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Maternal childhood adversity and inflammation during pregnancy: Interactions with diet quality and depressive symptoms

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A B S T R A C T

Inflammatory processes are a candidate mechanism by which early adversity may be biologically embedded and subsequently lead to poorer health outcomes; in pregnancy, this has been posited as a pathway for intergenerational transmission of adversity. Studies in non-pregnant adults suggest that factors such as mood, diet, BMI, and social support may moderate associations between childhood trauma history and inflammation in adulthood, though few studies have examined these associations among pregnant women. In a sample of healthy pregnant women (N = 187), we analyzed associations between maternal childhood adversity, including maltreatment and non-optimal caregiving experiences, with circulating Interleukin-6 (IL-6) levels during trimesters 2 (T2) and 3 (T3) of pregnancy. We also assessed whether these associations were moderated by psychosocial and lifestyle factors including depressive symptoms, social support, physical activity, and diet quality. History of childhood maltreatment was not associated with IL-6 in either T2 or T3 of pregnancy, either independently or in interaction with depressive symptom severity. However, in there was a significant positive association between childhood maltreatment and IL-6 in Trimester 2 in the context of poorer diet quality ($p = 0.01$), even after adjusting for BMI. Additionally, the quality of caregiving women received in childhood was associated with levels of IL-6 in Trimester 3, but only via interaction with concurrent depressive symptoms ($p = 0.02$). These findings provide evidence that for those with a history of childhood adversity, levels of inflammatory cytokines in pregnancy may be more sensitive to depressive symptoms and diet quality.

1. Introduction

Childhood adversity such as maltreatment – child abuse or neglect – is a severe and pervasive public health concern, affecting up to 10% of children in the USA, and posing risks for adverse psychological and physiological health that persist into adulthood (Gilbert et al., 2009; Sara and Lappin, 2017; Felitti ett al., 1998). A critical question raised by this epidemiological evidence is regarding the ways in which these early psychosocial experiences become biologically embedded. Candidate mechanisms include wide-ranging and interactive effects of childhood adversity on behavior, stress physiology, endocrine functioning, neural pathways, immune functioning, chronic pain conditions, and allergies (Berens et al., 2017; McLaughlin et al., 2016). In pregnancy, processes of biological embedding of experiences may result in altered gestational biology, affecting both the mother and the fetus via the in-utero environment, increasing the risk of adverse physical outcomes for both women and their offspring (Lev-Wiesel et al., 2009; Yampolsky et al., 2010), and is a risk factor for psychological distress in pregnancy, including post-traumatic stress disorder (PTSD) and depression (Lev-Wiesel et al., 2009; Yampolsky et al., 2010; Leeners et al., 2006).

Consistent with the concept of prenatal parenting, this vulnerability in pregnancy may extend to the fetus, and the role of biological pathways in intergenerational perpetuation of trauma effects is increasingly emphasized (Glover and Capron, 2017). It is well established that children born to mothers with histories of abuse are at higher risk of behavioral and emotional problems in childhood, even in the absence of experiencing maltreatment themselves (Roberts et al., 2004). While effects of parenting and the postnatal environment are important contributors to these outcomes, emerging evidence from studies guided by

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the Developmental Origins of Health and Disease (DOHAD) framework suggests that offspring of mothers with trauma histories are at risk even before birth: maternal childhood trauma history is associated with reduced birth weight and shorter gestational age at birth (Smith et al., 2016), altered stress physiology in fetuses (Moog et al., 2016) and infants (Bowers and Yehuda, 2016), decreased fetal heart rate reactivity (Gustafsson et al., 2016), and child structural brain development (Buss et al., 2017).

Inflammation is an important factor involved in the pathway from childhood adversity to poor health. A recent *meta*-analysis has indicated that exposure to early adversity is associated with systemic inflammation, measured by elevated levels of cytokines, including Interleukin-6 (IL-6), C-reactive protein (CRP) and tumor necrosis factor α (TNF-α) (Baumeister et al., 2015). While there are sex differences in IL-6 and CRP levels (Cartier et al., 2009; Wener et al., 2000), this *meta*-analysis found no significant moderation by sex in a subgroup analysis (Baumeister et al., 2015), and studies of all-female, nonpregnant samples have reported associations between adversity in childhood with circulating IL-6 (Bertone-Johnson et al., 2012; Tietjen et al., 2012; Witek Janusek et al., 2013) and CRP levels (Bertone-Johnson et al., 2012; Tietjen et al., 2012; Matthews et al., 2014).

Despite being posited as a potential mechanism by which trauma effects are transmitted from one generation to the next, associations between maternal childhood adversity and inflammation in pregnancy have been examined only in a few studies. Maternal childhood trauma was found to be associated with elevated circulating IL-6 levels in a study of pregnant adolescents, but only in the context of concurrent depression (Walsh et al., 2016). Hantsoo et al. (2019) found no difference in acute inflammatory response to an acute laboratory stressor between those with high exposure to childhood adversity. However, there was an interaction between adversity and diet on inflammation: women with high adversity exposure and higher dietary intake of polyunsaturated fatty acids versus those without this diet showed blunted inflammatory response (Hantsoo et al., 2019). Another study showed no direct association between maternal childhood maltreatment and prenatal serum IL-6 levels, though maltreatment was associated with higher serum CRP, and this effect was mediated by BMI (Mitchell et al., 2018). Indirect evidence of elevated inflammation associated with maternal childhood trauma comes from recent research showing maternal-fetal physiology also may be affected: maternal history of childhood maltreatment was associated with elevated placental corticotropin-releasing hormone (pCRH) assayed in maternal blood, which is directly stimulated by proinflammatory cytokines (Moog et al., 2016).

Associations between early life adversity and inflammation may only be apparent in the context of psychological distress, based on evidence from both pregnant (Walsh et al., 2016) and non-pregnant adults (Danese et al., 2008, 2007, 2011). Additionally, adverse psychosocial experiences have a cumulative effect on increasing allostatic load – the physiological "wear and tear" as the body maintains allostasis in the context of stressors – among those with histories of childhood maltreatment (Danese et al., 2009). Physical health and lifestyle factors may mitigate or exacerbate effects of early life adversity on inflammation during pregnancy. There is evidence that childhood physical and sexual abuse is associated with being overweight (Nagl et al., 2016) or obese (Nagl et al., 2016; Hollingsworth et al., 2012) in pregnancy, particularly in the context of elevated anxiety (Diesel et al., 2016). Diet quality may exert an effect on inflammation (independent of BMI): low carbohydrate diet has been associated with reduced cytokine levels including IL-6 in non-pregnant adults (Forsythe et al., 2008; Jonasson et al., 2014), and low-glycemic index (GI) diet is associated with a reduction in CRP (but not IL-6) (Neuhouser et al., 2011). Physical activity is another lifestyle factor associated with circulating inflammatory markers: though high intensity exercises is associated with short term and transient increase in CRP and IL-6, chronic exercise is associated with reduced levels of CRP in non-pregnant adults (Kasapis and Thompson, 2005). This has also been observed in pregnancy: among obese pregnant women, plasma CRP was lower in those who were physically active rather than inactive (Tinius et al., 2016).

Social support may also play a role in moderating associations between early life adversity and inflammation during pregnancy. Inflammatory processes have been identified as a key mechanism linking social support (or lack thereof) to physical health (Uchino, 2006; Kiecolt-Glaser et al., 2010; Cole et al., 2007; Miller et al., 2009). Among non-pregnant adults, higher social strain was associated with higher levels of several inflammation markers, including IL-6 (Yang et al., 2014), and low social support was associated with elevated CRP, an effect that was heightened among women with exposure to child abuse (Runsten et al., 2014). In pregnant women, social support in the third trimester is associated with lower serum CRP (Coussons-Read et al., 2007).

Elevated circulating IL-6 levels have been implicated as a mechanism relating pregnancy-specific distress with preterm birth (Coussons-Read et al., 2012), have been associated with increased risk of miscarriage (Galazios et al., 2011), and with higher depression and anxiety symptoms in the peripartum (Osborne et al., 2019). For these reasons and given aforementioned associations with childhood adversity in nonpregnant populations, IL-6 is among the leading candidate immune markers of interest.

There is a gap in current understanding of whether mood regulation and standard indices of physical health and wellbeing in adulthood may alter associations between early adversity and immune activation in pregnancy. Investigating these associations could inform interventions targeting modifiable risk factors to potentially limit the biological inflammatory pathway of intergenerational transmission of adversity. The aim of this study was to examine associations between maternal childhood maltreatment and inflammation during pregnancy, and to assess whether these associations are moderated by psychosocial and lifestyle factors, including depression, physical activity, diet, and social support.

2. Methods

2.1. Participants

Healthy pregnant women (n = 187, ages 19–44) were recruited during the years 2011–2016 through the Department of Obstetrics and Gynecology at Columbia University Irving Medical Center (CUIMC). Recruitment was via flyers, and referrals from obstetricians and midwives in affiliated clinics. Exclusion criteria were serious health conditions (including autoimmune disease), multifetal pregnancy, medications affecting the cardiovascular system, and tobacco, alcohol, or recreational drug use, and age younger than 18 or older than 45 years old. Sample characteristics are given in Table 1. The available N for each analysis varied according to patterns of missing data; the main reason for incomplete data was unavailable IL-6 data, and lower numbers of participants overall in T3 due to either early delivery or attrition (see Table 1). The number of participants with data available for analyses related to IL-6 at T2 ranged from 109 to 118, and in T3 from 93 to 104 (see Supplementary Table 1).

2.2. Study procedure

Participants provided written, informed consent prior to participating in the study, and all procedures were approved by the Institutional Review Board of the New York State Psychiatric Institute/CUIMC. Psychosocial assessments were conducted during in-person interviews at CUIMC in the first (T1; 13–16 weeks), second (T2; 24–27 weeks) and third (T3; 34–37 weeks) trimesters of pregnancy. Blood draws were taken at T2 and T3.

Table 1
Descriptive Data (total N = 186; 1 IL-6 outlier was excluded).

Variable	*n*	Min	Max	Mean	SD
Hispanic ethnicity – n (%)	129 (69.4)				
Income – n (%)					
$0–$15,000	27 (14.5)				
$16,000–$50,000	76 (41.4)				
$51,000–$100,000	47 (25.3)				
$101,000 +	35 (18.8)				
Receiving Medicaid – n (%)	93 (50.8)				
Working outside home – n (%)	102 (55.4)				
Pre-pregnancy BMI - mean	185	14.2	43.2	26.09	5.8
Underweight – n (%)	9				
Normal weight – n (%)	78				
Overweight – n (%)	58				
Obese – n (%)	35				
Maternal age (years)	186	19	44	29.64	6.25
First pregnancy (yes) – n (%)	46 (24.6)				
HAM-D score, Trimester 2	166	0	31	7.1	6.15
Moderate-severe depression – n (%)	19 (11.4)				
HAM-D score, Trimester 3	143	0	29	6.91	5.06
n moderate depression	12 (8.4)				
CTQ					
Sexual abuse - *n* (%); subscale score	26 (16.1)	4	24	6.52	3.81
Physical abuse - *n* (%); subscale score	19 (11.7)	4	20	6.64	2.83
Emotional abuse - *n* (%); subscale score	19 (11.7)	5	25	7.77	3.78
Physical neglect - *n* (%); subscale score	18 (11.1)	5	17	6.19	2.31
Emotional neglect - *n* (%); subscale score	20 (12.3)	5	25	9.06	4.61
Number of maltreatment types (0–5)		0	5	0.63	1.18
One or more forms of maltreatment – n (%)	50 (30.06)				
CTQ Total score	161	23	86	36.18	13.27
PBI					
Both optimal - n (%)	34 (21.7)				
One parent not optimal - n (%)	47 (30.9)				
Neither optimal - n (%)	72 (47.4)				
Healthy eating index					
Trimester 2	153	22.6	89.1	53.58	14.23
Trimester 3	137	27.2	86.4	53.29	13.64
Average physical activity					
Trimester 2	141	0	3	0.67	0.57
Trimester 3	119	0	3	0.62	0.55
Inflammatory Markers					
IL-6 at T2, pg/mL	137	0.33	10	1.42	1.12
IL-6 at T3, pg/mL	123	0.37	22.2	1.83	2.21
Baby birth weight (g)	169	1310	4470	3321	511
Gestational age at birth	181	16	41.4	38.7	3.2

SD = standard deviation; BMI = Body Mass Index; HAM-D = Hamilton Depression Rating Scale; CTQ = Childhood Trauma Questionnaire; PBI = Parental Bonding Instrument; IL-6 = Interleukin-6; T2/3 = Trimester 2/3.

3. Measures and data preparation

3.1. Demographic and BMI data

Demographic data were self-reported during the T1 interview. Pre-pregnancy BMI was calculated using weight and height from medical records. Weight was also measured by researchers at study visits in each trimester with an electronic scale.

3.2. Maternal childhood adversity

Two aspects of maternal childhood adversity were assessed: experience of childhood maltreatment (MT), and quality of caregiving (MCC). MT was defined as abuse or neglect that occurred prior to 18 years of age. The Childhood Trauma Questionnaire (CTQ) (Bernstein and Fink, 1998), a self-report questionnaire containing 28 items on a 5-point Likert scale was used at the T2 interview to assess exposure to 5 sub-types of childhood maltreatment: physical abuse, physical neglect, sexual abuse, emotional abuse, and emotional neglect. Established cut-off scores indicating the presence or absence of abuse/neglect on each of the 5 subscales was used to dichotomize the presence or absence of each type of maltreatment (Moog et al., 2016). A score from 0 to 5 was then calculated indicating the total number of maltreatment types to which the participant was exposed (MT Total).

Quality of mothers' own caregiving experienced in childhood was assessed with the Parental Bonding Instrument (PBI) at the T2 interview (Parker et al., 1979). Separate scales measured caregiving received from their mother and their father. The scale consists of two dimensions – care and overprotection – measuring fundamental parenting styles as perceived, retrospectively, in participants' own childhood (Parker et al., 1979). Categorization of "high" or "low" on each dimension was based on established cut-offs: for mothers, a care score of 27 and a protection score of 13.5; for fathers, a care score of 24 and a protection score of 12.5 (Gladstone et al., 2005). Based on these two subscales combined, parenting styles were assigned to one of four quadrants as per the established, validated method: affectionate constraint (high care, high overprotection), affectionless control (low care, high overprotection), neglectful parenting (low care, low overprotection), or optimal parenting (high care, low overprotection) (Parker et al., 1979; Gladstone et al., 2005; Rikhye et al., 2008). For the purpose of analyses, these quadrants were collapsed into a dichotomous variable: participants were categorized as either having received optimal parenting or non-optimal caregiving by each parent.

3.3. Depressive symptoms

Depressive symptoms were measured using the interviewer-administered Hamilton Depression Rating Scale – 21 Item version (HAM-D), at T2 and T3 (Hamilton, 1960). Total scores on the HAM-D were used in regression analyses.

3.4. Interleukin-6

Interleukin-6 was assayed from samples drawn at T2 and T3. Consistent with previous studies assessing IL-6 through a single blood draw from our group (Walsh et al., 2016) and others (Greig et al., 1997; Corwin et al., 2013); 10 ml blood samples were collected in EDTA tubes. Blood draws occurred between 8am and 6 pm, with the majority (T2 = 66%, T3 = 62%) occurring between 10am and 2 pm. Samples were placed on ice, spun down, and frozen at −80 °C within 60 min of collection. IL-6 was assayed using high-sensitivity commercial enzyme-linked immunosorbent assay kits (IL-6- ELISA: R&D Systems, Minneapolis, MN).

3.5. Maternal diet

Information about dietary intake was collected using the Automated Self-Administered 24-hour Dietary Recall (ASA-24) measure at T1, T2 and T3 interviews (Subar et al., 2007), which elicits information on food intake over the preceding 24 h using detailed probes and portion-size food images. Its interface has been validated for participants with at least some secondary school education (Subar et al., 2012). From ASA-24 data, the Healthy Eating Index 2015 (HEI) (National Cancer Institute, 2020) was calculated. The HEI is an established measure of diet quality, independent of quantity, that assesses compliance with the 2015 dietary recommendations for Americans, with higher HEI scores indicating a healthier diet.

3.6. Maternal physical activity

Physical activity was collected via a personal digital assistant device

Table 2
Correlations among Study Variables.

Variable	T2 IL-6	T3 IL-6	CTQ total	CTQ MT types	T2 HAM-D	T3 HAM-D	BMI Pre-pregnancy	T2 HEI	T3 HEI	T2 Physical activity	T3 Physical activity	Social support	Maternal Age	Gestational Age
T2 IL-6	–													
T3-IL-6	0.60**	–												
CTQ total	−0.03	0.13	–											
CTQ MT types	−0.02	0.15	0.77**	–										
T2 HAM-D	0.13	0.11	0.32**	0.20*	–									
T3 HAM-D	0.11	0.18*	0.43**	0.31**	0.63**	–								
BMI Pre-pregnancy	0.53**	0.37**	0.16*	0.14	0.12	0.14	–							
T2 HEI	−0.13	−0.06	−0.11	< −0.01	< −0.01	−0.05	−0.26**	–						
T3 HEI	−0.02	−0.06	−0.05	−0.03	0.03	−0.02	−0.14	0.29**	–					
T2 Physical activity	−0.08	0.03	0.19*	0.08	0.1	0.18	−0.16	0.08	0.03	–				
T3 Physical activity	−0.07	0.1	0.1	0.06	< 0.01	0.09	−0.08	0.06	0.01	0.53**	–			
Social support	0.01	−0.13	−0.45**	−0.32**	−0.45**	−0.41**	−0.11	0.01	0.06	−0.13	0.04	–		
Maternal Age	0.05	< −0.01	< −0.01	< 0.01	0.01	< −0.01	0.08	0.11	0.15	−0.11	−0.01	0.12	–	
Gestational Age	0.11	0.1	0.15	0.09	−0.04	< 0.01	0.04	−0.02	0.07	−0.03	−0.11	0.02	−0.07	–
Birth weight	0.04	0.03	0.12	0.04	0.17*	0.03	0.01	−0.05	0.07	0.04	−0.01	−0.1	0.06	0.56**

CTQ = Childhood Trauma Questionnaire; MT = Childhood Maltreatment; T1 = trimester 1; T2 = trimester 2; T3 = trimester 3; IL 6 = interleukin-6; BMI = body mass index, HEI – Healthy Eating Index. **$p < 0.01$, *$p < 0.05$.

every 30 min for a 24-hour period, timed to begin with the lab assessment. Participants were asked how active they were in the past 30 min on a scale from 0 (not active) to 3 (very active). The total physical activity score used in analyses was an average of scores from the respective visit.

3.7. Social support

Perceived availability of social support was measured by total score on the Support Evaluation List (ISEL) (Cohen and Hoberman, 1983), which includes three dimensions: tangible support, appraisal support, and belonging support. Tangible support refers to material aid, appraisal support refers to emotional support, and belonging support relates to the perception of being a member of a social group (Brookings and Bolton, 1988).

3.8. Statistical analysis

For the key characteristics, descriptive statistics such as mean (standard deviation) and percent are reported for continuous and categorical variables, respectively. Missing data was handled separately for each analysis via listwise deletion; total N available for each regression analysis is given in Supplementary Table 1. To test longitudinal changes in the key biomarker variable (IL6), linear mixed effect models were used with IL6 as the dependent variable and time (two-levels: T2, T3) as the fixed effect. Log transformation of IL-6 values was performed because of non-normally distributed data. To account for within-subject correlation, subject ID was used as a random intercept.

To test correlations between key predictors and outcomes, and determine covariates to be included in subsequent models, Spearman's rank-order correlation analysis was conducted.

To test the hypothesis that maternal childhood maltreatment would be associated with IL-6 in pregnancy, separate linear regressions were performed with childhood maltreatment (MT Total) as the independent variable and IL-6 at T2 and T3 as the dependent variable, controlling for maternal pre-pregnancy BMI (Model 1). We also examined whether the association between childhood maltreatment and IL-6 was moderated by concurrent depressive symptoms (Model 2) or diet quality (Model 3), or physical activity. This was done using linear regression with the moderator (depressive symptoms or diet quality), childhood maltreatment, and their interactions as independent variables, with BMI included as a covariate in all models. When the interaction was significant, *post-hoc* contrast tests were conducted to evaluate the association between depressive symptoms and IL-6 for each MT group. Each of these models was run separately using data from T2 and T3.

MCC was categorized into three groups: optimal care from both parents, suboptimal care from one parent, or suboptimal care from both parents. IL-6 at each time point was compared by the three groups controlling for the same sets of covariates. To test the hypothesis that maternal MCC would be associated with IL-6 in pregnancy, and whether concurrent depressive symptoms or diet quality moderated this association, linear regressions were run as above but with MCC as independent variable; this was repeated for data from each time period (Models 4–6).

4. Results

4.1. Sample characteristics

Information on sample size and key characteristics are given in Table 1. One outlier was removed due to an extreme value of IL-6 at T2 and T3. Maternal mean age was 29.64 (S.D 6.25). The majority of the sample (69.4%) were of Hispanic ethnicity, and 50.5% were receiving Medicaid. For only 24.6% of the sample this was their first pregnancy. According to conservative cut-off scores on the CTQ thought to indicate moderate to severe maltreatment (Moog et al., 2016), 30.1% of this

sample had a history of one or more forms of childhood abuse or neglect. Sexual abuse was the most commonly reported form of maltreatment (16.1%). Depression at levels considered clinically significant, measured by the Hamilton depression scale (Hamilton, 1960) (scores 14 and above), was reported by 11.4% of the sample in T2 (n = 19) and 8.4% of the sample in T3 (n = 12). According to the Parental Bonding Instrument (PBI), 21.7% of the sample received optimal caregiving from both their mother and father in childhood, 30.7% reported non-optimal caregiving from at least one parent, and 47.4% reported receiving non-optimal caregiving from both their mother and father. Mean levels of IL-6 are also given in Table 1. IL-6 increased from T2 to T3: a regression model confirmed this temporal trend was significant ($\beta = 0.20$, $p = 0.02$).

4.2. Associations among study variables

Spearman correlations between key covariates, predictors and outcomes are given in Table 2. Since it has previously been reported that carrying a male fetus may be associated with a different maternal inflammatory response (Taylor et al., 2018), we examined differences in IL-6 levels by fetal sex; no difference were found at T2 (t = -0.02, p = 0.98) or T3 (t = -0.075, p = 0.46). Childhood maltreatment (MT Total) was not correlated with IL-6 at T2 or T3, nor were scores on any individual CTQ subscale. Depressive symptoms, diet quality (Healthy Eating Index, HEI), physical activity, and social support were also not correlated with concurrent IL-6 levels at T2 or T3. IL-6 in T2 was correlated with pre-pregnancy BMI in T2 ($r = 0.53$, $p < 0.001$) and T3 ($r = 0.37$, $p < 0.001$). MT Total was correlated with depressive symptoms at T2 ($r = 0.20$, $p < 0.05$) and T3 ($r = 0.31$, $p < 0.01$). This was also true for all individual subscales except for sexual abuse. Pre-pregnancy BMI was not correlated with physical activity level, and was only correlated with HEI in T2. Finally, social support showed moderate negative correlations with all forms of childhood maltreatment, with the exception of sexual abuse, which was only weakly negatively correlated with the “appraisal” social support subscale.

Though the CTQ and the PBI measure distinct aspects of childhood adversity, there was a high degree of concordance between exposure to childhood maltreatment and maternal childhood caregiving experiences ($\chi^{2=}18.33$, $p < 0.001$). Among those reporting at least 1 form of childhood maltreatment, 75% also reported experiencing non-optimal caregiving from both parents; only 4.55% of those exposed to childhood maltreatment report having received optimal caregiving from both parents. In contrast, 29.7% of participants with no exposure to childhood maltreatment also reported experiencing optimal care from both parents (Supplementary Table 2).

4.3. Maternal exposure to childhood maltreatment and inflammation in pregnancy

Linear regression models were run to examine direct effects of maternal childhood maltreatment (MT Total) on IL-6 at T2 and T3. Pre-pregnancy BMI was included as a covariate in all models given its association with inflammation and trauma history. There was no main effect of MT on IL-6 at T2 or T3 (Model 1, Table 3). There was no interaction between depressive symptoms and MT on IL-6 at either time point (Model 2, Table 3), nor between social support or physical activity and MT on IL-6 at either time point (Supplementary Table 3).

There was, however, an observed interaction between MT and maternal diet on IL-6 at T2 (Model 3, Table 3); specifically, higher exposure to childhood maltreatment together lower HEI in T2 predicted higher levels of IL-6 in T2. In contrast, among those with no history of childhood maltreatment, there was no association between diet quality and IL-6 in T2 (Fig. 1). This association remained significant after Bonferroni correction for the 6 primary analyses.

4.4. Maternal experiences of caregiving from parents and inflammation in pregnancy

Linear regression models were run to examine direct effects of maternal childhood caregiving experiences (MCC) on IL-6 at T2 and T3, dichotomized to indicate optimal or sub-optimal caregiving (as defined above), with BMI again included as a covariate in all models. There was no difference between participants who had experienced suboptimal or optimal caregiving in IL-6 at T2 or T3 (Model 4, Table 3). There was no significant interaction between MCC and diet quality on IL-6 at T2 or T3 (Model 5, Table 3). There was, however, a significant interaction effect between MCC and depressive symptoms on IL-6 at T3 (Fig. 2): specifically, compared to those with optimal care from both parents, participants who experienced non-optimal caregiving from 1 or both parents showed a significant, positive association between depressive symptoms at T3 and IL-6 at T3 (Table 3, model 5). However, this association was not statistically significant after Bonferroni correction for the 6 primary analyses. There was no interaction between social support or physical activity and MCC on IL-6 at either time point (Supplementary Table 2).

4.5. Sensitivity analyses

To investigate patterns of missing data, we compared demographics of those women with complete data with those who were missing data at either T2 or T3. Missing data at either time point was associated with younger maternal age, primiparity, lower HAM-D scores, and younger gestational age at birth. To determine whether patterns of missing data affected outcomes, we performed a sensitivity analysis by entering maternal age, parity, and gestational age at birth as covariates in regression models. Our original findings remained, with consistent effect sizes and *p*-values observed (data not shown).

To account for potential diurnal variation in IL-6 levels, we repeated these regression analyses adjusting for time of day of blood draw (AM vs PM), and found consistent effect sizes and statistical significance (data not shown).

5. Discussion

Contrary to predictions, history of childhood maltreatment was not associated with IL-6 in either T2 or T3 of pregnancy, either independently or in interaction with depressive symptom severity. This is not consistent with findings of a previous study of pregnant adolescents, which reported a significant interaction between depressive symptoms and child abuse on IL-6, such that adolescents with more severe maltreatment history and depressive symptoms had elevated IL-6 in T2 (Walsh et al., 2016), or with existing literature showing interactions between childhood trauma and depressive symptoms on inflammation in non-pregnant adults (Danese et al., 2008, 2007, 2011). This inconsistency may be due to the current sample’s overall higher psychological health (lower stress, depression and anxiety levels) compared with prior samples, or the less proximal exposure to childhood trauma in adults compared with adolescents. This relatively low rate of depression despite similar rates of childhood maltreatment seen in the general population may suggest overall better support and functioning following maltreatment exposure.

The current study considered several lifestyle factors as potential moderators of effects of childhood maltreatment on inflammation during pregnancy. In T2, there was a significant positive association between MT and IL-6 in the context of poorer diet quality. Since BMI was controlled for in analyses, this effect was not attributable to increased body weight with poorer diet quality. Another recent study demonstrated interactions between maternal diet and IL-6 activity: maternal adverse childhood experiences were not associated with IL-6 response to stress during pregnancy overall, but among those with higher childhood adversity, intake of polyunsaturated fatty acids was

Table 3
Regression models: Childhood adversity and prenatal inflammation.

Predictor	Model/Moderator	Parameter	IL-6 at T2			IL-6 at T3		
			Estimate	SE	*p*-value	Estimate	SE	*p*-value
MT	Model 1	Pre-pregnancy BMI	0.04	0.01	< 0.0001**	0.03	0.01	0.01
		MT Total	−0.02	0.04	0.58	0.05	0.05	0.30
	Model 2/HAM-D	Pre-pregnancy BMI	0.04	0.01	< 0.0001**	0.03	0.01	0.01*
		MT Total	0.02	0.06	0.79	0.09	0.10	0.37
		HAM_D	0.01	0.01	0.21	0.02	0.01	0.16
		MT Total*HAM_D	−0.01	0.01	0.33	−0.01	0.01	0.51
	Model 3/HEI	Pre-pregnancy BMI	0.04	0.01	< 0.0001**	0.03	0.01	0.01*
		MT Total	0.41	0.17	0.02	0.04	0.20	0.85
		Diet	0.00	0.00	0.27	0.00	0.00	0.67
		MT Total*Diet	−0.01	0.00	0.01**	0.00	0.00	0.95
MCC	Model 4	Pre-pregnancy BMI	0.05	0.01	< 0.0001**	0.03	0.01	< 0.001**
		MCC - One parent not optimal	0.14	0.14	0.31	0.08	0.16	0.63
		MCC - Neither optimal	0.11	0.13	0.40	0.14	0.15	0.35
		MCC - Both optimal	0.00	.	.	0.00	.	.
	Model 5/HAM-D	Pre-pregnancy BMI	0.05	0.01	< 0.0001**	0.04	0.01	< 0.001**
		MCC - One parent not optimal	−0.04	0.22	0.87	−0.56	0.27	0.04*
		MCC - Neither optimal	0.26	0.20	0.20	0.06	0.27	0.81
		MCC - Both optimal	0.00	.	.	0.00	.	.
		HAM_D	0.02	0.03	0.55	−0.02	0.04	0.69
		HAM_D*MCC (One parent not optimal)	0.02	0.04	0.58	0.10	0.04	0.03*
		HAM_D*PBI (Neither optimal)	−0.03	0.03	0.39	0.02	0.04	0.71
		HAM_D*PBI (both optimal)	0.00	.	.	0.00	.	.
	Model 6/HEI	Pre-pregnancy BMI	0.05	0.01	< 0.0001**	0.03	0.01	< 0.01**
		MCC - One parent not optimal	0.36	0.53	0.49	−0.08	0.66	0.90
		MCC - Neither optimal	0.60	0.52	0.25	0.73	0.62	0.25
		MCC - Both optimal	0.00	.	.	0.00	.	.
		Diet	0.01	0.01	0.42	0.00	0.01	0.93
		Diet* MCC (One parent not optimal)	0.00	0.01	0.69	0.00	0.01	0.80
		Diet* MCC (Neither optimal)	−0.01	0.01	0.34	−0.01	0.01	0.33
		Diet* MCC (both optimal)	0.00	.	.	0.00	.	.

*MT = Childhood maltreatment; MCC = Maternal childhood caregiving; HEI = Healthy Eating Index; HAM-D = Hamilton Depression scale; IL-6 = Interleukin-6; T2/3 = Trimester 2/3; SE = Standard Error; *p < 0.05; **p < 0.01.*

associated with blunted inflammatory response to laboratory induced stress (Hantsoo et al., 2019).

The present findings are also consistent with prior research in non-pregnant adults showing that higher carbohydrate diet is associated with elevated levels of IL-6 (Forsythe et al., 2008; Jonasson et al., 2014); yet association with diet quality was only seen among women with a history of childhood maltreatment, suggesting that in these participants with higher levels of adversity in their backgrounds, circulating inflammatory cytokines may be more sensitive to diet. Given that childhood maltreatment overall was not associated with higher inflammation in pregnancy, future studies of larger samples could further investigate whether diet quality moderates the effects of maternal

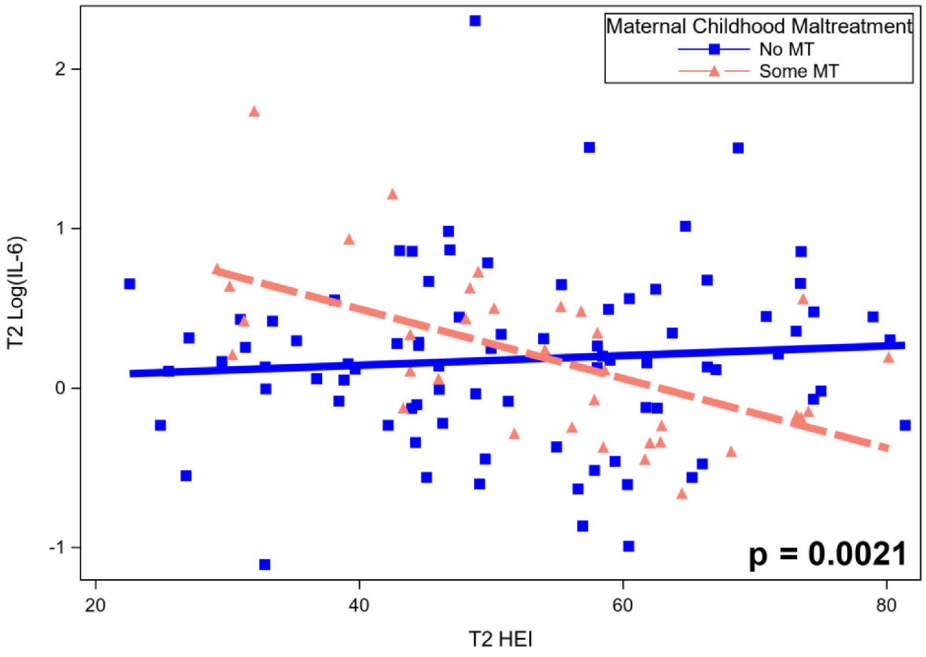

Fig. 1. IL-6 in Trimester 2 is negatively associated with diet quality, for those with a history of childhood maltreatment only.

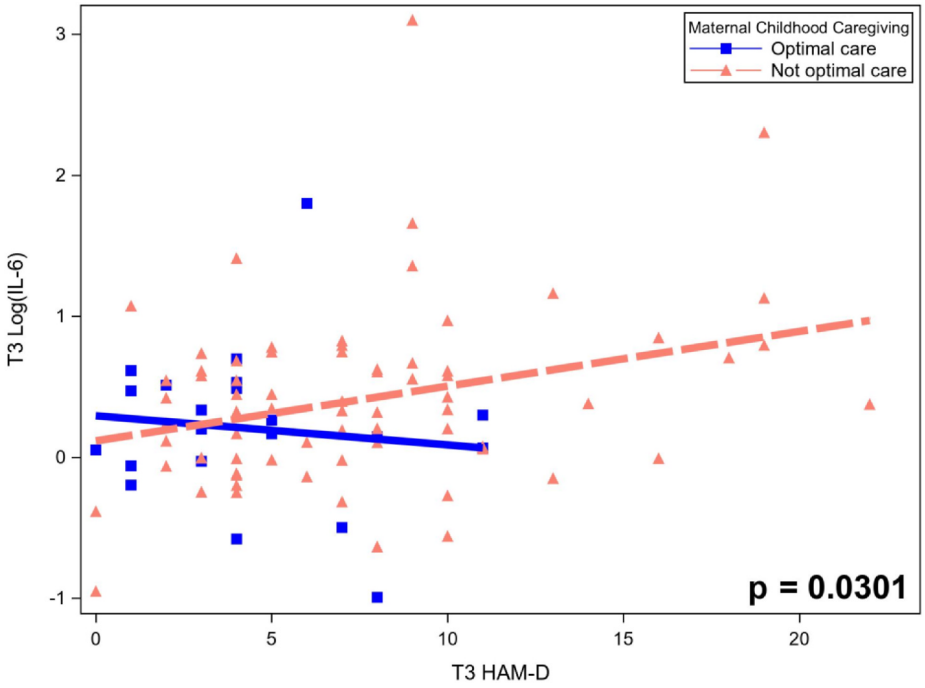

Fig. 2. IL-6 in Trimester 3 is positively associated with depression, for those with a history of non-optimal care in childhood only.

childhood maltreatment on inflammation.

In addition to childhood maltreatment, we examined childhood adversity in the form of non-optimal caregiving in childhood as a potential predictor of IL-6 in pregnancy. In the present study, the quality of caregiving women received in childhood affected their levels of IL-6 in pregnancy, but only in T3 and only in association with concurrent depressive symptoms. Specifically, for women who experienced suboptimal caregiving in childhood from one parent, there was a positive association between depressive symptoms in T3 and levels of IL-6 in T3. This effect was not observed in T2. This is somewhat consistent with findings from a healthy pregnant population showing that IL-6 increased from T2 to T3, among depressed women only (Osborne et al., 2019); and with findings in a non-pregnant sample that experiencing warm maternal care in childhood buffers the effects of adversity on inflammatory signaling in adulthood (Chen et al., 2010). However, in the present study, women with elevated depressive symptoms did not show higher levels of IL-6 in T3 in isolation – only when a history of suboptimal caregiving was also present. These data add to evidence that maternal experience of non-optimal caregiving in childhood may affect gestational biology and the offspring. Inadequate caregiving received early in life can affect the developing brain and have a range of long-term health consequences (Charmandari et al., 2003), and has been identified as a leading contributing factor to adult psychopathology (Enns et al., 2002). In the perinatal period, women who experienced non-optimal caregiving from their own mother in childhood are at higher risk of depression (Della Vedova et al., 2011; Ohara et al., 2018). Inflammation may be affected by childhood caregiving experiences: in non-pregnant adults, non-optimal caregiving, in combination with psychosocial stress in adulthood, is associated with elevated pro-inflammatory signaling (Chen et al., 2010).

We also investigated social support as a potential moderator of the effect of childhood adversity on IL-6 in pregnancy based on evidence suggesting higher levels of social support can be a buffer against the negative consequences of early life adversity (Maschi et al., 2013) including inflammation (Runsten et al., 2014), though survivors of trauma may also be at risk of having lower levels of social support in adulthood than the general population (Stesssman et al., 2008). In the present sample, correlations between social support and both childhood maltreatment and depression were among the strongest observed associations, consistent with previously published data from the same sample which showed dimensions of social support were the leading factors differentiating physically and psychologically stressed from healthy groups in pregnancy (Walsh et al., 2019). However, social support was not correlated with IL-6, and in regression analyses, social support did not moderate associations between either measure of childhood adversity (MT or MCC) and IL-6 in pregnancy. This could be due to the social support dimension used, which assessed overall subjective evaluation of positive social support, as opposed to actually capturing “loneliness” or social isolation, which may be conceived of as a distinct construct, rather than the opposite end of a unidimensional scale (Eisenberger and Cole, 2012). Though social isolation has previously been associated with increased expression of pro-inflammatory genes (Cole et al., 2007, 2015), it may not necessarily be the case that positive experiences of social support shows the inverse association. Further research is needed to investigate the role of social isolation or loneliness as a potential moderator of associations between childhood adversities on inflammation during pregnancy.

Associations between maternal psychological distress (i.e., depression, anxiety, or stress) and immune activation have been more extensively studied than associations with childhood maltreatment or childhood caregiving experiences. Building on the inflammation hypothesis of depression originating in studies of non-pregnant adults (Miller and Raison, 2015; Raison et al., 2006), research has pointed to heightened immune activation as a candidate physiological pathway that may explain perinatal depression (Osborne and Monk, 2013). Associations between perinatal depression and inflammatory markers in pregnancy (in the absence of infection) are mixed, with some studies reporting lower levels of pro-inflammatory cytokines among depressed women (Edvinsson et al., 2017), no difference between depressed and non-depressed women (Blackmore et al., 2011; Cassidy-Bushrow et al., 2012; Christian et al., 2009; Shelton et al., 2015), or elevated levels of particular cytokines (IL-2, IL-13, and IL-12) but not others (TNF-α, IL-6) (Karlsson et al., 2017); in contrast, other studies study reported elevated serum TNF-α and IL-6 in the context of elevated prenatal stress (Coussons-Read et al., 2007, 2005). Given the evidence presented here and in previous literature that early life adversity may be associated

with inflammation during pregnancy, particularly in the context of concurrent elevated depressive symptoms and poorer diet quality, future research examining inflammation in depressed pregnant women should also consider the role of trauma and early life adversity in these associations.

A notable strength of this study was the collection of prospective data on a range of physical and psychosocial health factors, along with biological assays, which enabled modeling of several different pathways of associations between maternal experiences of maltreatment on inflammation in pregnancy. Using multiple measures of childhood adversity also enabled sensitivity to detect outcomes associated with specific forms of adverse experiences.

Findings of this study should be interpreted with consideration of several important limitations. First, we only measured IL-6. While this cytokine is a prime candidate, other inflammatory markers have shown associations with childhood trauma history in pregnant and non-pregnant adults, notably CRP and TNF-α (Baumeister et al., 2015). Future studies including a broad panel of inflammatory markers would be beneficial in order to assess the relative balance of levels of multiple cytokines and chemokines (pro- and anti-inflammatory), which may be most important in affecting brain and behavior during pregnancy, a period of immunomodulation (Osborne et al., 2019; Karlsson et al., 2017; Sherer et al., 2017). Reliance on retrospective self-report measures of childhood adversity may have led to an underestimation exposure to adversity. Additionally, our measure of physical activity was limited to a self-report measure that may not capture true intensity of activity. Maternal diet was based on self-reported 24-hour recall using the ASA-24, which may be subject to recall biases or not representative of diet in general. We did not control for the presence of an active infection during pregnancy, so this potential confounder associated with inflammation has not been accounted for. Sample size and missing data was also a limitation since some of our observed effect sizes were small, and did not retain statistical significance after adjusting for multiple comparisons. The variations in available sample for each analysis may also account for inconsistent findings across timepoints. Future studies with larger samples may allow detection of smaller effect sizes, and also would allow for subgroup analyses such as stratification by fetal sex, parity, or clinically significant depression. Finally, although there was a substantial portion of the sample with exposure to childhood adversity, this was a relatively high-functioning, healthy group of women. Therefore, findings may not generalize to more vulnerable groups, or to those with health problems or who use alcohol or substances as these were exclusion criteria of the present study.

6. Conclusions

Findings of the current study provide evidence that for those with a history of childhood adversity, levels of inflammatory cytokines in pregnancy may be more sensitive to depressive symptoms and diet quality. Inflammatory pathways have been frequently posited as a potential mechanism for the intergenerational transmission of effects of childhood adversity, yet present findings demonstrate that this association is not straightforward, and may be contingent on other maternal health and lifestyle factors including quality of diet and levels of depressive symptomatology.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2020.09.023.

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