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Prenatal maternal Inflammation, childhood cognition and adolescent depressive symptoms

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ABSTRACT

Background: Accumulating evidence indicates that higher prenatal maternal inflammation is associated with increased depression risk in adolescent and adult-aged offspring. Prenatal maternal inflammation (PNMI) may increase the likelihood for offspring to have lower cognitive performance, which, in turn, may heighten risk for depression onset. Therefore, this study explored the potential mediating role of childhood cognitive performance in the relationship between PNMI and adolescent depressive symptoms in offspring.

Methods: Participants included 696 mother-offspring dyads from the Child Health and Development Studies (CHDS) cohort. Biomarkers of maternal inflammation [interleukin (IL)-6, IL-8, IL-1 receptor antagonist (IL-1RA) and soluble TNF receptor-II (sTNF-RII)] were assayed from first (T1) and second trimester (T2) sera. Childhood (ages 9–11) cognitive performance was assessed via standardized Peabody Picture Vocabulary Test (PPVT), a measure of receptive vocabulary correlated with general intelligence. Adolescent (ages 15–17) depressive symptoms were assessed via self-report.

Results: There were no significant associations between T1 biomarkers and childhood PPVT or adolescent depressive symptoms. Higher T2 IL1-RA was directly associated with lower childhood PPVT (b = -0.21, SE = 0.08, t = -2.55, p = 0.01), but not with adolescent depressive symptoms. T2 IL-6 was not directly associated with childhood PPVT, but higher T2 IL-6 was directly associated at borderline significance with greater depressive symptoms in adolescence (b = 0.05, SE = 0.03, t = 1.96, p = 0.05). Lower childhood PPVT predicted significantly higher adolescent depressive symptoms (b = -0.07, SE = 0.02, t = -2.99, p < 0.01). There was a significant indirect effect of T2 IL-1RA on adolescent depressive symptoms via childhood PPVT (b = 0.03, 95 % CI = 0.002–0.03) indicating a partially mediated effect. No significant associations were found with T2 sTNF-RII nor IL-8.

Conclusions: Lower childhood cognitive performance, such as that indicated by a lower PPVT score, represents a potential mechanism through which prenatal maternal inflammation contributes to adolescent depression risk in offspring.

1. Introduction

Cognitive dysfunction (e.g., deficits in attention, learning, memory, problem solving and/or processing speed) is a well-studied, correlate of depression in youth (Pan et al., 2019). In recent years, findings suggest that, in some children, lower cognitive performance in childhood may actually precede and contribute to the emergence of adolescent depressive symptoms (Scult et al., 2017; Allott et al., 2016). There are multiple potential explanations for this association, including shared neural pathways that contribute to susceptibility to psychopathology when the brain rapidly matures during adolescence (e.g., synaptic pruning) (Chavez-Baldini et al., 2023; Troller-Renfree et al., 2018;

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Zhang et al., 2020). Further, these early cognitive differences in childhood may interact across development with contextual factors (e.g., peers, parents, teachers), creating a cascade to psychopathology through a variety of pathways (Barnett et al., 2006; Ellman et al., 2018; Irani et al., 2023; Koenen et al., 2009). For these reasons, it has been suggested that lower cognitive performance, such as lower global IQ (Barlati et al., 2022), may arise early in childhood and confer risk for recurrent, more severe depressive symptoms across development (Hung et al., 2016).

Although recent global estimates predict 37 percent of children will go on to exhibit depressive symptomatology in adolescence, notably 13 percent higher than in 2010 (Shorey et al., 2022), these estimates are even greater for children with below average cognitive performance (Bowe et al., 2021). Thus, for some individuals, lower emerging childhood cognitive performance may represent one pathway between early risk factors and depressive symptomatology in adolescence (Barlati et al., 2022; Jaekel et al., 2019; Johnson et al., 2010).

The Developmental Origins of Health and Disease (DOHaD) hypothesis (Barker, 2004) suggests that mental and physical health outcomes may begin *in utero* (Amgalan et al., 2021; Glynn & Sandman, 2011; Monk et al., 2019). Within this framework, accumulating evidence indicates that prenatal factors potentially contribute to risk for depression and related intermediate cognitive phenotypes (Lipner et al., 2024; Maxwell et al., 2018; Monk et al., 2019; Murphy et al., 2017). Further, animal models indicate that insults in the prenatal period are associated with depressive-like symptomatology as well as cognitive-like changes in offspring, such as impaired working memory (Ronovsky et al., 2016). Although several perinatal factors have been directly linked to offspring depression risk, including maternal health behaviors (e.g., smoking (Taylor et al., 2017)) psychological stress (Glover, 2015; Maxwell et al., 2018), environmental pollution and toxins (Williams and Ross, 2007), infection (Lipner et al., 2022; Murphy et al., 2017) and other obstetric complications (O'Keane and Scott, 2005), the neurodevelopmental pathways by which the *in utero* environment confers risk for offspring depression are less understood.

As pregnancy is a complex, immunomodulatory state, the maternal immune system is central in promoting a healthy pregnancy (Ross et al., 2022). Inflammatory biomarkers shift in concentration depending on the stage of fetal development (Ross et al., 2022), beginning with a pro-inflammatory state during embryo implantation, shifting to a more anti-inflammatory state during mid-pregnancy to decrease rejection of the fetus (Makinson et al., 2019), and peaking in pro-inflammatory cytokines prior to parturition to prepare for labor and delivery (Challis et al., 2009). Therefore, deviations from healthy maternal inflammatory patterns of cytokines can pose risk for fetal neurodevelopment (Camerota et al., 2022; Han et al., 2021; Zhang et al., 2020). Relatedly, prenatal maternal inflammation (PNMI) has been proposed as one mechanism by which *in utero* exposures can predispose offspring to the development of depression and related psychopathology in both animal and human models (Babri et al., 2014; Gilman et al., 2016; Majidi-Zolbanin et al., 2015; Morelli et al., 2015; Ronovsky et al., 2016). Importantly, higher levels of inflammatory cytokines and chemokines have been repeatedly associated with other prenatal risk factors linked to offspring depression, such as environmental pollutants (Margolis et al., 2022), infections (Ashdown et al., 2006) and maternal psychosocial stress (Zhang et al., 2020) (see Kwon et al., 2022 for review). Moreover, there is evidence that some cytokines (e.g., IL-6 and TNF-α) can cross the blood placental barrier in humans, directly influencing fetal development (Aaltonen et al., 2005; Zaretsky et al., 2004). Hence, proinflammatory cytokines may be one mechanism by which a variety of prenatal risk factors facilitate the maternal–fetal transmission of vulnerability to depression among offspring (Shi et al., 2005; Wu et al., 2021).

Summarized by several empirical reviews, animal models have provided strong support of the connection between prenatal maternal immune activation (MIA) and offspring depressive behaviors (e.g., anhedonia, decreased exploration or increased threat sensitivity) (Conway & Brown, 2019; Gumusoglu & Stevens, 2018; Ronovsky et al., 2016). For example, induction of MIA in mice has demonstrated a depression-like behavioral phenotype in adult offspring, including long-term deficits in cognition (Khan et al., 2014; Reisinger et al., 2016).

In human research, PNMI models have been investigated in the onset of offspring psychiatric disorders like schizophrenia (Ashdown et al., 2006; Babulas et al., 2006; Brown, 2006), yet far less is known about its relationship with offspring depression (Mac Giollabhui et al., 2019). Our team has found that higher second trimester (T2) interleukin (IL)-6 was directly and significantly associated with higher depressive symptoms in adolescence (Lipner et al., 2024). In addition, our previous findings demonstrated that higher T2 IL-1 receptor antagonist (IL-1RA) is directly and significantly associated with higher child internalizing symptoms (Mac Giollabhui et al., 2019), a symptom cluster commonly linked with risk for depression later in development (Vacaru et al., 2022). Others have found *decreased* odds of major depressive disorder (MDD) in adults exposed to high maternal TNF-α averaged across pregnancy (Gilman et al., 2016). Yet, this same study also found that a higher proinflammatory state during pregnancy, measured by an interaction of TNF-α and IL-10, is associated with increased risk for MDD in males and a decreased odds in females (Gilman et al., 2016). There appears to be a general trend supporting an association between multiple cytokine markers of PNMI and offspring depressive symptoms, suggesting further exploration of potential developmental pathways to depressive outcomes is warranted.

One possible developmental pathway between PNMI and offspring depressive symptoms could be through childhood cognitive abilities. Yet, although the research on PNMI and depression is strong, to date, evidence for the link between PNMI and childhood cognitive abilities is relatively new and mixed. Some studies of early cognitive abilities reported that higher prenatal maternal concentrations of cytokines, including averaged IL-6, third trimester (T3) C-reactive protein (CRP), and T3 TNF-α, were associated with poorer general cognitive ability and working memory as measured by the Bayley Scales of Infant Development as early as six months old (Camerota et al., 2022; Rasmussen et al., 2019). Other studies have documented opposite findings, in which heightened PNMI may be protective and associated with *enhanced* cognitive abilities in children (Dozmorov et al., 2018; von Ehrenstein et al., 2012). In addition, several studies have found no association between PNMI and cognitive abilities in childhood (Ramsay et al., 2021; Andrews et al., 2008). Variations in findings may reflect the methodological inconsistencies in the PNMI-cognition literature, specifically pertaining to the specific cytokines examined and collection protocols (Estes & McAllister, 2016), timing of PNMI exposure, and cognitive outcome measures and the developmental time point at which they are assessed.

1.1. Timing of PNMI exposure

Previous studies suggest that understanding the differential effects of timing of PNMI exposure may clarify how PNMI contributes to childhood cognitive outcomes (Davis and Sandman, 2010; Lipner et al., 2024; Mac Giollabhui et al., 2019). In the animal literature of MIA, results appear to be time-dependent, with MIA later in gestation (corresponding to the human second trimester) associated with deficits similar to internalizing behaviors in humans in comparison to early gestational exposure (Babri et al., 2014). To date, human studies that examined multiple prenatal timepoints have documented differential effects on cognition based on trimester, with greater associations appearing in T2 and T3 compared to T1 (Morgan et al., 2020; Rudolph et al., 2018).

1.2. The current study

Taken together, findings suggest that lower cognitive performance is associated with later depressive symptoms in youth and possibly to prenatal risk factors implicated in higher levels of PNMI. As such, we

have reason to suspect that differences in aspects of cognitive functioning could be one pathway between PNMI and offspring depressive symptoms.

The present study examined the relationship between four biomarkers of PNMI in the first and second trimesters of pregnancy and a measure of receptive vocabulary, the Peabody Picture Vocabulary Test (PPVT), correlated with general intelligence, in child-aged offspring (ages 9–11). Furthermore, we examined whether PPVT scores mediate the relationship between PNMI and adolescent (ages 15–17) depressive symptomatology. As a critical period for the onset of depression, adolescence provides a key developmental window into depressive symptomatology . We hypothesized that: 1) Higher levels of PNMI biomarkers would be associated with lower PPVT scores in childhood; 2) Lower childhood PPVT would significantly and partially mediate the relationship between higher PNMI and higher depressive symptoms in adolescence; and 3) these associations will be specific to inflammation in the second trimester.

2. Materials and Methods

2.1. Description of cohort

Participants included mother-offspring dyads drawn from the prospective, longitudinal Child Health and Development Studies cohort (CHDS; N = 19,044 live births) (van den Berg et al., 1988). CHDS enrolled pregnant women seeking prenatal care under the Kaiser Permanente Health Plan (KFHP) while living in Alameda County, California, between the years of 1959 and 1966. At the time of recruitment, approximately 30 % of the population of Alameda County, which included the cities of Oakland, Berkeley, and Hayward, received care through KFHP.

CHDS has continued to follow these mothers and their offspring over multiple time points across development. Children in the CHDS born between 1960 and 1963 were initially invited to participate in the CHDS early childhood follow-up study (1972–1973), resulting in a total of 9,708 enrolled mother-offspring dyads. A total of 6,614 dyads were still residing in Alameda County when offspring were 9 years old and were invited to participate in a second follow-up study from ages 9–11 years old. A total of 3,737 dyads were enrolled in this follow-up. Of this subgroup, 2,020 dyads subsequently agreed to participate in the CHDS "Adolescent study" when offspring were 15–17 years old (1977–1979). In comparison to the original CHDS cohort, the adolescent study subgroup was shown to have a smaller proportion of firstborn offspring and a greater proportion of mothers who were 1) married and living with their partner at the original intake, 2) White, and 3) high school graduates, though these differences were small (van den Berg et al., 1988).

Current analyses drew from the 736 mother-offspring dyads from the adolescent study for whom archived maternal serum samples were analyzed from the first (T1) and/or second (T2) trimesters of pregnancy. Of these dyads, 40 offspring were missing depressive symptom data in adolescence, resulting in a final analytic sample of 696 mother-offspring dyads (see Table 1).

The research protocol and analyses were approved by the Institutional Review Boards (IRBs) at Temple University, University of California, Los Angeles, and the Public Health Institute. The initial recruitment of the CHDS cohort predated the ethical standards of the national and institutional committees on human experimentation and the Helsinki Declaration of 1975, as revised in 2008; however, all participants provided assent after receiving a complete description of the study.

2.2. Demographics variables

Detailed sociodemographic information was collected for all mothers primarily during the second trimester of pregnancy (mean gestation = 15.3 weeks, SD = 6.8 weeks). Maternal education was chosen as a proxy for socioeconomic status, as it had the most complete data of the available SES measures in this dataset and has been shown to be correlated with other, less complete measures of SES (e.g., annual household income) in prior studies of this cohort (Fineberg et al., 2016; Lipner et al., 2022; Mac Giollabhui et al., 2019). Maternal education also was used as a proxy for postnatal adversity (Schlotz and Phillips, 2009). Maternal education was categorized as "Did not complete High School," "Completed High School" *or* "Completed more than High School" and were dummy coded for analyses. At the time of the study creation (circa 1959), ethnicity was not separated from race nor was offspring sex examined with today's understanding of sex and gender identity. Race instead was categorized in this study as "White/Non-Hispanic," "Mexican/Hispanic," "Black" and "Asian." Offspring sex assigned at birth was categorized as "Male" or "Female".

Table 1
Demographic characteristics (N = 696).

	N	%	Mean	SD	Range
Maternal Variables					
Maternal race	696				
White	497	71.4			
Black	138	19.8			
Mexican/Hispanic	22	3.2			
Asian	39	5.6			
Maternal education	696				
< High school	69	9.9			
= High school	249	35.8			
> High school	378	54.3			
Maternal age at offspring birth (years)	695		28.8	5.8	18–47
Maternal parity	696		2.1	2.0	0–10
Pre-pregnancy BMI (kg/m^2)	623		22.3	3.6	15.8–40.4
Gestational age at blood draw (weeks)					
T1	612		12.2	2.6	5–23
T2	609		23.7	3.0	15–33
T1 PNMI (pg/mL)					
IL-6	643		4.3	26.2	0.05–500
IL-8	643		921	1729	2.5–18000
IL-1RA	600		597	556	89–3211
sTNF-RII	600		2717	725	759–7924
T2 PNMI (pg/mL)					
IL-6	649		3.2	12.1	0.1–197.6
IL-8	647		836	1612	2.5–16000
IL-1RA	616		539	383	89–3211
sTNF-RII	616		3107	762	1634–6808
Maternal depressive symptoms	657		14.7	3.3	8–26
Offspring Variables					
Biological sex	696				
Female	335	48.1			
Male	361	51.9			
Birthweight (oz.)	696		118.3	17.6	37–174
Gestational age at birth (weeks)	691		39.9	2.1	21–49
Child age	680		9.34	0.64	8–11
Childhood raw PPVT	680		80.6	10.44	55–128
Child standardized PPVT	680		51.8	9.8	24–94
Adolescent age	680		16.4	0.7	15–18
Adolescent depressive symptoms	696		23.5	5.3	14–41

Notes: Raw (non-transformed) biomarker values are presented above in pg/mL; due to limitations in serum volume in some archived maternal samples, biomarker assays were prioritized IL6 > IL8 > IL-1RA > sTNF-RII. Maternal depressive symptoms were measured at adolescent timepoint.
Abbreviations: PNMI = Prenatal Maternal Inflammation; PPVT = Peabody Picture Vocabulary Test; T1 = Trimester 1; T2 = Trimester 2; BMI = Body Mass Index; IL = interleukin; IL1-RA = IL-1 receptor antagonist; sTNF-RII = soluble TNF receptor II.

2.3. Prenatal maternal inflammation (PNMI)

Data for four biomarkers of PNMI in CHDS sera, generated as previously described (Mac Giollabhui et al., 2019), were included in present analyses: Interleukin-6 (IL-6), IL-8, IL-1 receptor antagonist (IL-1RA)

and soluble tumor necrosis factor receptor-II (sTNF-RII). PNMI concentrations are reported in picograms per milliliter (pg/mL). The study team originally selected these PNMI biomarkers for analyses due to 1) detectability in CHDS serum samples and 2) documented clinical relevance to outcomes associated with offspring psychopathology. Specifically, all four of these biomarkers have unique roles in the maintenance of human pregnancy and are shown to influence fetal neurodevelopment, the placenta, and regulation of gestation that may lead to premature birth when dysregulated (Yockey & Iwasaki, 2018). For instance, IL-6 is a pro-inflammatory cytokine mediating the acute phase response, as well as an anti-inflammatory myokine (Pal et al., 2014). IL-8 is a pro-inflammatory chemokine produced by a variety of tissue and blood cells, with distinct target specificity for the neutrophils in inflammatory regions (Bickel, 1993). sTNF-RII and IL-1RA are valid and reliable estimates of TNF-α and IL-1β activity respectively due to their greater measurement stability in frozen serum and smaller diurnal variation (Liu et al., 2007). Moreover, sTNF-RII and IL-1RA are present at much higher concentrations in maternal sera than their respective cytokines, increasing the consistent detectability of cytokine activity (Diez-Ruiz et al., 1995; Irwin et al., 2007). TNF-α is a pro-inflammatory cytokine that regulates many facets of macrophage function (Jang et al., 2021). Similarly, IL-1β is a pro-inflammatory cytokine and important mediator of the inflammatory response, involved in a variety of cellular activities, including cell proliferation, differentiation, and apoptosis (Yaseen et al., 2023).

Biomarker assays were conducted on archived CHDS prenatal T1 and T2 sera of 737 mothers using high-sensitivity (IL-6, IL-8) and regular sensitivity (sTNF-RII, IL-1RA) ELISAs (R&D Systems, Inc., Minneapolis, MN). Inter-assay correlation coefficients were less than 9 % and mean intra-assay correlation coefficients less than 4 % for all assays. Further details about sample storage, assay specifications, and biomarker selection can be found in Lipner et al. (2024).

2.4. Peabody Picture vocabulary Test (PPVT)

At the child's age 9–11-year visit (sample mean age = 9.67 years, SD = 0.70 years), children completed the Peabody Picture Vocabulary Test 1st Edition (PPVT-1), administered by a trained assessor. The PPVT is a validated receptive vocabulary measure that can be administered to individuals aged 2.5 years old and above (Dunn, 1958). The PPVT-1 (referred from here on out as PPVT) consists of 175 stimulus words and 175 corresponding images. It has high test–retest reliability (>0.90) and does not require reading, writing or verbal responses.

Although a measure of receptive vocabulary, the PPVT has been shown to be correlated with general intelligence (Lezak et al. 2004). Further, vocabulary subtests have been shown to be one of the best cognitive correlates of general mental ability ("g") (Jensen, 2001). For example, in the national standardization study of the Wechsler Intelligence Scales for Adults (WAIS), vocabulary had the largest "g" loading of the eleven subtests (0.87) (Jensen, 2001). Further, the PPVT has been significantly positively correlated with the WISC-R Full Scale IQ (0.77), Verbal IQ (0.71) and Performance IQ (0.74) (Altepeter, 1989). As such, the PPVT has been used as an approximation for general intelligence in several past studies (Castellino et al., 2011; Krasileva et al., 2017; Maxwell et al., 2018). Thus, in the current study, PPVT was used to understand general cognitive performance, with the added caution that the PPVT is a receptive vocabulary measure by design.

The sample's raw scores approximated national norms in terms of distributions. Raw PPVT scores were standardized by the age, race and sex of the full sample pool of 3,737 children at the age 9–11 years visit, standardized to a mean of 50 and a standard deviation of 10, using the following formula, rounded to the nearest whole integer: $\left(\left(\frac{X_i-\overline{X}}{StdDevX}*10\right)+50\right)$, where X_i is an individual's raw PPVT, $\overline{X}$ is the mean of the PPVT for a given age, race and sex group, and *StdDevX* is the standard deviation of the mean for a given age, race and sex group (Maxwell et al., 2018). Group means and standard deviations also were respectively pulled from the full sample pool of 3,737 children at the age 9–11 years visit. One standard deviation on either side of the mean is considered within average cognitive performance. This standardization method has been utilized by previously published CHDS studies (Maxwell et al., 2018). Of note, the PPVT was standardized by race to mitigate the known implicit racial biases of the original version of the PPVT (Dunn, 1958), similar to that of other cognitive tests during the study time period (Halpin et al., 1990; Miele, 1979). In the current sample, 680 offspring had childhood PPVT data, with childhood standardized PPVT ranging from 24 to 94 points [mean (SD) = 51.8 (9.8) points].

2.5. Adolescent depressive symptoms scale

At the adolescent (ages 15–17) study visit, adolescent (sample mean age = 16.4 years, SD = 0.7 years) participants completed a self-report inventory regarding their lives, mood, and personal beliefs, including depression symptom items. The adolescent depression symptom scale drew from this questionnaire, including 14 items related to primarily cognitive symptoms of depression (e.g., feelings of worthlessness, inadequacy, failure) on a 4-point Likert scale. Responses to these items were summed and examined continuously, with possible scores ranging from 14 to 60. See supplementary materials for the full scale (Methods s1).

The internal consistency of the depression scale is high (Cronbach's α = .81) (Murphy et al., 2017). The scale also demonstrated excellent predictive validity to major depressive disorder (MDD) diagnoses using the Structured Clinical Interview for DSM-IV-TR Disorders at a 20–30-year-old follow-up of these offspring (First et al., 1994). Specifically, offspring who received a diagnosis of MDD had significantly higher depressive scores during adolescence compared to those who did not receive a diagnosis (p = 0.04, Cohen's d = 0.62) (First et al., 1994). Previously published CHDS studies have found this scale of depression symptomatology demonstrated high concurrent validity (Maxwell et al., 2018, Murphy et al., 2017; Lipner et al., 2022). See Murphy et al. (2017) for more details on the adolescent depression symptoms scale. In the current sample, 696 offspring had depressive symptoms data, with depressive symptom scores ranging from 14 to 41 points [mean (SD) = 23.5 (5.3) points].

2.6. Analytic Plan

All analyses were conducted in SPSS (v24). The dependent variable (adolescent depressive symptoms) was examined for normality statistically, by examining skewness and kurtosis values, and visually, through inspection of graphic representations of these data. Similar to other inflammatory studies (e.g., Mac Giollabhui et al., 2019), all biomarkers were natural log-transformed due to skewness. PNMI biomarkers were analyzed separately rather than as a total PNMI composite score due to the pleiotropic nature of cytokines (e.g., the ability of one cytokine to exhibit diverse functions) (Moriarity et al., 2021), which is particularly important to recognize in the changing inflammatory milieu of pregnancy.

Bivariate analyses using Pearson correlations were conducted to determine whether significant relationships existed between the main PNMI independent variables, the potential mediator (childhood PPVT), and the dependent variable (adolescent depressive symptoms). We also used Pearson correlations to test whether the potential mediator (childhood PPVT) was associated with the dependent variable (adolescent depressive symptoms) (Baron & Kenny, 1986).

Maternal education was included in adjusted analyses as a covariate due to the importance of accounting for a proxy for postnatal adversity in perinatal work. Other potential covariates—maternal age at offspring birth, pre-pregnancy maternal body mass index (BMI), maternal depressive symptoms at adolescent time point, parity and fetal

sex—were identified as variables with sufficient theoretical link to the proposed analyses and only were included in adjusted analyses if they were significantly associated with both the independent and dependent variables.

In the first set of analyses, hierarchical linear regressions were conducted for each inflammatory biomarker predicting to PPVT in separate models. Next, mediation analyses were run between PNMI, childhood PPVT, and adolescent depressive symptoms. The mediation regression models were estimated utilizing the Hayes SPSS Process v3.3 macro for simple mediation (Hayes, 2013), controlling for covariates, to assess for indirect effects of child PPVT on PNMI and adolescent depressive symptoms. Bootstrapped standard errors (based on 500 samples) were used to conduct the above analyses. Significant mediation was determined by confidence intervals, such that if the confidence interval did not include zero, it indicates that the parameter was statistically significant. All model results were examined for evidence of regression assumptions, including linearity, homoscedasticity, independence between observations, and normality of residuals.

3. Results

3.1. Descriptives and Bivariate correlations

Demographics and raw mean scores for clinical characteristics are displayed in Table 1, and bivariate correlations are reported in Table 2. Of note, on average, concentrations of IL-6, IL-8 and IL-RA decreased from T1 to T2, whereas sTNF-RII increased from T1 to T2 in this sample, similar to other healthy pregnant samples (Abu-Raya et al., 2020; Aghaeepour et al., 2017; Morelli et al., 2015). Additionally, of the potential covariates, only maternal education was included in regression models. No significant associations were observed between fetal sex and PNMI in either trimester in addition to childhood PPVT and adolescent depressive symptoms. See Table 1 for more details. Albeit not within the scope of this manuscript, fetal gestational age (in weeks) at maternal blood draw was not correlated with most reported biomarkers in this sample; rather, only T1 sTNF-RII was weakly correlated with gestational age (data not shown). Despite lacking associations with both the IV and/or DV in the model, we have provided additional adjusted analyses in supplementary tables based on theoretical associations; these analyses were adjusted for: 1) maternal education, 2) maternal depression, and 3) parity (see supplementary materials). Further, we also have provided two additional supplemental tables to adjust for annual household income rather than maternal education as our SES/postnatal adversity covariate in our main analyses (see supplementary tables S5 and S6).

There were no statistically significant associations between T1 PNMI and childhood PPVT nor adolescent depressive symptoms. A significant negative association was observed between T2 IL-1RA and T2 IL-6 and childhood PPVT ($r = -0.13, p < 0.01, r = -0.09, p < 0.05$ respectively). In addition, T2 IL-6 was significantly associated with adolescent depressive symptoms ($r = 0.09$, $p < 0.05$). No other statistically significant associations were found between T2 PNMI and childhood PPVT nor adolescent depressive symptoms.

3.2. Hierarchical linear regressions

Adjusted and unadjusted hierarchical regression analyses, predicting to childhood PPVT, are presented in Table 3. Adjusted regressions controlled for maternal education at offspring birth as a proxy measure for postnatal adversity (Schlotz and Phillips, 2009). No significant associations were found between T1 PNMI and childhood PPVT in both the adjusted and unadjusted regression models. Of the T2 PNMI measures, T2 IL-6 and T2 IL-1RA were significantly associated with childhood PPVT prior to adjusting for maternal education. With the addition of maternal education, only T2 IL-1RA remained significantly associated with childhood PPVT (b = -0.21, SE = 0.08, $p = 0.01$).

Table 2
Bivariate Correlations.

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. Childhood PPVT	1															
2. Adolescent depressive symptoms	−0.14**	1														
3. Offspring sex	0.01	0.03	1													
4. Maternal education	0.25**	−0.07	0.84	1												
5. Maternal age at enrollment	0.14**	−0.06	<-0.01	0.07	1											
6. Maternal depressive symptoms	−0.02	0.15**	−0.09*	−0.05	0.09*	1										
7. Pre-pregnancy BMI	−0.04	−0.01	−0.03	−0.15**	0.20**	.03	1									
8. Parity	−0.13**	0.03	−0.03	−0.20**	0.50**	0.05	0.24**	1								
9. T1 IL-8	0.03	−0.04	−0.02	<0.01	<-0.01	−0.04	0.01	<-0.01	1							
10. T1 IL-1RA	0.02	−0.03	0.03	<0.01	0.02	−0.03	0.08	0.09*	0.29**	1						
11. T1 IL-6	−0.04	−0.03	<-0.01	−0.07	0.04	0.02	0.15**	0.1**	0.49**	0.43**	1					
12. T1 sTNF-RII	−0.02	−0.04	−0.04	<-0.01	0.02	−0.04	0.09*	0.07	0.21**	0.41**	0.27**	1				
13. T2 IL-8	<0.01	0.03	0.02	−0.04	−0.02	0.01	−0.03	0.01	0.13**	<-0.01	0.04	0.04	1			
14. T2 IL-1RA	−0.13**	0.03	0.02	−0.11**	−0.04	<-0.01	0.11**	0.04	−0.01	0.41**	0.07	0.24**	0.36**	1		
15. T2 IL-6	−0.09*	0.09*	<-0.01	−0.15**	<-0.01	0.06	0.13**	0.07	−0.04	−0.05	0.09*	0.04	0.49**	0.40**	1	
16. T2 sTNF-RII	−0.05	−0.02	0.05	<0.01	−0.03	−0.01	0.02	−0.03	0.11*	0.17**	0.08	0.52**	0.18**	0.37**	0.24**	1

Notes: * Indicates $p < 0.05$, ** indicates $p < 0.01$; PNMI variables are natural log-transformed. PPVT scores were standardized. Childhood = Age 9–11 timepoint; Adolescent = Age 15–17 timepoint; Maternal education reference category: < High School; Maternal depressive symptoms measured at adolescent timepoint. Ns for correlations reflect Ns reported in Table 1.
Abbreviations: PNMI = Prenatal Maternal Inflammation; PPVT = Peabody Picture Vocabulary Test; T1 = Trimester 1; T2 = Trimester 2; BMI = Body Mass Index; IL = interleukin; IL1-RA = IL-1 receptor antagonist; sTNF-RII = soluble TNF receptor II.

Table 3
PNMI predicting to childhood standardized PPVT.

	Outcome: Standardized childhood PPVT (Ages 9 – 11)			
	Adjusted (Maternal education)		Unadjusted	
	Beta (SE)	p-value	Beta (SE)	p-value
T1 PNMI				
IL-6	−0.03 (0.04)	0.54	−0.04 (0.04)	0.33
IL-8	0.02 (0.02)	0.42	0.02 (0.02)	0.43
IL1-RA	0.02 (0.07)	0.73	0.03 (0.07)	0.73
sTNF-RII	−0.05 (0.16)	0.75	−0.06 (0.16)	0.70
T2 PNMI				
IL-6	−0.06 (0.05)	0.22	−0.10 (0.05)	0.03*
IL-8	0.01 (0.03)	0.73	0.003 (0.03)	0.92
IL1-RA	−0.21 (0.08)	0.01*	−0.27 (0.09)	0.002**
sTNF-RII	−0.20 (0.17)	0.24	−0.20 (0.18)	0.27

Notes: * Indicates p < .05, ** indicates p < .01. Unstandardized betas reported. PNMI variables are natural log-transformed. PPVT scores were standardized. Childhood = Age 9–11 timepoint; Adolescent = Age 15–17 timepoint; Maternal education reference category: < High School.
Abbreviations: PNMI = Prenatal Maternal Inflammation; PPVT = Peabody Picture Vocabulary Test; T1 = Trimester 1; T2 = Trimester 2; IL = interleukin; IL1-RA = IL-1 receptor antagonist; sTNF-RII = soluble TNF receptor II.

3.3. Mediation models

Mediation results are shown in Tables 4 and 5, controlling for maternal education (see supplementary Tables 1 and 2 for the unadjusted mediation model results). In the adjusted analyses, a direct effect was observed between lower childhood PPVT and higher depressive symptoms in adolescence (b = -0.07, SE = 0.02, t = -2.99, p < 0.01). Of the PNMI measures, results demonstrated a direct effect of higher T2 IL-6 on increased depressive symptoms in adolescence approaching significance (b = 0.05, SE = 0.03, t = 1.96, p = 0.05). However, the indirect effect of childhood PPVT on T2 IL-6 and adolescent depressive symptoms was not significant. Higher T2 IL1-RA also was significantly associated with lower PPVT scores (b = -0.21, SE = 0.08, t = -2.55, p = 0.01), but not with depressive symptoms. Finally, there was a significant indirect effect of T2 IL-1RA on adolescent depressive symptoms via childhood PPVT (b = 0.03, 95 % CI = 0.002–0.03) indicating a partially mediated effect. No other significant results were found.

Table 4
Mediation analysis of T1 PNMI and adolescent depressive symptoms via childhood standardized PPVT (adjusted for maternal education).

Model	Path Estimates	b(SE)	LLCI	ULCI	p
T1 IL-6	T1 IL-6 → PPVT (a)	−0.03 (0.04)	−0.11	0.06	0.54
	PPVT → Dep (b)	−0.07 (0.02)	−0.11	−0.02	0.004**
	T1 IL-6 → Dep (c')	−0.02 (0.02)	−0.07	0.03	0.41
	Indirect Effect (a*b)	0.002 (0.003)	−0.004	0.01	–
T1 IL-8	T1 IL-8 → PPVT (a)	0.02(0.02)	−0.03	0.06	0.42
	PPVT → Dep (b)	−0.07 (0.02)	−0.11	−0.02	0.005**
	T1 IL-8 → Dep (c')	−0.01 (0.01)	−0.04	0.01	0.42
	Indirect Effect (a*b)	−0.001 (0.002)	−0.005	0.002	–
T1 IL-1RA	T1 IL-1RA → PPVT (a)	0.02(0.07)	−0.11	0.16	0.73
	PPVT → Dep (b)	−0.05 (0.02)	−0.10	−0.003	0.04*
	T1 IL-1RA → Dep (c')	−0.02 (0.04)	−0.10	0.06	0.63
	Indirect Effect (a*b)	−0.001 (0.004)	−0.01	0.01	–
T1 sTNF-RII	T1 sTNF-RII → PPVT (a)	−0.05 (0.16)	−0.36	0.26	0.75
	PPVT → Dep (b)	−0.05 (0.02)	−0.10	−0.004	0.04*
	T1 sTNF-RII → Dep (c')	−0.08 (0.09)	−0.25	0.10	0.40
	Indirect Effect (a*b)	0.003(0.01)	−0.01	0.02	–

Notes: * Indicates p < .05, ** indicates p < .01. PNMI variables are natural log-transformed. PPVT scores were standardized. Childhood = Age 9–11 timepoint; Adolescent = Age 15–17 timepoint; Maternal education reference category: < High School.
Abbreviations: SE = standard error; LLCI = lower limit confident interval, ULCI = upper limit confident interval; PNMI = Prenatal Maternal Inflammation; PPVT = Peabody Picture Vocabulary Test; T1 = Trimester 1; T2 = Trimester 2; IL = interleukin; IL1-RA = IL-1 receptor antagonist; sTNF-RII = soluble TNF receptor II.

Table 5
Mediation analysis of T2 PNMI and adolescent depressive symptoms via childhood standardized PPVT (adjusted for maternal education).

Model	Path Estimates	b(SE)	LLCI	ULCI	p
T2 IL-6	T2 IL-6 → PPVT (a)	−0.06 (0.05)	−0.15	0.03	0.22
	PPVT → Dep (b)	−0.07 (0.02)	−0.11	−0.02	0.003**
	T2 IL-6 → Dep (c')	0.05(0.03)	<0.001	0.10	0.05*
	Indirect Effect (a*b)	0.004 (0.004)	−0.003	0.01	–
T2 IL-8	T2 IL-8 → PPVT (a)	0.01(0.03)	−0.04	0.06	0.73
	PPVT → Dep (b)	−0.07 (0.02)	−0.11	−0.03	0.002**
	T2 IL-8 → Dep (c')	0.01(0.01)	−0.02	0.04	0.45
	Indirect Effect (a*b)	−0.001 (0.002)	−0.004	0.003	–
T2 IL-1RA	T2 IL-1RA → PPVT (a)	−0.21 (0.08)	−0.38	−0.05	0.01**
	PPVT → Dep (b)	−0.06 (0.02)	−0.11	−0.02	0.006**
	T2 IL-1RA → Dep (c')	0.03(0.05)	−0.07	0.12	0.59
	Indirect Effect (a*b)	0.01(0.01)	0.002	0.03	–
T2 sTNF-RII	T2 sTNF-RII → PPVT (a)	−0.20 (0.17)	−0.54	0.14	0.24
	PPVT → Dep (b)	−0.07 (0.02)	−0.11	−0.02	0.005**
	T2 sTNF-RII → Dep (c')	−0.02 (0.10)	−0.21	0.17	0.84
	Indirect Effect (a*b)	0.01(0.01)	−0.008	0.05	–

Notes: * Indicates p < .05, ** indicates p < .01. PNMI variables are natural log-transformed. PPVT scores were standardized. Childhood = Age 9–11 timepoint; Adolescent = Age 15–17 timepoint; Maternal education reference category: < High School.
Abbreviations: SE = standard error; LLCI = lower limit confident interval, ULCI = upper limit confident interval; PNMI = Prenatal Maternal Inflammation; PPVT = Peabody Picture Vocabulary Test; T1 = Trimester 1; T2 = Trimester 2; IL = interleukin; IL1-RA = IL-1 receptor antagonist; sTNF-RII = soluble TNF receptor II.

4. Discussion

To our knowledge, the present study is the first to isolate a pathway to adolescent depressive symptoms via childhood cognitive performance from fetal exposure to PNMI. As depression is a heterogeneous syndrome with a complex etiology, global cognitive impairments, as measured here by childhood PPVT, may represent one potential mechanism that, combined with PNMI, can help predict adolescent depressive symptoms. Additionally, this is the first study to demonstrate a significant direct effect of T2 IL-1RA on a measure of child receptive vocabulary correlated with general intelligence. Moreover, our results uniquely documented lower childhood PPVT as a potential risk factor for elevated

depressive symptoms in adolescence. Our mediation model also demonstrated a novel indirect effect of T2 IL-1RA on adolescent depressive symptoms via lower child cognitive abilities that remained significant even when controlling for maternal education.

Notably, there was *no* significant direct effect of T2 IL-1RA on adolescent depressive symptoms. As such, lower childhood cognitive performance may act as a potential mediator in the cascade of risk from T2 IL-1RA to adolescent depressive risk. Our team and others have hypothesized that subtle changes following an adverse fetal exposure could be a risk factor for a cascade of developmental difficulties triggered by the prenatal event (Ellman et al., 2018; Lipner et al., 2019). In line with this framework, our results suggest that PNMI alone may not be sufficient to directly increase risk for youth depression, and rather may act as a neurodevelopmental disorder primer, exerting compounding effects throughout brain development and resulting in early intermediate phenotypes. This argument is substantiated by recent findings that higher second trimester IL-1RA is associated with higher child internalizing symptoms, an additional childhood risk factor for adolescent depression and related disorders (Mac Giollabhui et al., 2019). Current immune models argue that it is likely a combination of genetic predisposition/other biological vulnerabilities and environmental stressors during childhood and adolescence (e.g., postnatal stress and adversity) that combine with the sequalae of higher PNMI exposure to increase the likelihood of offspring developing psychiatric disorders (Estes & McAllister, 2016).

Although we documented an indirect pathway from T2 IL-1RA to adolescent depressive symptoms through childhood PPVT, we instead found a *direct* pathway between T2 IL-6 and adolescent depressive symptoms, replicating findings from Lipner and colleagues (2024). This being said, it should be noted that the relationship between T2 IL-6 and adolescent depressive symptoms was no longer statistically significant ($p = 0.05$ to 0.11) when adjusting for theoretically-based (adjusted for maternal education, maternal depression, and parity) (supplemental Table S4) rather than statistically-based covariates (adjusted only for maternal education) and we encourage further exploration of this relationship by other researchers. Sparse literature exists on potential biological mechanisms behind why IL-6 and IL-1RA may operate through direct and indirect pathways respectively, despite IL-6 and IL-1β, being among the most studied PNMI (Gumusoglu & Stevens, 2018). IL-6 consistently has been related to depression among postnatal and non-pregnant samples (Ting et al., 2020), hypothalamic–pituitary–adrenal (HPA) axis functioning (Bethin et al., 2000), and is known to cross the human placenta (Zaretsky et al., 2004), On the other hand, IL-1RA is also linked to depression in the literature, but through intermediate phenotypes, such as internalizing symptoms (Mac Giollabhui et al., 2019). Consequently, one possibility is that T2 IL1-RA may impact more specific brain regions related to cognition and affect regulation at earlier stages in development. Future studies are needed to understand the mechanism underlying these new findings.

In the current study, we documented that higher T2 IL1-RA was directly associated with lower PPVT scores. IL-1RA is the receptor antagonist of interleukin-1 beta (IL-1β), member of the interleukin-1 family, and peripheral proinflammatory cytokine (Tsai, 2017). Elevated IL-1β has been extensively implicated in risk for cognitive impairments across species and lifespan (Huang & Sheng, 2010), potentially due to the cytokine's pleiotropic effects on neuroinflammation, neural plasticity, and neurogenesis (Tsai, 2017). Only one human study has attempted to explore and successfully document the relationship between higher IL-1β in pregnancy and lower generalized cognition in early childhood (e.g., General Conceptual Abilities) (Dozmorov et al., 2018). The interleukin-1 receptor antagonist (IL-1RA), also a member of the interleukin-1 family with the capability to bind to IL-1 receptors (Arend et al., 1998), has been shown to potentially be a more valid and reliable estimate of IL-1β activity in pregnancy because it is present at much higher concentrations in maternal sera than IL-1β itself, increasing the consistent detectability of cytokine activity (Diez-Ruiz et al., 1995; Irwin et al., 2007). Because of this, our findings not only reinforce and strengthen the link between fetal exposure to maternal IL-1 family cytokines and cognition, but also extend past associations into later childhood.

Interestingly, *prior* to controlling for maternal education, second trimester interleukin-6 (T2 IL-6) also was directly associated with childhood PPVT. The loss of statistical significance of T2 IL-6 on childhood PPVT with the addition of maternal education, used in this model as an approximation for both maternal socioeconomic status (SES) and pre- and postnatal adversity (Fineberg et al., 2016; Lipner et al., 2022; Mac Giollabhui et al., 2019; Schlotz and Phillips, 2009), indicates that the relationship of T2 IL-6 and lowered cognition in childhood could partially be explained by contextual socioeconomic and adversity-related factors that build in potency over development (Anglin et al., 2021). Similarly, steeper increases in maternal IL-6 over the course of pregnancy have been previously explained, in part by, lower SES (Ross et al., 2022), potentially placing these offspring at greater risk for altered neurodevelopment. Nonetheless, our adjusted results are limited by the lack of a more current, precise measurement of SES and postnatal exposure to environmental stressors [e.g., adverse childhood experiences (ACES)]: a necessary improvement for future studies.

Notably, the correlations found between T2 IL-1RA and IL-6 and childhood PPVT were −0.13 and 0.09 respectively, suggesting that they explain a small amount of variance in PPVT scores; however, it is important to note that effect sizes for prenatal findings are often small and that small effect sizes can still be meaningful when considering complex etiologies (Ellman et al., 2018). Within a developmental trajectory framework, PNMI is likely only one pathway by which offspring may be at risk for lowered PPVT in childhood. Moreover, animal and human studies have documented the potential role of prenatal IL-1RA and IL-6 in the emergence of offspring cognition and neurodevelopment (Adelantado-Renau et al., 2020; Barlati et al., 2022; Smith et al., 2007; Zhang et al., 2020). The consistency between our results and previous studies reduces the likelihood that our findings are due to chance. Nonetheless, given that eight analyses were conducted, there is the potential risk of Type I error, and we encourage other researchers to replicate our results.

Although interleukin-8 (IL-8) and soluble tumor necrosis factor receptor-II (sTNF-RII) were not directly associated with PPVT outcomes in offspring in this sample, exposure to higher levels of IL-8 and sTNF-RII in both the prenatal period (Rasmussen et al., 2019) and adulthood (Marsland et al., 2006) have been connected to cognitive impairments and related neurodevelopmental risk factors, including variation in frontolimbic white matter, memory, and executive function. Further, the current status of PNMI research is only beginning to tap the surface of the neurobiological mechanisms and sequelae of abnormally elevated PNMI exposure in cognitive outcomes (Morgan et al., 2020; Zhang et al., 2020). For instance, some evidence exists for the maternal–fetal transfer of IL-6 and TNF-α across the placenta (Zaretsky et al., 2004), thereby directly influencing the fetal immune environment; yet, we do not know if other maternal cytokines, like IL-1β, can cross the placental barrier, or if and how their presence indirectly alters the fetal environment (Aaltonen et al., 2005). Consequently, although we did not uncover a direct relationship between IL and 8 or sTNF-RII and childhood PPVT or adolescent depressive symptoms, it is possible that other, more indirect pathways will emerge with future efforts.

Our findings reflected a significant relationship between lower PPVT in childhood and greater depressive symptoms in adolescence. Studies of adolescents with depression have substantially and consistently shown evidence of functional impairment in various cognitive and social domains (Kovacs & Goldston, 1991), yet the concept that lower cognitive performance may *precede* depressive symptoms is less studied (Scult et al., 2017). Some have suggested that lower cognitive performance may contribute to depression risk by disrupting the cognitive processes needed for coping with stress (Evans et al., 2016). As such, our findings may further substantiate the possibility that lower child cognitive

performance presents as one mediator of emerging depressive symptoms for some individuals. Notably, a recent *meta*-analysis examining the association between cognitive function and subsequent depression concluded that research on this trajectory is complicated by the presence of concurrent depression symptoms at the time of cognitive assessment (Scult et al., 2017), which we did not measure. Nonetheless, our findings add to a growing body of literature on early cognitive function and subsequent depression outcomes.

4.1. Timing of PNMI exposure

In our study, we identified that only T2 PNMI, and not T1, was associated with childhood PPVT and adolescent depression symptoms. As stated earlier, mid-to-late gestation is a critical period for fetal brain myelination and synaptogenesis (Graham et al., 2021), suggesting that early cognitive pathways may be at heightened vulnerability to PNMI in T2. Several other studies examining multiple trimesters also have found significant T2 findings, including heightened T2 IL1-RA with increased childhood internalizing symptoms (Mac Giollabhui et al., 2019) and heightened T2 IL-6 with adolescent depressive symptoms (Lipner et al., 2024). Similarly, studies of prenatal infection, a prominent source of PNMI, have found interactions of T2 infection and cortisol as well as T2 infection and prenatal maternal stress with depressive symptoms in adolescence (Lipner et al., 2022; Murphy et al., 2017), further providing evidence of the predominant influences of later gestation on depression risk. More research is needed to understand the complex role of timing of PNMI exposure in cognitive development.

4.2. Strengths and Limitations

This study had several important strengths. First, our sample utilized a large, prospective cohort of pregnant women. The longitudinal nature of our study also allowed for the analysis of PNMI sequalae nearly two decades after pregnancy. Second, our study was enhanced by the precision of the selected PNMI indices (e.g., robust proxies of both TNF-α and IL1-β), and the serological assessment of PNMI, with levels of biomarkers in CHDS samples that were similar to those obtained in current laboratory quality control samples (Mac Giollabhui et al., 2019), demonstrating no evidence of serological degeneration in these analytes despite the age of the CHDS sera. Likewise, our study benefited from the multi-informant nature of our analyses, including analytes, reporter-administered cognitive performance, and adolescent-reported outcome.

Potential limitations of our study are important to consider. First, as our sample was seeking prenatal care under KFHP while living in a socio-economically diverse county of California, between the years of 1959 and 1966, our results may have limited generalizability to present day cohorts with different demographic and cultural characteristics. Second, results were limited by the scope of the childhood cognitive measure used; as a measure of receptive vocabulary, the PPVT is only correlated with general intelligence (Maxwell & Wise, 1984), and our study may have been strengthened by a more comprehensive measure of general intelligence. Similarly, our self-report depressive symptoms questionnaire only addressed cognitive symptoms of depression, such as feelings of hopelessness or worthlessness. Therefore, it is difficult to know whether our findings generalize to other domains of depressive symptoms. This being said, in CHDS previous studies, we found that our depressive symptoms measure in adolescence predicted later depression diagnoses (Murphy et al., 2017). Moreover, in the existing literature, subthreshold levels of depressive symptoms during adolescence have been shown to be clinically relevant and predictive of later depressive disorder onset (Fergusson et al., 2005; Noyes et al., 2022). Due to the time period of data collection preceding the publication of DSM-III that included formal diagnostic criteria by nearly 20 years, this study could not utilize contemporary, so-called "gold-standard" measures of psychological outcomes. Further, although all of our sample's pregnant individuals identified as female and mothers, potentially due to the sociopolitical constraints of the time period, we acknowledge that our results are limited by our binary operationalization of gender. Finally, due to the increase of PNMI prior to labor, it can be difficult to reliably observe differences in PNMI across individuals in the third trimester (Christiaens et al., 2008); for this reason, our study team chose to not conduct serological analyses of T3 and therefore cannot extend our findings into later pregnancy.

This study also did not examine potential sources of heightened PNMI in our sample, and consequently cannot disregard the impact of these factors on our results. It is outside of the scope of the study to examine causal sources of PNMI, as elevated PNMI can be triggered by vast, interacting prenatal factors, including obesity, infection, sleep disruption, preeclampsia, environmental pollutants or toxins, low socioeconomic status, maternal psychosocial stress, and/or genetic predisposition (Han et al., 2021). However, the effect sizes for these perinatal risk factors are notably small, as in line with other perinatal studies, and are only one piece of the developmental narrative of depression etiology (Ellman et al., 2018). Postnatal events and environments—such as parental psychosocial stress, peer relationships, and parenting styles—may partially explain the associations found, as they have been shown to either buffer or exacerbate the consequences of early perinatal factors on offspring psychopathology depending on the context and study (Bush et al., 2017; Koo et al., 2003). This being said, in related CHDS studies, maternal worries during the offspring's childhood were not associated with adolescent depressive symptoms (Mac Giollabhui et al., 2019; Murphy et al., 2017).

4.3. Future Directions

We have several suggestions to enhance PNMI research on neurodevelopmental and youth psychiatric outcomes. To begin, improvement in methodological considerations for the complex shifting immune functioning in pregnant woman are warranted; specifically, markers of cytokine activity that can be measured more reliably in serum than the cytokines that induce their production, such as IL-1RA and sTNF-RII, may be more strongly suited than their cytokine counterparts to pregnancy research. Additionally, investigation of the sources of inflammation is necessary in order to develop intervention strategies during pregnancy that could reduce inflammation [e.g., maternal psychosocial stress, sleep disruptions, infection (Berk et al., 2013)]. We also encourage future studies to consider more precise measurement of PNMI to account for potential gradation of PNMI concentrations within trimester.

We are hopeful about future applications of the trajectory model of perinatal exposures and encourage fellow researchers to continue to explore and account for intermediate phenotypes of psychiatric disorders. To advance this trajectory framework, continued research efforts are needed to better understand this potential cognitive phenotype in the relationship between PNMI and offspring depression. In uncovering these new associations, it is now necessary for future research to generate greater specificity; for example, do specific subtypes of cognitive function and abilities better predict adolescent depressive symptoms, and if so, what are moderating biopsychosocial factors that can better explain the pathway to depression? Further, could perturbations in childhood cognition impact other aspects of development that may confer depression risk, such as relational interactions with peer, family, and teachers or heightened psychosocial stress? Similarly, questions persist about whether PNMI influences the age of onset of depression, given previous studies that suggest that other obstetric complications (e.g., fetal hypoxia) can lead to an earlier age of onset for disorders, such as schizophrenia (M. Cannon et al., 2002; T. D. Cannon et al., 2002). Answering such questions can begin to unravel the effects of early cognitive functioning, such as lower performance on the PPVT, on emerging psychopathology and offer more tailored interventions.

Finally, there is a strong literature suggesting that the effects of PNMI may be dependent upon fetal sex (Lipner et al., 2024; Mac Giollabhui

et al., 2019); as such, we encourage future PNMI studies to evaluate the role of fetal sex in differential cognitive and psychological outcomes. We also encourage researchers to explore more gender-inclusive language in perinatal research. We support the growing initiative to "unsex" pregnancy (Fontana & Schoenbaum, 2019) by employing more gender-neutral pregnancy measures to better capture pregnant individuals who do not identify with the labels of female or mother. Given our archival data and 1960's time period, we were unfortunately unable to justly represent this population. Likewise, our findings with maternal education further the importance of accounting for social determinants of PNMI, such as environmental toxins, racial discrimination, and other markers of SES (Anglin et al., 2021).

5. Conclusions

Lower childhood cognitive performance, measured here by receptive vocabulary abilities on the PPVT, represents a new potential mechanism through which PNMI, and specifically second trimester IL-1RA, contributes to adolescent depressive symptoms. These findings emphasize the importance of investigating early intermediate phenotypes in emerging psychopathology; similarly, PNMI exposure likely acts as a neurodevelopmental disease primer, exerting small yet compounding effects on fetal brain development, that may contribute to early mediators such as lowered cognitive abilities, including lower receptive vocabulary abilities. Contextualizing these results within a developmental trajectory framework of PNMI allows for a more comprehensive understanding of how small prenatal insults can rapidly build. As such, incorporating mediators into PNMI-psychopathology research is warranted. Importantly, adolescent depression is a growing public health crisis, and current treatment effects remain modest (LoPilato et al., 2023). As untreated adolescent depression can result in lasting emotional, behavioral and health problems (Lu, 2019), investigating these modifiable risk factors could provide important clues for early intervention and prevention strategies for depression onset in youth.

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Madeline R. Pike: Writing – original draft, Methodology, Formal analysis, Writing – review & editing. **Emily Lipner:** Writing – review & editing, Supervision, Methodology. **Kathleen J. O'Brien:** Writing – review & editing, Supervision, Methodology, Formal analysis. **Elizabeth C. Breen:** Writing – review & editing, Investigation. **Barbara A. Cohn:** Writing – review & editing, Investigation, Funding acquisition. **Piera M. Cirillo:** Writing – review & editing, Project administration. **Nickilou Y. Krigbaum:** Writing – review & editing, Project administration. **Ann M. Kring:** Writing – review & editing, Investigation. **Thomas M. Olino:** Writing – review & editing, Visualization, Supervision, Formal analysis. **Lauren B. Alloy:** Writing – review & editing. **Lauren M. Ellman:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Resources, Methodology, Investigation, Funding acquisition, Conceptualization.

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.

Data availability

The authors do not have permission to share data.

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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.2024.05.012.

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