-6 FA metabolites also have anti-inflammatory effects including 20-hydroxyeicosatetraenoic acid (HETE) which resolves oxidative stress [32]; prostaglandin E_2 (PGE_2) which inhibits neutrophil activation [33]; and 13-hydroxy-octadecadienoic acid (HODE) which inhibits the formation of inflammatory cytokines [30]. The effects of other n-6 FA metabolites,

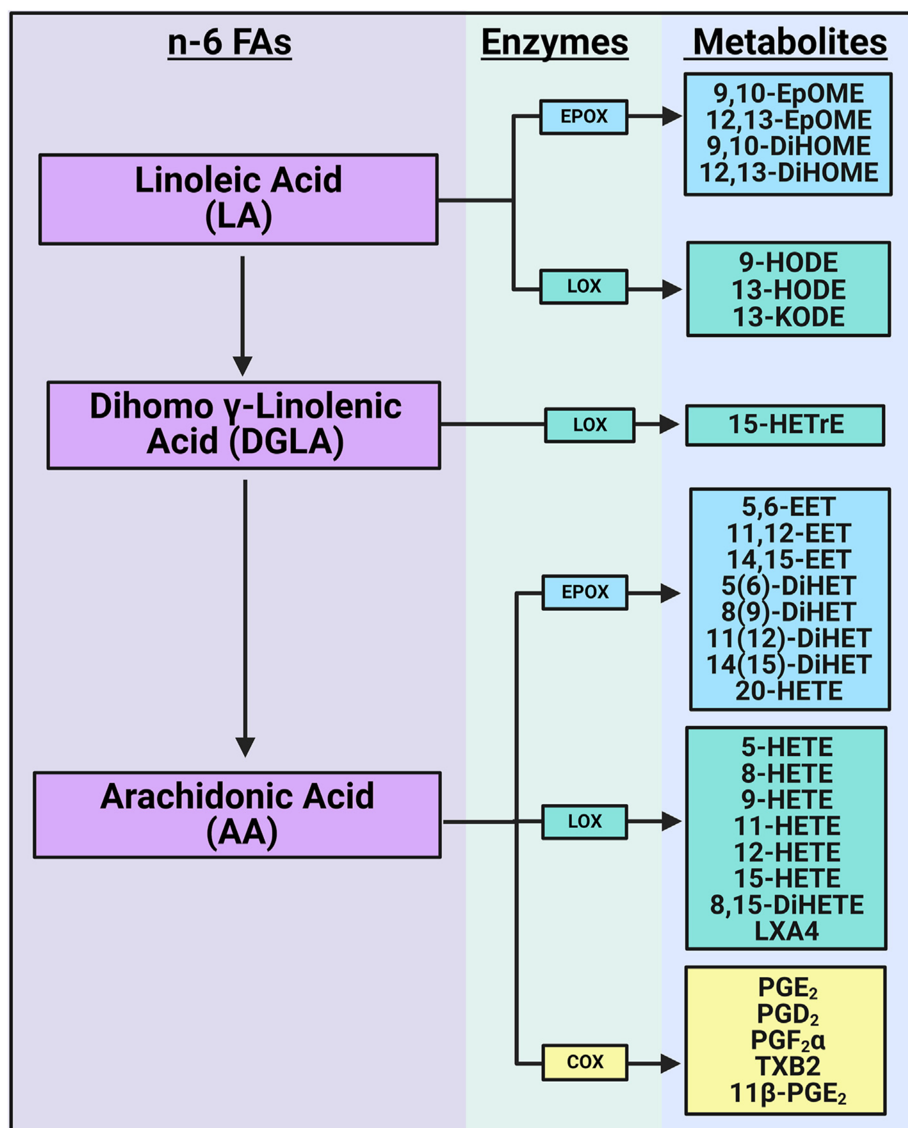

Fig. 2. Biological pathway of n-6 FA metabolites assessed in this study. Metabolites produced via the EPOX pathway are shown in blue, via the LOX pathway in green, and via the COX pathway in yellow [82]. Intermediate compounds in the enzymatic pathway are not shown. Created with BioRender.com. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

such as dihydroxy-eicosatrienoic acid (DiHET), on inflammation are unknown. In contrast, metabolites produced from the n-3 FAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), including 19,20-dihydroxydocosapentaenoic acid (DiHDPA), 15-hydroxyeicosapentaenoic acid (HEPE), and 7-hydroxydocosahexaneoic acid (HDHA), generally have an anti-inflammatory effect by inhibiting the recruitment of immune cells, inhibiting inflammatory cytokine production, or inducing T_{reg} cell differentiation [34–37].

Although increased dietary intake of n-3 FAs is associated with increased maternal erythrocyte concentrations of n-3 FAs [38,39] and reduced maternal inflammation markers [40,41], diets with a high intake of n-3 FAs have shown mixed results in preventing inflammation-driven pregnancy complications [40–44]. Investigating FA metabolites could provide mechanistic insight into the relationship between dietary intake of FAs and pregnancy outcomes, but few studies have evaluated how the bioactive metabolites of n-6 and n-3 FA impact inflammation in pregnant women and their infants. This study aims to fill this gap in the scientific literature and predict the influence of n-6 and n-3 FA metabolites on inflammatory biomarkers in maternal and umbilical cord plasma at the time of delivery.

2. Materials and methods

2.1. Participant enrollment

The University of Nebraska Medical Center Institutional Review Board provided ethical approval for this study (#112-15-EP). Maternal-infant dyads were enrolled upon admission to the Labor and Delivery Unit at Nebraska Medicine from June 2017 through August 2017. Written consent from the mother was obtained prior to participation. Inclusion criteria included maternal age ≥19 years and delivery of a single live-born infant. Exclusion criteria included infants deemed wards of the state and maternal or infant conditions which could affect normal nutrient metabolism such as gastrointestinal disease, kidney disease, liver disease, inborn errors of metabolism, or certain congenital abnormalities.

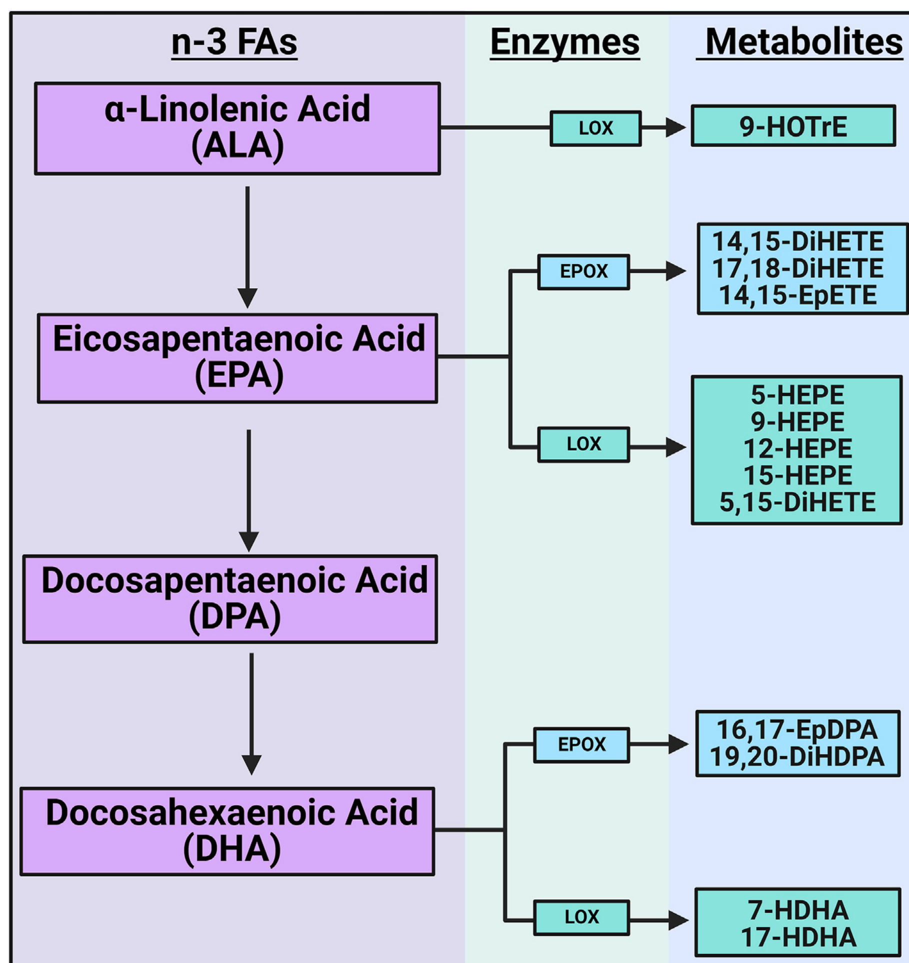

Fig. 3. Biological pathway of n-3 FA metabolites assessed in this study. Metabolites produced via the EPOX pathway are shown in blue and via the LOX pathway in green [82]. Intermediate compounds in the enzymatic pathway are not shown. Created with BioRender.com. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2.2. Plasma sample collection and analysis

Maternal and infant umbilical cord whole blood samples were collected in K2 EDTA tubes during routine clinical blood draws at the time of delivery. Samples were protected from heat and light, separated into plasma and red blood cell components via centrifugation, and frozen within 12 h of collection.

Metabolite concentrations were then analyzed by high performance liquid chromatography-mass spectrometry. Chromatographic separation was achieved on an Ascentis Express column (2.1 × 150 mm, 2.7 μm particles; Sigma-Aldrich Supelco, Darmstadt, Germany) using a gradient of 90:10 volume/volume acetonitrile-isopropanol with 0.1% acetic acid at a flow rate of 0.35 mL/min at 40 °C. Standard preparations were used to build a 12-point calibration curve. Data was processed using Skyline software and Microsoft Excel. Metabolites assessed in this study are shown in Figs. 2 and 3.

Plasma concentrations of TNFα, IL-1β, IL-2, IL-6, IL-8, and IL-10 were quantified per manufacturer's instructions using a commercially available multi-analyte bead array (Millipore; Burlington, MA). Briefly, plasma samples or control samples were incubated with Assay Buffer, Matrix Solution, and magnetic beads for 2 h at room temperature with shaking. Samples were then washed twice with Wash Buffer and incubated at room temperature for 1 h with Detection Antibodies. Samples were incubated with Streptavidin-Phycoerythrin for 30 min at room temperature prior to adding Sheath Fluid and reading sample fluorescence.

2.3. Demographic and clinical data collection

Annual household income and number of people in the household were self-reported in participant surveys. The income:poverty ratio was calculated by dividing the annual household income by the federal poverty level for the appropriate household size. Average daily maternal intake of n-6 and n-3 FA over the past year was collected using the Harvard Food Frequency Questionnaire administered at the time of delivery [45]. All other demographic and clinical variables reported in this study, including maternal smoking status, were collected from the maternal electronic health record. Maternal smoking status was categorized as never versus current/former smoker. Participants without pre-pregnancy BMI recorded in their electronic health record provided self-reported pre-pregnancy BMI.

2.4. Statistical analysis

Medians and interquartile ranges (IQR) were calculated for continuous variables and frequencies and percentages were calculated for categorical variables. Spearman's correlation coefficients were used to assess relationships between n-6 and n-3 FA metabolite plasma concentrations and inflammatory marker plasma concentrations. Linear regression modeling was performed on metabolites that correlated with inflammatory marker concentrations at a significance level of $p \leq 0.05$ in univariate analysis.

Directed acyclic graphing was utilized to identify maternal smoking status as the primary confounder, since smoking is associated with both inflammation during pregnancy and alterations in n-6 FA metabolism [46]. Metabolites and inflammatory biomarkers concentrations were log-transformed to satisfy model assumptions. To prevent model bias towards participants with high expression of metabolites or inflammatory markers, samples with non-detectable metabolite or inflammatory plasma concentration were assigned a value of 0.001 nM (nM).

3. Results

3.1. Demographic characteristics

Thirty-nine maternal-infant dyads were included in this study. Table 1 summarizes the demographic characteristics of the sample population. The median maternal age was 29.0 years (IQR 24.0–33.0) and the median gestational age was 39.4 weeks (IQR 39.0–40.3). Twenty-three percent of mothers were current or former smokers, 26.3% had an obese pre-pregnancy BMI, 25.6% had hypertension, and 5.0% had diabetes.

The median maternal intake of total n-6 FA was 16.38 g/day, including 0.17 g/day of arachidonic acid (AA) and 14.98 g/day of linoleic acid (LA; Table 1). The median maternal intake of total n-3 FA was 1.90 g/day, including 0.02 g/day of EPA, 0.09 g/day of DHA, and 1.75 g/day of α-linolenic acid (ALA). Median maternal and infant plasma concentrations of n-6 and n-3 FA metabolites analyzed in this study are shown in Table 2. The median plasma concentrations of AA metabolites were higher in cord plasma for some metabolites, but higher in maternal plasma for others. All LA metabolites assessed had a higher median concentration in maternal plasma compared to cord plasma. Median plasma concentrations of EPA metabolites produced via the LOX pathway were also higher in maternal samples; however, median plasma concentrations of DHA metabolites and EPA metabolites produced by the EPOX pathway tended to be higher in cord samples.

Median plasma concentrations of inflammatory markers are shown in Table 3. Cord plasma had a higher median concentration of IL-10 (19.86 vs 9.84 nM), IL-8 (10.22 vs 5.30 nM), and TNFα (58.11 vs 26.21 nM) compared to maternal plasma. In contrast, cord plasma had a lower median concentration IL-1β (3.38 vs 4.22), IL-2 (3.55 vs 5.16), and IL-6 (3.24 vs 3.65) compared to maternal plasma.

Table 1
Baseline characteristics of maternal and infant participants.

	Median (IQR)
Maternal Age (years)	29.0 (24.0–35.0)
Infant Gestational Age (weeks)	39.4 (39.0–40.3)
Pre-Pregnancy BMI (kg/m^2)	25.4 (22.3–31.5)
Income:Poverty Ratio (N = 32)	2.2 (1.12–3.6)
Caloric Intake (kcal/day)	2120 (1844–2786)
Total n-6 FA Intake (g/day)	16.38 (12.65–19.71)
AA Intake (g/day)	0.17 (0.11–0.22)
LA Intake (g/day)	14.98 (11.42–17.71)
Total n-3 Intake (g/day)	1.90 (1.48–2.46)
EPA Intake (g/day)	0.02 (0.01–0.05)
DHA Intake (g/day)	0.09 (0.04–0.17)
ALA Intake (g/day)	1.75 (1.33–2.35)
	Count (Percent)
Infant Sex	
Female (n (%))	16 (41.0)
Male (n (%))	23 (59.0)
Delivery Mode	
Vaginal Delivery (n (%))	29 (74.4)
Caesarean Section (n (%))	10 (25.6)
Maternal Diabetes	
Diabetes- Gestational or Chronic (n (%))	2 (5.1)
No Diabetes (n (%))	37 (94.9)
Maternal Hypertension	
Hypertension-Gestational or Chronic (n (%))	10 (25.6)
Normotension (n (%))	24 (61.5)
Unknown (n (%))	5 (12.8)
Maternal Smoking Status	
Never Smoker (n (%))	30 (76.9)
Current/Former Smoker (n (%))	9 (23.1)
Maternal Race/Ethnicity	
Non-Hispanic White (n (%))	27 (69.2)
Non-Hispanic Black (n (%))	6 (15.4)
Hispanic (n (%))	1 (2.6)
Other/Unknown (n (%))	5 (12.9)

3.2. Relationship between maternal n-6 FA metabolites and maternal and infant inflammatory markers

Maternal AA metabolites were positively correlated with maternal IL-10, IL-1β, IL-2, IL-6, and IL-8 (Table S1). Maternal AA metabolite plasma concentrations were also positively correlated with infant IL-1β, IL-6, IL-8, and TNFα, but negatively correlated with infant IL-10 (Table S1). Maternal LA metabolites were not correlated with any maternal or infant inflammatory markers assessed in this study.

After adjustment for maternal smoking status, maternal AA metabolites produced via the EPOX pathway were significantly associated with multiple maternal inflammatory marker concentrations (Fig. 4; Table S2). 11 (12)-DiHET (β = 1.81, p = 0.03) and 8 (9)-DiHET (β = 1.23, p = 0.02) were positively associated with maternal IL-8. 20-HETE (β = 0.97, p = 0.001) and 11 (12)-DiHET (β = 2.14, p = 0.03) were positively associated with maternal IL-6. 5 (6)-DiHET (β = 5.80, p = 0.003) and 5,6-epoxyeicosatrienoic acid (EET; β = 2.87, p = 0.01) were positively associated with maternal IL-2. 5 (6)-DiHET was also positively associated with maternal IL-10 (β = 2.95, p = 0.02) and IL-1β (β = 4.18, p = 0.03).

In contrast, maternal metabolites produced via the COX pathway were significantly associated with infant inflammatory marker concentrations after adjustment for maternal smoking status (Fig. 4; Table S2). Maternal PGE_2 was positively associated with cord IL-6 (β = 0.60, p = 0.03) and cord IL-8 (β = 0.43, $p < 0.001$). A 1 nM increase in log-transformed maternal $PGF_2α$ predicted a 0.34 nM increase in log-transformed cord IL-8 (p = 0.04). A 1 nM increase in log-transformed maternal thromboxane B2 (TXB2) predicted a 0.17 nM decrease in log-transformed cord IL-10 (p = 0.002).

3.3. Relationship between maternal n-3 FA metabolites and maternal and infant inflammatory marker levels

Maternal plasma concentrations of EPA and DHA metabolites were significantly correlated with multiple maternal and infant inflammatory markers (Table S3). After adjustment for maternal smoking status, maternal plasma concentrations of 17,18-dihydroxy-eicosatetraenoic acid (DiHETE; β = 2.33, p = 0.002) and 19,20-DiHDPA (β = 3.18, p = 0.001) remained significantly associated with maternal IL-10 plasma concentrations (Fig. 5; Table S4). 17,18-DiHETE was also significantly associated with maternal IL-1β (β = 2.92, p = 0.02). Maternal 16,17-epoxydocosapentaenoic acid (EpDPA) was significantly associated with maternal IL-6 (β = 0.99, $p < 0.001$) and cord IL-10 (β = 0.10, p = 0.04).

3.4. Relationships between cord n-6 FA metabolites and infant inflammatory marker levels

Cord AA metabolites were positively correlated with cord IL-1β, IL-6, and IL-8, but negatively correlated with cord IL-10

Table 2
Median n-6 and n-3 FA metabolite concentrations in maternal and infant umbilical cord plasma.

n-6 FA Metabolites	Maternal Plasma (n = 36)	Infant Cord Plasma (n = 37)
AA COX Pathway	**Median (IQR)**	**Median (IQR)**
PGE_2 (nM)	0.71 (0.001–1.12)	2.73 (1.05–3.35)
PGD_2 (nM)	0.27 (0.14–0.46)	0.22 (0.12–0.36)
$PGF_2\alpha$ (nM)	0.001 (0.001–0.17)	0.48 (0.35–0.82)
TXB2 (nM)	0.36 (0.17–1.01)	2.42 (1.39–5.93)
11β-PGE_2 (nM)	0.22 (0.11–0.42)	0.19 (0.10–0.37)
AA LOX Pathway	**Median (IQR)**	**Median (IQR)**
5-HETE (nM)	9.97 (6.66–17.05)	8.30 (5.71–9.92)
8-HETE (nM)	1.79 (0.99–2.71)	1.96 (1.64–2.57)
9-HETE (nM)	1.53 (1.01–2.34)	2.22 (1.17–2.60)
11-HETE (nM)	2.60 (1.68–3.50)	2.39 (1.90–3.73)
12-HETE (nM)	3.95 (2.74–7.55)	6.90 (3.92–15.91)
15-HETE (nM)	3.97 (2.44–5.20)	5.35 (3.81–7.84)
8,15-DiHETE (nM)	0.35 (0.001–0.71)	0.29 (0.001–0.45)
LXA4 (nM)	12.47 (5.14–18.71)	5.20 (4.26–7.47)
AA EPOX Pathway	**Median (IQR)**	**Median (IQR)**
5,6-EET (nM)	9.41 (7.03–15.50)	27.17 (18.90–42.29)
11,12-EET (nM)	0.16 (0.001–0.26)	0.28 (0.20–0.43)
14,15-EET (nM)	0.34 (0.18–0.50)	0.50 (0.38–0.66)
5 (6)-DiHET (nM)	1.26 (0.99–1.53)	6.20 (5.23–7.79)
8 (9)-DiHET (nM)	12.24 (6.15–19.13)	7.88 (5.24–11.81)
11 (12)-DiHET (nM)	1.85 (0.99–3.04)	1.09 (0.84–1.71)
14 (15)-DiHET (nM)	8.50 (4.18–13.37)	3.43 (2.92–4.78)
20-HETE (nM)	0.10 (0.001–0.15)	0.14 (0.10–0.17)
LA LOX Pathway	**Median (IQR)**	**Median (IQR)**
9-HODE (nM)	24.09 (17.99–36.98)	8.39 (5.80–13.08)
13-HODE (nM)	23.43 (18.90–38.12)	10.81 (8.15–16.56)
13-KODE (nM)	2.26 (1.65–3.84)	1.19 (0.92–1.75)
LA EPOX Pathway	**Median (IQR)**	**Median (IQR)**
9,10-EpOME (nM)	5.91 (3.56–10.01)	3.96 (2.58–5.39)
12,13-EpOME (nM)	9.32 (6.36–15.80)	4.76 (3.12–6.41)
9,10-DiHOME (nM)	4.66 (3.30–7.12)	1.65 (1.36–2.15)
12,13-DiHOME (nM)	6.77 (3.90–10.91)	2.70 (2.10–3.98)
GDLA LOX Pathway	**Median (IQR; nM)**	**Median (IQR; nM)**
15-HETrE (nM)	0.90 (0.58–1.33)	1.35 (1.01–1.85)
n-3 FA Metabolites	**Maternal Plasma (n=36)**	**Infant Cord Plasma (n=37)**
ALA LOX Pathway	**Median (IQR)**	**Median (IQR)**
9-HOTrE (nM)	1.72 (1.13–2.68)	0.46 (0.23–0.72)
EPA LOX Pathway	**Median (IQR)**	**Median (IQR)**
5-HEPE (nM)	0.56 (0.33–0.98)	0.37 (0.24–0.48)
9-HEPE (nM)	0.04 (0.001–0.15)	0.001 (0.001–0.10)
15-HEPE (nM)	0.17 (0.001–0.26)	0.14 (0.001–0.18)
5,15-DiHETE (nM)	0.17 (0.001–0.28)	0.12 (0.001–0.18)
EPA EPOX Pathway	**Median (IQR)**	**Median (IQR)**
14,15-DiHETE (nM)	1.57 (0.51–2.54)	4.72 (3.52–7.39)
17,18-DiHETE (nM)	1.65 (1.30–2.36)	5.62 (4.41–7.61)
14,15-EpETE (nM)	0.001 (0.001–0.19)	0.001 (0.001–0.43)
DHA LOX Pathway	**Median (IQR)**	**Median (IQR)**
7-HDHA (nM)	1.19 (0.56–1.60)	0.87 (0.49–1.31)
17-HDHA (nM)	1.99 (1.12–3.13)	2.16 (1.69–2.95)
DHA EPOX Pathway	**Median (IQR)**	**Median (IQR)**
16,17-EpDPA (nM)	0.12 (0.001–0.24)	0.34 (0.19–0.57)
19,20-DiHDPA (nM)	1.27 (0.94–1.59)	3.75 (2.64–4.47)

Table 3
Median inflammatory marker levels in maternal and infant umbilical cord plasma.

	Maternal Plasma (n = 38)	Infant Cord Plasma (n = 39)
Inflammatory Marker	Median (IQR)	Median (IQR)
IL-10 (nM)	9.84 (5.97–20.61)	19.86 (8.00–25.25)
IL-1β (nM)	4.22 (0.001–8.92)	3.38 (0.001–9.22)
IL-2 (nM)	5.16 (0.001–10.10)	3.55 (0.001–7.99)
IL-6 (nM)	3.65 (0.001–17.12)	3.24 (0.001–17.57)
IL-8 (nM)	5.30 (0.001–9.89)	10.22 (5.34–25.45)
TNFα (nM)	26.21 (19.93–42.27)	58.11 (46.15–25.45)

(Table S5). Cord LA metabolites were not significantly correlated with any infant inflammatory markers. After adjustment for maternal smoking status, cord 11-HETE ($\beta = 4.38$, $p = 0.004$) and 8,15-DiHETE ($\beta = 0.62$, $p = 0.04$) were positively associated with cord IL-6 (Fig. 6, Table S6). Cord 14 (15)-DiHET was positively associated with cord IL-1β ($\beta = 4.33$, $p = 0.01$), while cord 11 (12)-DiHET was negatively associated with cord IL-10 ($\beta = -1.19$, $p = 0.04$).

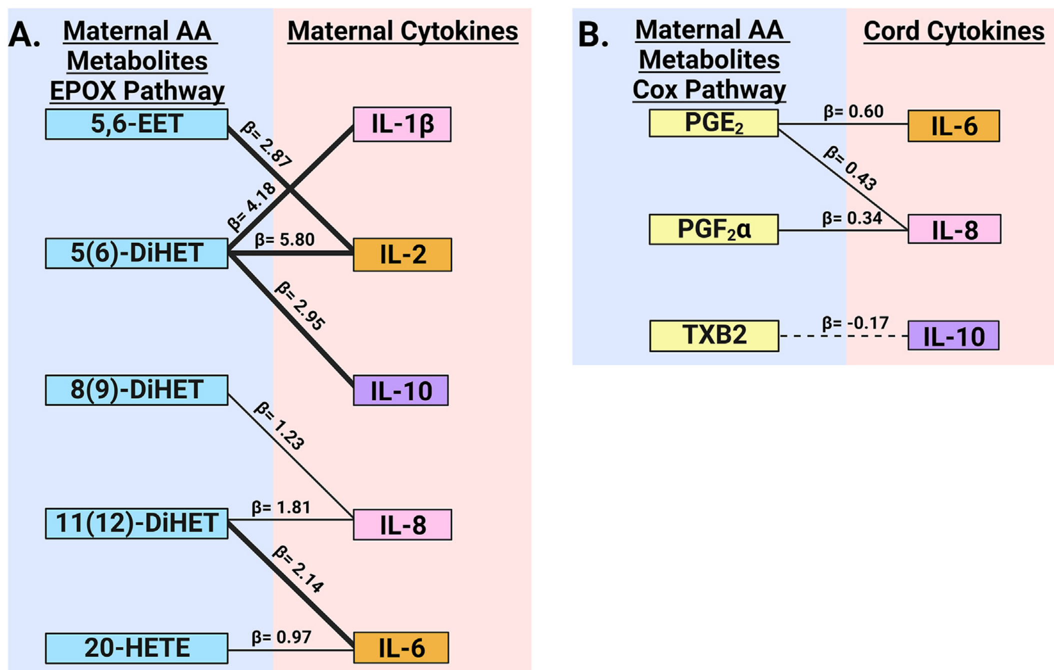

Fig. 4. Linear regression model β coefficients between maternal AA metabolites and (a) maternal (N = 35) or (b) cord (N = 36) inflammatory marker concentrations. Positive associations are indicated by a solid line, while negative associations are indicated by a dashed line. Strong associations ($\beta \geq 2.00$) are indicated with a bold line. Metabolites produced via the COX pathway are shown in yellow and via the EPOX pathway in blue. Pro-inflammatory cytokines are shown in pink, anti-inflammatory cytokines in purple, and pleiotropic cytokines in orange. Only relationships significant at $p < 0.05$ are shown. Models were adjusted for maternal smoking status. Metabolite and inflammatory marker concentrations were log-transformed to meet model assumptions. This figure was created using Biorender.com. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

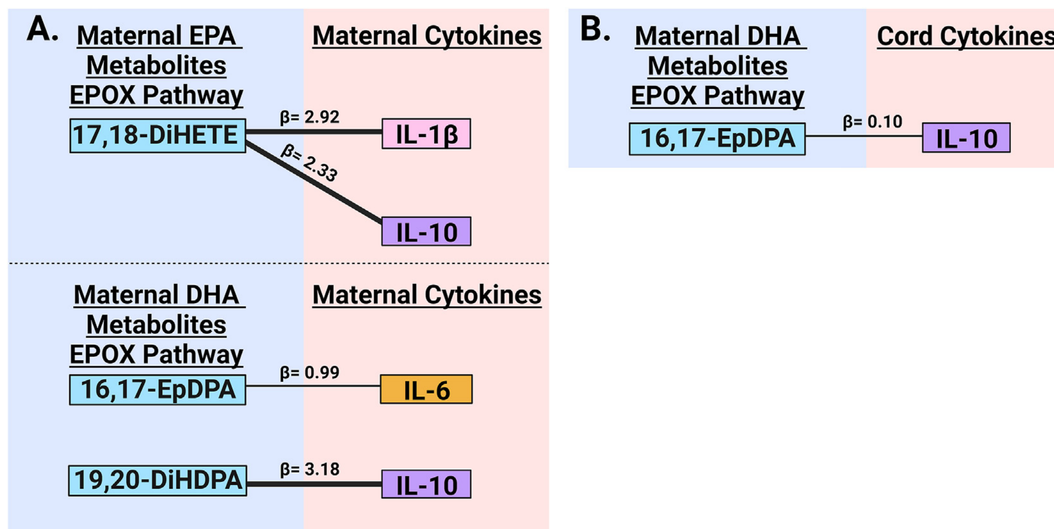

Fig. 5. Linear regression model β coefficients between maternal n-3 metabolites and (a) maternal (N = 35) or (b) cord (N = 36) inflammatory marker concentrations. Strong associations ($\beta \geq 2.00$) are indicated with a bold line. Metabolites produced via the EPOX pathway are shown in blue. Pro-inflammatory cytokines are shown in pink, anti-inflammatory cytokines in purple, and pleiotropic cytokines in orange. Only relationships significant at $p < 0.05$ are shown. Models were adjusted for maternal smoking status. Metabolite and inflammatory marker concentrations were log-transformed to meet model assumptions. This figure was created using Biorender.com. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.5. Relationships between cord n-3 FA metabolites and infant inflammatory marker levels

Cord plasma concentrations of EPA and DHA metabolites were significantly correlated with cord IL-1β Table S7). After adjustment for maternal smoking status, a 1 nM increase in log-transformed maternal 7-HDHA predicted a 4.14 nM increase in log-transformed cord IL-1β ($p < 0.001$) (Table S8).

4. Discussion

Our results showed that multiple n-6 and n-3 FAs metabolites in maternal and umbilical cord plasma predicted inflammatory marker concentrations in linear regression models. In maternal plasma, we found that higher concentrations of AA metabolites produced via the COX pathway (PGE_2, $PGF_2\alpha$, and TXB2) were predictive of a pro-inflammatory cytokine environment in mothers.

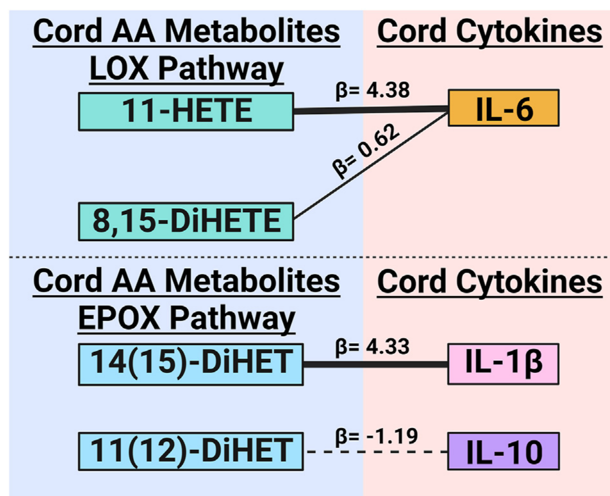

Fig. 6. Linear regression model β coefficients between cord AA metabolites and cord (N = 37) inflammatory marker concentrations. Positive associations are indicated by a solid line, while negative associations are indicated by a dashed line. Strong associations (β ≥ 2.00) are indicated with a bold line. Metabolites produced via the LOX pathway are shown in green and via the EPOX pathway in blue. Pro-inflammatory cytokines are shown in pink, anti-inflammatory cytokines in purple, and pleiotropic cytokines in orange. Only relationships significant at $p < 0.05$ are shown. Models were adjusted for maternal smoking status. Metabolite and inflammatory marker concentrations were log-transformed to meet model assumptions. This figure was created using Biorender.com. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Given that maternal plasma concentrations were taken upon admission for delivery, these findings align well with previous studies which have established prostaglandins, especially PGE_2 and PGF2α, as important regulators of inflammation during parturition [47]. In addition to promoting cervical ripening, myometrial contraction, and membrane rupture [47], PGE_2 and PGF2α contribute to the acute inflammatory response during labor by increasing pro-inflammatory cytokine production [48,49]. Denison et al. found that PGE_2 participates in a positive feedback loop to increase IL-8 production [48], while Xu et al. found that PGF2α elevates IL-1β, IL-6, and IL-8 production [49]. This study similarly found that maternal AA metabolites were associated with higher maternal plasma concentrations of the pro-inflammatory cytokine IL-1β and the pleotropic cytokine IL-6, but lower concentrations of the anti-inflammatory cytokine IL-10.

Higher concentrations of cord LOX (11-HETE and 8,15-DiHETE) and EPOX (11 (12)-DiHET and 14 (15)-DiHET) AA metabolites were also predictive of a pro-inflammatory cytokine environment in infants. Cord AA metabolites were associated with higher cord plasma concentrations of IL-1β (pro-inflammatory) and IL-6 (pleiotropic), and lower concentrations of IL-10 (anti-inflammatory). These findings align with previous studies which have established n-6 FAs as pro-inflammatory nutrients in a variety of settings [30]. Although little is known about the effects of HETEs on inflammation during parturition, HETEs have been shown to promote inflammation by regulating neutrophil chemotaxis [50] and mast cell activation [51]. The effects DiHETs have on markers of inflammation are unknown, but higher serum concentrations of 11 (12)-DiHET are associated with preterm labor, a common inflammation-driven pregnancy complication [52], indicating that DiHETs may also contribute to the inflammatory response during pregnancy.

We also found significant relationships between n-3 FA metabolites and inflammatory markers. In maternal plasma, higher concentrations of EPA (17,18-DIHETE) and DHA (19,20-DiHDPA) metabolites were associated with higher concentrations of maternal IL-10. These findings are supported by previous studies which have reported that n-3 FA metabolites are anti-inflammatory [34–36,53]. Our previous work found that placental trophoblast treatment with resolvin D2 (RvD2), an EPA-derived specialized pro-resolving mediator, increased the mRNA expression of IL-10 [53]. Askari et al. reported that 19,20-DiHDPA inhibits inflammatory cytokine production in endothelial cells [37]. Similarly, Jurado-Fasoli et al. and Aoki et al. found that 17,18-DiHETE is negatively correlated with markers of inflammation-driven diseases including metabolic syndrome and nonalcoholic steatohepatitis [54,55].

Surprisingly, higher concentrations of maternal 17,18-DiHETE and 16,17-EpDPA (DHA metabolites) were also associated with higher maternal plasma concentrations of the pro-inflammatory IL-1β and pleiotropic IL-6, respectively. Similarly, higher cord concentrations of the DHA metabolite 7-HDHA were predictive of higher cord plasma concentrations of pro-inflammatory IL-1β. It is possible that some n-3 FA metabolites contribute to increased maternal and infant inflammation, despite n-3 FAs generally promoting inflammation resolution [34–37]. Hu et al. demonstrated that accumulation of 19,20-DiHDPA in retinal tissue contributes to the development of non-proliferative diabetic retinopathy by altering cell membrane compositions [56], which may support the hypothesis that some n-3 FA metabolites promote inflammation. Alternatively, it is possible that n-3 FA metabolites are upregulated as a compensatory measure in response to inflammation. Previous studies by Zhang et al. show that although 17,18-DiHETE is an anti-inflammatory metabolite, it is positively associated with mortality in patients with systolic heart failure [57], which may support our theory that n-3 metabolites were elevated to counteract inflammation. Finally, it is possible that the observed relationships between n-3 metabolites and pro-inflammatory cytokines are an artifact of low n-3 fatty acid intake. The World Health Organization recommends pregnant women consume 200–500 mg/day of EPA + DHA [58], but the average EPA + DHA intake in our cohort was only 110 mg/day. Our previous work found a similar trend of insufficient EPA + DHA intake in pregnant women across the United States [59], suggesting that EPA + DHA nutritional status may be inadequate to promote an anti-inflammatory cytokine environment in pregnant women and their infants.

Interestingly, *maternal* n-6 and n-3 FA metabolite concentrations were also predictive of *infant* inflammatory marker concentrations, highlighting the importance of maternal nutrition for infant health. Higher maternal concentrations of AA metabolites produced via the EPOX pathway (5,6-EET, 5 (6)-DiHET, 8 (9)-DiHET, 11 (12)-DiHET, and 20-HETE) were predictive of a pro-inflammatory cytokine environment in infants. Additionally, higher maternal concentrations of the DHA metabolite 16,17-EpDPA was predictive of an anti-inflammatory infant cytokine environment. Given that n-6 FA and n-3 FA metabolites regulate inflammation to promote a healthy pregnancy [60], modifying maternal diet may be an effective strategy to reduce perinatal inflammation [61,62] and improve pregnancy outcomes [63–65]. Increasing n-3 FA intake may be beneficial [59], as increased intake is associated with increased maternal blood concentrations of n-3 FAs [38,39]. However, results have been mixed in clinical trials assessing the effect of n-3 FA supplementation on pregnancy outcomes [40,44,66,67]. For example, Haghiac et al. reported that obese women who consumed EPA + DHA supplements beginning in the first trimester of pregnancy had reduced inflammatory cytokine levels in adipose and placental tissue [40]. Similarly, Hamazaki et al. reported a beneficial effect of maternal fish intake (a major source of n-3 FAs) on infant neurodevelopment up to 1 year of age [66]. However, meta-analyses by Lehner et al. and Serra et al. found no association between n-3 FA supplementation during

pregnancy and risk of preterm birth, neurodevelopmental delays, or low birthweight [44,67]. Further research studies are needed to assess how n-3 FA supplementation may improve pregnancy outcomes for women at-risk for high levels of inflammation during pregnancy.

Reducing maternal n-6 FA intake may also be beneficial, as the western diet is high in these pro-inflammatory nutrients. Dietary intake of n-6 FAs, including AA and LA, has dramatically increased in the past century from an n-6: n-3 ratio of 6:1 to 20:1 [68]. Excessive exposure to n-6 FAs is associated with inflammation-driven morbidities including poor infant neurodevelopmental outcomes [42,66], low birthweight [69], and gestational hypertension [43,70,71]. Our data suggests that n-6 and n-3 FA metabolites may play a role in regulating inflammation in pregnancy, but further studies are needed to understand how changes in n-6 and n-3 FA intake during pregnancy may affect markers of inflammation in mothers and infants.

This study was limited by a small sample size from a single academic medical institution (University of Nebraska Medical Center/Nebraska Medicine). Multiple factors contribute to maternal and infant inflammation during pregnancy including maternal diet [40], smoking status [72], delivery mode [73], psychological stressors such as poverty or discrimination [6], and chronic disease processes such as obesity, hypertension, or diabetes [74–77]. We were unable to adjust for all potential variables associated with inflammation due to sample size limitations, but the baseline characteristics of our study population were reported. We did adjust for maternal smoking status, as exposure to tobacco smoke is associated with changes in fatty acid metabolism and inflammation [46].

A small sample size also limited our ability to examine the effects of metabolite interactions on maternal and infant inflammation. We did perform a principal component analysis as a proof of concept to detect patterns of clustering maternal metabolites and their association with maternal inflammatory markers; however, these results should be interpreted with caution due to our sample size limitations [78,79]. We found that the maternal metabolites assessed in this study clustered into 4 principal components (Figure S1), which accounted for 71% of the variance in maternal cytokine concentrations. Component 4 included the n-3 metabolites 14,15-DiHETE, 17,18-DiHETE, and 19,20-DiHDPA, as well as the n-6 metabolites 20-HETE, 5,6-DiHET, and 12-HETE. This component was positively correlated with maternal IL-10 ($r_s = 0.62$; $p < 0.0001$), IL-1β ($r_s = 0.44$; $p = 0.008$), IL-2 ($r_s = 0.39$; $p = 0.02$), and IL-6 ($r_s = 0.36$; $p = 0.04$; Table S9), which supports our findings that individual maternal n-3 metabolites are positively correlated with both inflammatory and anti-inflammatory maternal cytokines. Although additional studies in larger samples sizes are needed to confirm our results, this study and our supporting principal component analysis suggests that bioactive n-3 and n-6 metabolites interact to regulate maternal and infant inflammation.

Additionally, further studies are needed to assess the relationship between inflammation and bioactive metabolites of n-3 and n-6 FAs in special populations, including maternal-infant dyads affected by psychological stressors or chronic diseases. Similarly, more research is needed to determine whether bioactive metabolites of n-3 and n-6 FAs directly affect plasma concentrations of the inflammation markers assessed in this study, or if the observed relationship between metabolites and inflammation is mediated through other molecules not measured in the present study, such as platelet activating factor [80,81]. Finally, our study examined the relationship between n-6 and n-3 FA metabolites and inflammatory markers at a single time-point in pregnancy (delivery). Future studies are needed to assess how n-6 and n-3 FA nutritional status affects maternal and infant inflammation throughout pregnancy.

Statement of authorship

Rebecca Slotkowski: Conceptualization, Methodology, Validation, Formal Analysis, Investigation, Data Curation, Writing – Original Draft, Writing – Review & Editing, Visualization. **Matthew VanOrmer**: Conceptualization, Methodology, Investigation, Data Curation, Visualization, Writing - Review & Editing, Project Administration. **Anum Akbar**: Conceptualization, Investigation, Writing – Review & Editing. **Taija Hahka**: Conceptualization, Investigation, Writing – Review & Editing. **Maranda Thompson**: Conceptualization, Investigation, Writing – Review & Editing. **Rebekah Rapoza**: Conceptualization, Investigation, Writing – Review & Editing. **Arzu Ulu**: Conceptualization, Methodology, Investigation, Writing – Review & Editing. **Melissa Thoene**: Conceptualization, Methodology, Resources, Visualization, Writing – Review & Editing, Supervision. **Elizabeth Lyden**: Conceptualization, Methodology, Formal Analysis, Writing – Review & Editing. **Maheswari Mukherjee**: Conceptualization, Writing – Review & Editing, Supervision. **Ana Yuil-Valdes**: Conceptualization, Writing – Review & Editing, Supervision. **Sathish Natarajan**: Conceptualization, Writing – Review & Editing, Supervision. **Tara Nordgren**: Conceptualization, Resources, Methodology, Writing – Review & Editing, Supervision. **Corrine Hanson**: Conceptualization, Methodology, Resources, Visualization, Writing – Review & Editing, Supervision. **Ann Anderson Berry**: Conceptualization, Methodology, Resources, Visualization, Writing – Review & Editing, Supervision, Funding Acquisition.

Conflict of interest statement

The authors have no competing interests to declare.

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Appendix A. Supplementary data

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References

[1] Yockey LJ, Iwasaki A. Interferons and proinflammatory cytokines in pregnancy and fetal development. Immunity 2018;49(3):397–412.
[2] Han X, Ghaemi MS, Ando K, Peterson LS, Ganio EA, Tsai AS, et al. Differential dynamics of the maternal immune system in healthy pregnancy and preeclampsia. Front Immunol 2019;10:1305.
[3] Hart PMB, Stephenson NL, Scime NV, Tough SC, Slater DM, Chaput KH. Second trimester cytokine profiles associated with gestational diabetes and hypertensive disorders of pregnancy. PLoS One 2022;17(12):e0279072.
[4] Haghikia A, Kaya Z, Schwab J, Westenfeld R, Ehlermann P, Bachelier K, et al. Evidence of autoantibodies against cardiac troponin I and sarcomeric myosin in peripartum cardiomyopathy. Basic Res Cardiol 2015;110(6):60.
[5] Koczo A, Marino A, Rocco J, Ewald G, Givertz MM, Rajagopalan N, et al. Proinflammatory TH17 cytokine activation, disease severity and outcomes in peripartum cardiomyopathy. Int J Cardiol 2021;339:93–8.
[6] Keenan-Devlin LS, Smart BP, Grobman W, Adam EK, Freedman A, Buss C, et al. The intersection of race and socioeconomic status is associated with

inflammation patterns during pregnancy and adverse pregnancy outcomes. Am J Reprod Immunol 2022;87(3):e13489.
[7] Armstrong-Wells J, Donnelly M, Post MD, Manco-Johnson MJ, Winn VD, Sébire G. Inflammatory predictors of neurologic disability after preterm premature rupture of membranes. Am J Obstet Gynecol 2015;212(2):212.e1–9.
[8] Massaro AN, Wu YW, Bammler TK, Comstock B, Mathur A, McKinstry RC, et al. Plasma biomarkers of brain injury in neonatal hypoxic-ischemic encephalopathy. J Pediatr 2018;194:67–75.e1.
[9] Nist MD, Pickler RH. An integrative review of cytokine/chemokine predictors of neurodevelopment in preterm infants. Biol Res Nurs 2019;21(4):366–76.
[10] Chawes BL, Stokholm J, Bønnelykke K, Brix S, Bisgaard H. Neonates with reduced neonatal lung function have systemic low-grade inflammation. J Allergy Clin Immunol 2015;135(6):1450. -6.e1.
[11] Collaco JM, McGrath-Morrow SA, Griffiths M, Chavez-Valdez R, Parkinson C, Zhu J, et al. Perinatal inflammatory biomarkers and respiratory disease in preterm infants. J Pediatr 2022;246:34. -9.e3.
[12] Shim YJ, Choi BY, Park KH, Lee H, Jung YM, Kim YM. Inflammatory and immune proteins in umbilical cord blood: association with hearing screening test failure in preterm neonates. Mediat Inflamm 2018;2018:4209359.
[13] Thoene MK, Van Ormer MC, Lyden ER, Thompson MK, Yuil-Valdes AG, Natarajan SK, et al. Concentrations of fat-soluble nutrients and blood inflammatory compounds in mother-infant dyads at birth. Pediatr Res 2021;90(2):436–43.
[14] Chen LW, Aubert AM, Shivappa N, Bernard JY, Mensink-Bout SM, Geraghty AA, et al. Associations of maternal dietary inflammatory potential and quality with offspring birth outcomes: an individual participant data pooled analysis of 7 European cohorts in the ALPHABET consortium. PLoS Med 2021;18(1): e1003491.
[15] Chen LW, Lyons B, Navarro P, Shivappa N, Mehegan J, Murrin CM, et al. Maternal dietary inflammatory potential and quality are associated with offspring asthma risk over 10-year follow-up: the Lifeways Cross-Generation Cohort Study. Am J Clin Nutr 2020;111(2):440–7.
[16] Chen YS, Lee-Sarwar KA, Mirzakhani H, O'Connor GT, Bacharier LB, Zeiger RS, et al. The association of prenatal C-reactive protein levels with childhood asthma and atopy. J Allergy Clin Immunol Pract 2022;10(12):3213. -9.e11.
[17] Canetta S, Sourander A, Surcel HM, Hinkka-Yli-Salomäki S, Leiviskä J, Kellendonk C, et al. Elevated maternal C-reactive protein and increased risk of schizophrenia in a national birth cohort. Am J Psychiatr 2014;171(9):960–8.
[18] Vassiliadis S, Ranella A, Papadimitriou L, Makrygiannakis A, Athanassakis I. Serum levels of pro- and anti-inflammatory cytokines in non-pregnant women, during pregnancy, labour and abortion. Mediat Inflamm 1998;7(2):69–72.
[19] Zelová H, Hošek J. TNF-α signalling and inflammation: interactions between old acquaintances. Inflamm Res 2013;62(7):641–51.
[20] Romanowska-Próchnicka K, Felis-Giemza A, Olesińska M, Wojdasiewicz P, Paradowska-Gorycka A, Szukiewicz D. The role of TNF-α and anti-TNF-α agents during preconception, pregnancy, and breastfeeding. Int J Mol Sci 2021;22(6).
[21] Dinarello CA. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. Blood 2011;117(14):3720–32.
[22] Matsushima K, Yang D, Oppenheim JJ. Interleukin-8: an evolving chemokine. Cytokine 2022;153:155828.
[23] Vilotić A, Nacka-Aleksić M, Pirković A, Bojić-Trbojević Ž, Dekanski D, Jovanović Krivokuća M. IL-6 and IL-8: an overview of their roles in healthy and pathological pregnancies. Int J Mol Sci 2022;23(23).
[24] Saraiva M, Vieira P, O'Garra A. Biology and therapeutic potential of interleukin-10. J Exp Med 2020;217(1).
[25] Azizieh FY, Raghupathy R. IL-10 and pregnancy complications. Clin Exp Obstet Gynecol 2017;44(2):252–8.
[26] Ross SH, Cantrell DA. Signaling and function of interleukin-2 in T lymphocytes. Annu Rev Immunol 2018;36:411–33.
[27] Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. Cold Spring Harbor Perspect Biol 2014;6(10):a016295.
[28] Calder PC. Functional roles of fatty acids and their effects on human health. JPEN - J Parenter Enter Nutr 2015;39(1 Suppl):18s–32s.
[29] Thompson M, Ulu A, Mukherjee M, Yuil-Valdes AG, Thoene M, Van Ormer M, et al. Something smells fishy: how lipid mediators impact the maternal-fetal interface and neonatal development. Biomedicines 2023;11(1).
[30] Gabbs M, Leng S, Devassy JG, Monirujjaman M, Aukema HM. Advances in our understanding of oxylipins derived from dietary PUFAs. Adv Nutr 2015;6(5): 513–40.
[31] Hildreth K, Kodani SD, Hammock BD, Zhao L. Cytochrome P450-derived linoleic acid metabolites EpOMEs and DiHOMEs: a review of recent studies. J Nutr Biochem 2020;86:108484.
[32] Sugumaran P, Narayanan V, Zhu D, Medhora M, Jacobs ER, Chandramohan Y, et al. Prophylactic supplementation of 20-HETE ameliorates hypoxia/reoxygenation injury in pulmonary vascular endothelial cells by inhibiting apoptosis. Acta Histochem 2020;122(1):151461.
[33] Cheng H, Huang H, Guo Z, Chang Y, Li Z. Role of prostaglandin E2 in tissue repair and regeneration. Theranostics 2021;11(18):8836–54.
[34] Miller C, Yamaguchi RY, Ziboh VA. Guinea pig epidermis generates putative anti-inflammatory metabolites from fish oil polyunsaturated fatty acids. Lipids 1989;24(12):998–1003.
[35] Onodera T, Fukuhara A, Shin J, Hayakawa T, Otsuki M, Shimomura I. Eicosapentaenoic acid and 5-HEPE enhance macrophage-mediated Treg induction in mice. Sci Rep 2017;7(1):4560.
[36] Shen Z, Wang D, Yu C, Peng Y, Cheng L, Zhang Y. Quantitative profiling of differentially expressed oxylipins in ADSCs under proinflammatory cytokine stimulation. Biomed Chromatogr 2022;36(11):e5452.
[37] Askari AA, Thomson S, Edin ML, Lih FB, Zeldin DC, Bishop-Bailey D. Basal and inducible anti-inflammatory epoxygenase activity in endothelial cells. Biochem Biophys Res Commun 2014;446(2):633–7.
[38] Barrera C, Valenzuela R, Chamorro R, Bascuñán K, Sandoval J, Sabag N, et al. The impact of maternal diet during pregnancy and lactation on the fatty acid composition of erythrocytes and breast milk of Chilean women. Nutrients 2018;10(7).
[39] Liu MJ, Li HT, Yu LX, Xu GS, Ge H, Wang LL, et al. A correlation study of DHA dietary intake and plasma, erythrocyte and breast milk DHA concentrations in lactating women from Coastland, Lakeland, and Inland Areas of China. Nutrients 2016;8(5).
[40] Haghiac M, Yang XH, Presley L, Smith S, Dettelback S, Minium J, et al. Dietary omega-3 fatty acid supplementation reduces inflammation in obese pregnant women: a randomized double-blind controlled clinical trial. PLoS One 2015;10(9):e0137309.
[41] Mozurkewich EL, Berman DR, Vahratian A, Clinton CM, Romero VC, Chilimigras JL, et al. Effect of prenatal EPA and DHA on maternal and umbilical cord blood cytokines. BMC Pregnancy Childbirth 2018;18(1):261.
[42] Bernard JY, De Agostini M, Forhan A, de Lauzon-Guillain B, Charles MA, Heude B. The dietary n6:n3 fatty acid ratio during pregnancy is inversely associated with child neurodevelopment in the EDEN mother-child cohort. J Nutr 2013;143(9):1481–8.
[43] Arvizu M, Minguez-Alarcon L, Wang S, Mitsunami M, Stuart JJ, Rich-Edwards JW, et al. Pre-pregnancy fat intake in relation to hypertensive disorders of pregnancy. Am J Clin Nutr 2022;116(3):750–8.
[44] Lehner A, Staub K, Aldakak L, Eppenberger P, Rühli F, Martin RD, et al. Impact of omega-3 fatty acid DHA and EPA supplementation in pregnant or breast-feeding women on cognitive performance of children: systematic review and meta-analysis. Nutr Rev 2021;79(5):585–98.
[45] Suitor CJ, Gardner J, Willett WC. A comparison of food frequency and diet recall methods in studies of nutrient intake of low-income pregnant women. J Am Diet Assoc 1989;89(12):1786–94.
[46] Wheeler E, Walsh-Wilcox M, Shah M, Achrekar A, Anderson JR, Walker MK. Interactive effects of omega-3 polyunsaturated fatty acids and secondhand smoke in mice and human subjects. Cardiovasc Toxicol 2021;21(2):115–26.
[47] Li W-J, Lu J-W, Zhang C-Y, Wang W-S, Ying H, Myatt L, et al. PGE2 vs PGF2α in human parturition. Placenta 2021;104:208–19.
[48] Denison FC, Calder AA, Kelly RW. The action of prostaglandin E2 on the human cervix: stimulation of interleukin 8 and inhibition of secretory leukocyte protease inhibitor. Am J Obstet Gynecol 1999;180(3 Pt 1):614–20.
[49] Xu C, Liu W, You X, Leimert K, Popowycz K, Fang X, et al. PGF2α modulates the output of chemokines and pro-inflammatory cytokines in myometrial cells from term pregnant women through divergent signaling pathways. Mol Hum Reprod 2015;21(7):603–14.
[50] Goetzl EJ, Brash AR, Tauber AI, Oates JA, Hubbard WC. Modulation of human neutrophil function by monohydroxy-eicosatetraenoic acids. Immunology 1980;39(4):491–501.
[51] Vanderhoek JY, Tare NS, Bailey JM, Goldstein AL, Pluznik DH. New role for 15-hydroxyeicosatetraenoic acid. Activator of leukotriene biosynthesis in PT-18 mast/basophil cells. J Biol Chem 1982;257(20):12191–5.
[52] Svenvik M, Raffetseder J, Brudin L, Lindberg R, Blomberg M, Axelsson D, et al. Plasma oxylipin levels associated with preterm birth in preterm labor. Prostagl Leukot Essent Fat Acids 2021;166:102251.
[53] Ulu A, Sahoo PK, Yuil-Valdes AG, Mukherjee M, Van Ormer M, Muthuraj PG, et al. Omega-3 fatty acid-derived resolvin D2 regulates human placental vascular smooth muscle and extravillous trophoblast activities. Int J Mol Sci 2019;20(18).
[54] Jurado-Fasoli L, Di X, Kohler I, Osuna-Prieto FJ, Hankemeier T, Krekels E, et al. Omega-6 and omega-3 oxylipins as potential markers of cardiometabolic risk in young adults. Obesity 2022;30(1):50–61.
[55] Aoki H, Isobe Y, Yoshida M, Kang JX, Maekawa M, Arita M. Enzymatically-epoxidized docosahexaenoic acid, 19,20-EpDPE, suppresses hepatic crown-like structure formation and nonalcoholic steatohepatitis fibrosis through GPR120. Biochim Biophys Acta Mol Cell Biol Lipids 2023;1868(3): 159275.
[56] Hu J, Dziumbla S, Lin J, Bibli SI, Zukunft S, de Mos J, et al. Inhibition of soluble epoxide hydrolase prevents diabetic retinopathy. Nature 2017;552(7684): 248–52.
[57] Zhang Y, Guallar E, Blasco-Colmenares E, Harms AC, Vreeken RJ, Hankemeier T, et al. Serum-based oxylipins are associated with outcomes in primary prevention implantable cardioverter defibrillator patients. PLoS One 2016;11(6):e0157035.
[58] Diet, nutrition and the prevention of chronic diseases. World Health Organ Tech Rep Ser 2003;916(i-viii):1–149 [backcover].
[59] Cave C, Hein N, Smith LM, Anderson-Berry A, Richter CK, Bisselou KS, et al. Omega-3 long-Chain polyunsaturated fatty acids intake by ethnicity, income, and education level in the United States: NHANES 2003-2014. Nutrients 2020;12(7).
[60] Kikut J, Komorniak N, Ziętek M, Palma J, Szczuko M. Inflammation with the participation of arachidonic (AA) and linoleic acid (LA) derivatives (HETEs and HODEs) is necessary in the course of a normal reproductive cycle and pregnancy. J Reprod Immunol 2020;141:103177.

[61] Renault KM, Carlsen EM, Hædersdal S, Nilas L, Secher NJ, Eugen-Olsen J, et al. Impact of lifestyle intervention for obese women during pregnancy on maternal metabolic and inflammatory markers. Int J Obes 2017;41(4):598–605.
[62] Rodriguez-Santana Y, Ochoa JJ, Lara-Villoslada F, Kajarabille N, Saavedra-Santana P, Hurtado JA, et al. Cytokine distribution in mothers and breastfed children after omega-3 LCPUFAs supplementation during the last trimester of pregnancy and the lactation period: a randomized, controlled trial. Prostaglandins Leukot Essent Fatty Acids 2017;126:32–8.
[63] Assaf-Balut C, García de la Torre N, Durán A, Fuentes M, Bordiú E, Del Valle L, et al. A Mediterranean diet with additional extra virgin olive oil and pistachios reduces the incidence of gestational diabetes mellitus (GDM): a randomized controlled trial: the St. Carlos GDM prevention study. PLoS One 2017;12(10):e0185873.
[64] Khalesi N, Mazloomi Nobandegani N, Khosravi N, Saboute M, Farahi SF, Shakeri Z, et al. Effect of maternal diet on any necrotizing enterocolitis in neonates: a randomized double-blind study. Breastfeed Med 2022;17(8):647–52.
[65] Khoury J, Henriksen T, Christophersen B, Tonstad S. Effect of a cholesterol-lowering diet on maternal, cord, and neonatal lipids, and pregnancy outcome: a randomized clinical trial. Am J Obstet Gynecol 2005;193(4):1292–301.
[66] Hamazaki K, Matsumura K, Tsuchida A, Kasamatsu H, Tanaka T, Ito M, et al. Maternal dietary intake of fish and PUFAs and child neurodevelopment at 6 months and 1 year of age: a nationwide birth cohort-the Japan Environment and Children's Study (JECS). Am J Clin Nutr 2020;112(5):1295–303.
[67] Serra R, Peñailillo R, Monteiro LJ, Monckeberg M, Peña M, Moyano L, et al. Supplementation of omega 3 during pregnancy and the risk of preterm birth: a systematic review and meta-analysis. Nutrients 2021;13(5).
[68] Blasbalg TL, Hibbeln JR, Ramsden CE, Majchrzak SF, Rawlings RR. Changes in consumption of omega-3 and omega-6 fatty acids in the United States during the 20th century. Am J Clin Nutr 2011;93(5):950–62.
[69] Lee E, Kim H, Kim H, Ha EH, Chang N. Association of maternal omega-6 fatty acid intake with infant birth outcomes: Korean Mothers and Children's Environmental Health (MOCEH). Nutr J 2018;17(1):47.
[70] Bakheit KH, Ghebremeskel K, Pol K, Elbashir MI, Adam I. Erythrocyte omega-3 and omega-6 fatty acids profile in Sudanese women with pre-eclampsia. J Obstet Gynaecol 2010;30(2):151–4.
[71] Szczuko M, Kikut J, Komorniak N, Bilicki J, Celewicz Z, Zietek M. The role of arachidonic and linoleic acid derivatives in pathological pregnancies and the human reproduction process. Int J Mol Sci 2020;21(24):9628. https://doi.org/10.3390/ijms21249628.
[72] Chahal N, McLain AC, Ghassabian A, Michels KA, Bell EM, Lawrence DA, et al. Maternal smoking and newborn cytokine and immunoglobulin levels. Nicotine Tob Res 2017;19(7):789–96.
[73] Kiilerich P, Cortes R, Lausten-Thomsen U, Borbye-Lorenzen N, Holmgaard S, Skogstrand K. Delivery modality affect neonatal levels of inflammation, stress, and growth factors. Front Pediatr 2021;9:709765.
[74] Maguire RL, House JS, Lloyd DT, Skinner HG, Allen TK, Raffi AM, et al. Associations between maternal obesity, gestational cytokine levels and child obesity in the NEST cohort. Pediatr Obes 2021;16(7):e12763.
[75] Li YX, Long DL, Liu J, Qiu D, Wang J, Cheng X, et al. Gestational diabetes mellitus in women increased the risk of neonatal infection via inflammation and autophagy in the placenta. Medicine (Baltim) 2020;99(40):e22152.
[76] Gencheva D, Nikolov F, Uchikova E, Mihaylov R, Pencheva B, Vasileva M. Interleukin-6 and its correlations with maternal characteristics and echocardiographic parameters in pre-eclampsia, gestational hypertension and normotensive pregnancy. Cardiovasc J Afr 2022;33(2):65–73.
[77] Álvarez D, Muñoz Y, Ortiz M, Maliqueo M, Chouinard-Watkins R, Valenzuela R. Impact of maternal obesity on the metabolism and bioavailability of polyunsaturated fatty acids during pregnancy and breastfeeding. Nutrients 2020;13(1).
[78] Bollen KA. Structural equations with latent variables. New York: Wiley; 1989.
[79] Comrey AL, Lee HB. A first course in factor analysis. 2 ed. Lawrence Erlbaum Associates, Inc.; 1992.
[80] O'Neill C, Wells X, Battye K. Embryo-derived platelet activating factor: interactions with the arachidonic acid cascade and the establishment and maintenance of pregnancy. Reprod Fertil Dev 1990;2(5):423–41.
[81] Si Y, Xia H, Xiong Z, Li Y, Shan Z, Wei W. The change in plasma PAF activity before and after delivery. Adv Exp Med Biol 1997;407:551–4.
[82] Thompson M, Ulu A, Yuil-Valdes AG, Mukherjee M, Thoene M, Van Ormer M, et al. Omega-6 and omega-3 fatty acid-derived oxylipins from the lipoxygenase pathway in maternal and umbilical cord plasma at delivery and their relationship with infant growth. Int J Mol Sci 2022;23(2).