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Sex-Specific Pathways From Prenatal Maternal Inflammation to Adolescent Depressive Symptoms

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IMPORTANCE Prenatal maternal inflammation has been associated with major depressive disorder in offspring in adulthood as well as with internalizing and externalizing symptoms in childhood; however, the association between prenatal inflammation and offspring depression in adolescence has yet to be examined.

OBJECTIVE To determine whether maternal levels of inflammatory biomarkers during pregnancy are associated with depressive symptomatology in adolescent-aged offspring and to examine how gestational timing, offspring sex, and childhood psychiatric symptoms impact these associations.

DESIGN, SETTING, AND PARTICIPANTS This was an observational study of a population-based birth cohort from the Child Health and Development Studies (CHDS), which recruited almost all mothers receiving obstetric care from the Kaiser Foundation Health Plan (KFHP) in Alameda County, California, between June 1959 and September 1966. Pregnancy data and blood sera were collected from mothers, and offspring psychiatric symptom data were collected in childhood (ages 9-11 years) and adolescence (ages 15-17 years). Mother-offspring dyads with available maternal prenatal inflammatory biomarkers during first and/or second trimesters and offspring depressive symptom data at adolescent follow-up were included. Data analyses took place between March 2020 and June 2023.

EXPOSURES Levels of inflammatory biomarkers (interleukin 6 [IL-6], IL-8, IL-1 receptor antagonist [IL-1RA], and soluble tumor necrosis factor receptor-II) assayed from maternal sera in the first and second trimesters of pregnancy.

MAIN OUTCOMES AND MEASURES Self-reported depressive symptoms at adolescent follow-up.

RESULTS A total of 674 mothers (mean [SD] age, 28.1 [5.9] years) and their offspring (350 male and 325 female) were included in this study. Higher second trimester IL-6 was significantly associated with greater depressive symptoms in offspring during adolescence (*b*, 0.57; SE, 0.26); *P* = .03). Moderated mediation analyses showed that childhood externalizing symptoms significantly mediated the association between first trimester IL-6 and adolescent depressive symptoms in male offspring (*b*, 0.18; 95% CI, 0.02-0.47), while childhood internalizing symptoms mediated the association between second trimester IL-1RA and adolescent depressive symptoms in female offspring (*b*, 0.80; 95% CI, 0.19-1.75).

CONCLUSIONS AND RELEVANCE In this study, prenatal maternal inflammation was associated with depressive symptoms in adolescent-aged offspring. The findings of the study suggest that pathways to adolescent depressive symptomatology from prenatal risk factors may differ based on both the timing of exposure to prenatal inflammation and offspring sex.

Supplemental content

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Preclinical and human studies support the role of prenatal maternal inflammation (PNMI) in the pathogenesis of neuropsychiatric disorders in offspring.[1-3] PNMI, or higher systemic (circulating) levels of inflammatory cytokines, may occur because of adversities during pregnancy (eg, infection and psychosocial stress).[4,5] Aberrant levels of these cytokines, some of which may cross the placenta,[6] can impact fetal neurodevelopment and induce obstetric complications also linked to these adverse outcomes.[7] Cytokines, including interleukin 6 (IL-6), IL-8, IL-1β, and tumor necrosis factor (TNF-α), are involved in the maintenance of normal pregnancy and have been associated with risk for schizophrenia spectrum disorders and autism spectrum disorders.[3,8-10]

To date, only 1 nested case-control study examines the association between prenatal maternal cytokines and risk of affective disorders offspring. Higher maternal proinflammatory state (TNF-α:IL-10) in midgestation to late gestation was associated with increased depression risk in adult male offspring but lower risk in female offspring.[11] Additional evidence from preclinical studies and outcomes earlier in development point to an association between PNMI and depressive symptomatology.[12-14] Previous studies from our group demonstrated the co-occurrence of prenatal adversities linked to inflammation (eg, infection and stress) during midgestation are associated with depressive symptomatology in adolescent-aged offspring.[15,16] We also previously reported that PNMI was associated with internalizing and externalizing symptoms in childhood,[17] which are known risk factors for depression in adolescence.[18-20] Moreover, offspring sex and gestational timing of PNMI influenced these outcomes, such that first trimester PNMI was associated with externalizing symptoms among male children, and second trimester PNMI was associated with internalizing symptoms among female children.[17]

Further exploration of the association between PNMI and depression is warranted, particularly with respect to adolescent depression. Risk of depression and sex differences in depression prevalence increase considerably in adolescence. Between the ages of 13 and 17 years, female adolescents are more than twice as likely to have depression than their male counterparts.[21] Furthermore, to our knowledge, no human studies of PNMI examine depression dimensionally, despite the clinical relevance of subthreshold depressive symptoms in adolescence.[22] Our understanding of risk factors for depression in adolescence is especially important for intervention and prevention efforts, as individuals who develop depressive symptomatology in adolescence have a greater risk for recurrence in adulthood.[23] Exploration of the roles of gestational timing and offspring sex in the associations between PNMI and depression also serves to better characterize the developmental trajectories to depressive symptomatology.

As such, the present study examined whether 4 markers of PNMI previously found to be associated with psychiatric symptoms in child-aged offspring (IL-6, IL-8, IL-1 receptor antagonist [IL-1RA])[17] and depressive disorders in adult offspring (soluble TNF-receptor II [sTNF-RII], a marker of TNF-α activity[24]) were associated with depressive symptoms during adolescence and whether childhood psychiatric symptoms mediated any associations. Furthermore, we examined the roles of offspring sex and gestational timing of PNMI in these associations. First, we hypothesized that higher levels of PNMI in the first or second trimester would be associated with more depressive symptoms in adolescent offspring and that this association may be moderated by offspring sex. Second, we hypothesized that internalizing or externalizing symptoms in childhood might mediate this association. Based on our prior findings, we specifically hypothesized that (1) higher levels of IL-8 and IL-6 in the first trimester would be associated with more adolescent depressive symptoms via externalizing symptoms, primarily for male adolescents and (2) higher levels of IL-1 activity (as measured by IL-1RA[17]) and IL-6 in the second trimester would be associated with more adolescent depressive symptoms via internalizing symptoms, primarily for female adolescents.[17]

Key Points

Question What is the association between prenatal maternal inflammation and symptoms of depression in their adolescent-aged offspring?

Findings In this cohort study including 674 mother-offspring dyads, higher second trimester levels of interleukin 6 were associated with greater depressive symptoms in adolescent offspring. Moreover, childhood internalizing and externalizing symptoms mediated sex-differentiated pathways from maternal inflammation to offspring symptoms in adolescence.

Meaning The findings suggest that there may be specific pathways to adolescent depression that begin in utero and are differentiated by fetal sex and timing of exposure to prenatal inflammation.

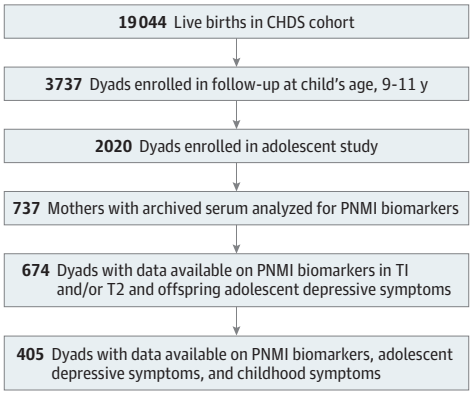
Methods

Analyses were approved by institutional review boards at Temple University; the University of California, Los Angeles; and the Public Health Institute. However, the original study predated institutional review boards and informed consent. All participants provided assent after receiving a complete description of the study. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline was used for this cohort study.[25]

Sample

The Child Health and Development Studies (CHDS) cohort recruited almost all pregnant women receiving prenatal care through Kaiser Foundation Health Plan (KFHP) at its clinics in Alameda County, California, from June 1959 to September 1966 (19 044 live births).[26,27] Follow-up studies were conducted with offspring born between April 1960 and March 1963 during childhood (1972-1973, ages 9-11 years; n = 3737) and adolescence (1977-1979, ages 15-17 years; n = 2020).[28] At follow-up points, mothers completed a series of interviews and questionnaires. Offspring only completed interviews in adolescence. There were more married White women who were high school graduates enrolled in the adolescent study compared

Figure 1. Participants Retained in Subsamples of the Child Health and Development Studies (CHDS)



Several follow-up studies were conducted among the original CHDS cohort and their offspring. Participants retained in each follow-up relevant to the present analyses are detailed here.

to the original CHDS sample; however, this sample is still representative of the women who received care from KFHP.[15,28]

Mother-offspring dyads from the adolescent study, for whom first or second trimester maternal biomarker data were available, were considered for inclusion in the current analyses (N = 737).[17] From these dyads, 674 had both maternal biomarker data in the first or second trimester and complete data on adolescent depression. A subset of 405 dyads had maternal biomarker data and complete offspring data on adolescent depression and childhood internalizing or externalizing symptoms (**Figure 1**).

Measures

Inflammatory Biomarkers

Biomarker data for IL-6, IL-8, IL-1RA, and sTNF-RII were available from assays conducted on archived frozen sera of 737 mothers, as previously described, using high-sensitivity (ie, IL-6 and IL-8) and regular sensitivity (ie, IL-1RA and sTNF-RII) enzyme-linked immunosorbent assays.[17] Details about sample storage, assay specifications, and biomarker selection are presented in the eMethods in Supplement 1.

Childhood Symptoms

Mothers completed a 100-item questionnaire about their child's behavior during the childhood follow-up (mean [SD] age, 9.7 [0.7] years). Items indicative of internalizing (eg, anxiety and depression) and externalizing symptomatology (eg, conduct problems) were summed and examined continuously. These scales have adequate reliability and validity.[17]

Adolescent Depressive Symptoms

Offspring completed questionnaires at their adolescent study visit (mean [SD] age, 16.4 [0.7] years). Items about depression were summed and examined continuously.[15] This scale previously demonstrated high internal consistency, high predictive validity of depression assessed via diagnostic interview in adulthood, and concurrent validity.[15,27]

Table 1. Descriptive Statistics for Mother-Offspring Dyads With Inflammatory Biomarkers and Adolescent Depressive Symptoms (N = 674)

	No. (%)	Mean (SD)	Missing No.
Maternal variables			
Age at offspring birth, y	NA	28.1 (5.9)	1
Education			
≤High school	310 (46.0)	NA	NA
>High school	364 (54.0)	NA	NA
Race[a]			
Asian	36 (5.3)	NA	NA
Black	130 (19.3)	NA	NA
White	508 (75.4)	NA	NA
Worries at offspring childhood visit	NA	0.3 (0.5)	40
Depressive symptoms at offspring adolescent visit	NA	14.7 (3.3)	70
First trimester biomarkers, pg/mL			
IL-6	NA	4.5 (27.2)	78
IL-8	NA	958 (1783)	78
sTNF-RII	NA	2726 (735)	108
IL-1RA	NA	604 (568)	108
Second trimester biomarkers, pg/mL	NA		
IL-6	NA	3.0 (10.6)	75
IL-8	NA	820 (1527)	76
sTNF-RII	NA	3121 (776)	97
IL-1RA	NA	535 (347)	97
Offspring variables			
Gestational age at delivery, wk	NA	40.0 (2.1)	5
Sex assigned at birth			
Male	350 (51.9)	NA	NA
Female	324 (48.1)	NA	NA
Internalizing symptoms in childhood[b]	NA	2.7 (2.2)	389
Externalizing symptoms in childhood[c]	NA	2.2 (2.1)	390
Depressive symptoms in adolescence[d]	NA	23.5 (5.3)	NA

Abbreviations: IL-1RA, interleukin 1 receptor antagonist; IL-6, interleukin 6; IL-8, interleukin 8; NA, not applicable; sTNF-RII, soluble tumor necrosis factor receptor II.

[a] Race and ethnicity data were collected via self-report by mothers at birth and considered due to known associations between race and obstetric complications and birth outcomes in the US.[32,33]

[b] Possible range of scores = 0-13.

[c] Possible range of scores = 0-15.

[d] Possible range of scores = 0-60.

Demographic Characteristics and Covariates

Maternal education was used as a proxy for socioeconomic status since maternal education was associated with other measures of socioeconomic status (ie, income) in previous CHDS studies.[29] Maternal education was also used as a proxy variable for postnatal adversity,[30] which is associated with increased risk of disease across development.[31] Maternal age at offspring birth and race were examined as potential covariates due to known differences in obstetric complications and birth outcomes in the US.[32,33]

Table 2. Moderation Analyses Predictive of Offspring Depressive Symptoms in Adolescence From Maternal Inflammatory Biomarkers[a]

First trimester					Second trimester			
8 Models for 4 biomarker values across 2 trimesters, adjusted for race and maternal education[b,c,d]								
Biomarker	sTNF-RII	IL-1RA	IL-8	IL-6	sTNF-RII	IL-1RA	IL-8	IL-6
b (SE)	−1.01 (0.90)	−0.28 (0.39)	−0.14 (0.13)	−0.18 (0.24)	−0.84 (0.96)	0.06 (0.46)	0.10 (0.14)	0.57 (0.26)
P value	.26	.46	.28	.44	.38	.89	.48	.03
Adjusted R^2	0.005	0.003	0.005	0.004	0.010	0.009	0.009	0.016
Addition of sex interaction to the above models[e]								
Biomarker × sex								
b (SE)	−1.32 (1.76)	0.19 (0.77)	0.04 (0.26)	−1.14 (0.47)	−0.15 (1.88)	1.71 (0.91)	0.01 (0.28)	−0.39 (0.52)
P value	.45	.80	.88	.02	.93	.06	.96	.45
Adjusted R^2	0.004	0.002	0.004	0.012	0.009	0.014	0.007	0.015

Abbreviations: IL-1RA, interleukin 1 receptor antagonist; IL-6, interleukin 6; IL-8, interleukin 8; sTNF-RII, soluble tumor necrosis factor receptor-II.

[a] All estimates are unstandardized.

[b] All biomarkers are natural log transformed.

[c] Race reference category is White.

[d] Maternal level of education at time of birth of offspring; education reference category is high school or less.

[e] Offspring sex reference category is male.

Demographic characteristics were collected from maternal report at birth. Maternal education was categorized as high school education or less vs more than high school. Race was self-identified by mothers at birth and categorized as Asian, Black, and White. The Asian subgroup was not sufficiently powered to be included as a separate racial category in this sample and thus Asian and Black race were combined. For sensitivity analyses excluding Asian participants, see the eResults in Supplement 1. Offspring sex assigned at birth was categorized as male or female.

At the childhood follow-up, mothers self-reported financial, marital, employment, or health worries.[15,17,27] Maternal worries were explored as a continuous covariate to potentially account for the incidence of postnatal stressors in the home on offspring symptomatology. Mothers also completed a self-report inventory of depressive symptoms at the adolescent follow-up.[15] The scale previously demonstrated high internal consistency[15] and was explored as a potential covariate.

Statistical Analysis

Analyses were conducted in RStudio version 2023.03.01 (R Foundation). Biomarkers were natural log transformed. Variables significantly associated with at least 1 biomarker and childhood or adolescent symptoms were included as covariates. First, separate hierarchical linear regression models examined the association of each biomarker, offspring sex, and their interaction, with adolescent depressive symptoms. In the case of significant interactions, the biomarker's association with adolescent depression was plotted separately by sex. Moderation analyses were descriptively conducted to justify the use of moderated mediation.

Moderated mediation models were estimated using the lavaan package in R.[34] These models examined whether internalizing or externalizing symptoms (childhood) mediated the association between PNMI (pregnancy) and depressive symptoms (adolescence). Moreover, the models tested whether indirect effects varied by offspring sex. The direct effect of PNMI on adolescent depressive symptoms was also estimated in all models. Bias-corrected bootstrapping with 5000 bootstrap samples were used to evaluate the significance of indirect effects paths. Full information maximum likelihood was used to handle missing data and reduce the likelihood of biased parameter estimates.[35] A 2-tailed significance level of $\alpha < .05$ was implemented. Data analyses took place between March 2020 and June 2023.

Results

Sample Overview

The final sample included dyads with both maternal biomarker data in the first or second trimester and offspring depressive symptoms (see **Table 1** for sample characteristics). Among 674 included mothers, the mean (SD) age was 28.1 (5.9) years; 350 of their offspring were male, and 325 were female. Maternal race, education, and offspring sex were significantly associated with either childhood or adolescent psychiatric symptoms and at least 1 biomarker and were included as covariates in all analyses (eTable 1 in Supplement 1). Maternal worries at childhood and maternal depressive symptoms at adolescence were significantly associated with childhood or adolescent psychiatric symptoms but not biomarkers. There were complete data for 327 dyads in the first trimester and 330 dyads in the second trimester. Of dyads with maternal biomarker data, differences were examined between those with offspring depressive outcome data (n = 674) and those without (n = 63) (eResults in Supplement 1). Mothers retained in the analytic sample had fewer pregnancies, higher first trimester IL-8, and a smaller proportion of Black and Asian participants.

Moderation Analyses Predictive of Adolescent Depressive Symptoms

Moderation analyses are presented in **Table 2.** Only T2 IL-6 was significantly, positively associated with adolescent depressive symptoms after adjusting for covariates (*b*, 0.57; SE, 0.26; *P* = .03). Conversely, in models examining biomarker and sex interactions, there was a significant (and opposite) interaction effect of first trimester IL-6 and offspring sex on depressive

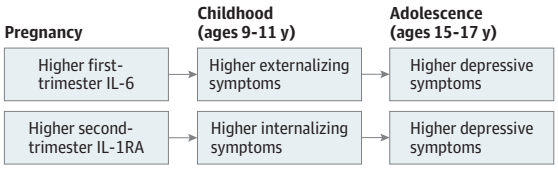
Table 3. Prenatal Maternal Inflammatory Biomarkers in the First Trimester Predictive of Adolescent Depressive Symptoms via Externalizing and Internalizing Childhood Symptoms (n = 327)

	IL-6		IL-8	
Variable	*b* (SE)	*P* value	*b* (SE)	*P* value
Path predictive of childhood externalizing symptoms				
Biomarker	0.21 (0.15)	.14	0.25 (0.08)	.003
Offspring sex	−0.44 (0.26)	.09	−0.47 (0.26)	.07
Biomarker × sex	−0.58 (0.29)	.045	−0.13 (0.16)	.41
Maternal race	0.52 (0.35)	.14	0.62 (0.35)	.07
Maternal education	−0.38 (0.26)	.15	−0.36 (0.27)	.17
Path predictive of adolescent depressive symptoms				
Biomarker	−0.23 (0.32)	.47	−0.30 (0.18)	.10
Externalizing symptoms	0.35 (0.16)	.03	0.38 (0.16)	.02
Offspring sex	0.56 (0.61)	.35	0.54 (0.60)	.37
Maternal race	−0.31 (0.74)	.68	−0.43 (0.73)	.55
Maternal education	−0.39 (0.61)	.52	−0.38 (0.62)	.54
	Second trimester (n = 330)			
Biomarker	IL-6		IL-1RA	
Path predictive of childhood internalizing symptoms				
Biomarker	0.26 (0.20)	.19	0.71 (0.30)	.02
Offspring sex	0.37 (0.29)	.20	0.40 (0.30)	.18
Biomarker × sex	−0.43 (0.39)	.27	1.38 (0.62)	.03
Maternal race	0.62 (0.36)	.08	0.56 (0.35)	.10
Maternal education	−0.13 (0.29)	.66	−0.09 (0.29)	.75
Path predictive of adolescent depressive symptoms				
Biomarker	0.21 (0.44)	.63	0.01 (0.68)	.99
Internalizing symptoms	0.55 (0.15)	<.001	0.55 (0.16)	<.001
Offspring sex	0.37 (0.29)	.20	0.66 (0.61)	.28
Maternal race	−1.45 (0.67)	.03	−1.39 (0.67)	.04
Maternal education	−0.75 (0.61)	.22	−0.77 (0.61)	.21

Abbreviations: IL-1RA, interleukin 1 receptor antagonist; IL-6, Interleukin-6; IL-8, interleukin-8.

[a] All analyses controlled for offspring sex, maternal race, and maternal education at the time of offspring birth. Slopes are unstandardized.

Figure 2. Sex- and Timing-Differentiated Pathways to Adolescent Depressive Symptoms From Prenatal Maternal Inflammation



We identified 2 sex- and timing-specific pathways from specific biomarkers of prenatal maternal inflammation to depressive symptoms in adolescence when controlling for maternal education and race and offspring sex. These findings are an extension of our prior study that identified associations between these biomarkers and childhood psychiatric symptoms, moderated by sex. IL-1RA indicates interleukin 1 receptor antagonist; IL-6, interleukin 6.

symptoms. On probing this interaction, for female offspring only, higher first trimester IL-6 levels were associated with lower levels of depressive symptoms (*b*, −0.79; SE, 0.34; *P* = .02).

Moderated Mediation Predictive of Adolescent Depressive Symptoms via Childhood Symptoms

Predictive paths from childhood depressive symptoms to adolescent depressive symptoms are modeled in **Table 3.** Childhood externalizing symptoms were significantly associated with adolescent depressive symptoms in both first trimester models. First trimester IL-8 was significantly associated with childhood externalizing symptoms; however, the interaction between sex and first trimester IL-8 was not significant. There was a significant interaction between first trimester IL-6 and sex predictive of childhood externalizing symptoms. As such, we examined the association between first trimester IL-6 and childhood externalizing symptoms for each offspring sex. These analyses revealed that the indirect effect was significant for male offspring (*b*, 0.18; 95% CI, 0.02 to 0.47) but not for female offspring (*b*, −0.03; 95% CI, −0.27 to 0.08). Furthermore, the indirect effects differed by offspring sex for first trimester IL-6 (*b*, 0.21; 95% CI, 0.01 to 0.60) but not first trimester IL-8 (*b*, 0.05; 95% CI, −0.07 to 0.22).

Childhood internalizing symptoms were significantly associated with adolescent depressive symptoms in both second trimester models. Second trimester IL-6 and its interaction with offspring sex were not significantly associated with adolescent depressive symptoms in these models. Nonetheless, there was a significant interaction between second trimester IL-1RA and offspring sex predictive of childhood internalizing symptoms. Analyses of conditional indirect effects revealed a significant indirect effect among female offspring (*b*, 0.80; 95% CI, 0.19 to 1.75) but not for male offspring (*b*, 0.04; 95% CI, −0.40 to 0.46). Furthermore, the indirect effects differed by offspring sex for second trimester IL-1RA (*b*, −0.76; 95% CI, −1.92 to −0.08) but not for second trimester IL-6 (*b*, 0.23; 95% CI, −0.16 to 0.73). In all models after accounting for model variables, there were no longer direct associations between inflammatory markers and depressive symptoms.

Discussion

To our knowledge, this is the first study to examine the association between serologically defined PNMI and offspring depression in adolescence. Higher second trimester maternal IL-6 was associated with more depressive symptoms in adolescent offspring when controlling for covariates. Contrary to our hypotheses, there were no differences in this association by offspring sex. Nonetheless, we identified 2 sex- and timing-differentiated pathways from PNMI to adolescent depressive symptoms through childhood symptoms (**Figure 2**).

The association of IL-6 with depression in offspring has the strongest support from preclinical studies[12,36-39] and human studies that examine depression in nonpregnant[40] and community samples of adolescents.[41] Furthermore, there is evidence of bidirectional transfer of IL-6 to the placenta in ex vivo studies of human placental perfusion[6] and from preclinical studies that the placenta may be more permeable in midgestation.[42] Additionally, prenatal maternal concentrations of IL-6 have been associated with a number of structural and functional brain alterations and patterns of cognitive development in infants

that may be predictive of later psychopathology, including depression.[43-46] Studies significantly associating prenatal infection with offspring depression show increased depression risk with infection in midgestation.[15,47-49] Evidence from both preclinical and human studies documents the potential role of prenatal IL-6 in the emergence of offspring depressive symptomatology and reduces the likelihood that results are due to chance; however, given that we conducted 8 analyses to examine our primary hypotheses, there is always the potential risk of type I error. That said, we cannot be sure why the other biomarkers were not directly associated with adolescent depression. Given that PNMI is associated with risk for numerous psychiatric disorders, it is also possible that specific markers are associated with specific psychopathological outcomes.[50] There is still much we do not understand about how these biomarkers impact fetal and placental development, as well as how they interact with other existing vulnerabilities (eg, maternal and fetal genetics). More precise research on the specificity of these biomarkers to psychiatric outcomes is needed.

In contrast to our hypotheses, we found that higher first trimester IL-6 levels were associated with fewer adolescent depressive symptoms but only in female offspring. The early first trimester is typically characterized as a proinflammatory period during which development of the placenta and fetal organ and body structure take place.[4,51] IL-6 is also characterized as a pleiotropic cytokine, meaning it shifts function depending on context and role.[52] It is possible that higher first trimester levels of IL-6 may positively influence these processes involved in fetal development. This is consistent with our findings that higher IL-6 in the first trimester is advantageous for the female fetus, at least in terms of reduced likelihood of later depressive symptoms, but inconsistent with our other first trimester findings for male offspring externalizing symptoms. Future research is necessary to delineate when, how (eg, interactions with placental cells which also are differentiated by fetal sex), and for whom first trimester inflammation may foretell risk vs resilience. Depression in adolescence may be the result of multiple hits in both the prenatal and postnatal period, such that the effect of offspring sex at adolescence is less salient.[2]

Our findings provide further evidence that offspring sex and timing of exposure to inflammation are meaningful moderators in the associations between various prenatal adversities related to inflammation (eg, stress, infection) and offspring outcomes. Examining earlier phenotypes of adolescent psychopathology facilitated the identification of these sex- and timing-related differences. Research on sex differences in child and adolescent psychopathology demonstrates that externalizing disorders are more common in male individuals, whereas internalizing disorders are more common in female individuals.[53] Moreover, female offspring exposed to PNMI may be more vulnerable for internalizing disorders, informing the developmental pathway to later neuropsychiatric disorders.[54,55] Evidence from animal studies also has illustrated the sex-specific manner in which PNMI alters the placenta and fetal brain, likely demonstrating mechanisms by which varied prenatal adversities differentially impact offspring outcomes.[56]

Strengths and Limitations

Strengths of this study include our use of an exceptional cohort with prenatal sera and a wealth of other data collected prospectively from before birth to adolescence. Furthermore, the availability of serologically defined, trimester-specific PNMI allows us to explore the influence of PNMI at a systemic immunological level. Despite the age of our samples, we obtained detectable levels of biomarkers in all samples and examined analytes found at higher concentrations in pregnant sera. Future studies may aim to measure inflammation that co-occurs with environmental stressors (eg, infection and stress) so these factors can be examined together with respect to offspring outcomes.

Limitations should be considered. This study used a cohort collected between 1959 and 1967 in the San Francisco Bay Area, representing a unique cultural subset in both place and time of collection. This cohort is, on average, educated beyond high school and predominantly White, which may limit the generalizability of these findings. More current, precise measurement of racial categories, socioeconomic status, and postnatal exposure to environmental stressors (eg, adverse childhood experiences) could strengthen future research examining similar models. Although beyond the scope of this study, future studies may consider examining intersectional effects of demographic variables in trajectories to offspring psychopathology beginning in utero.

Furthermore, due to the time of data collection, this study could not use gold-standard measures of psychological outcomes. Uncertain responses to items on the childhood questionnaire (which are then considered missing) account for substantial attrition from the sample of women who had sera evaluated for biomarkers,[17] decreasing the analytic sample for moderated mediation analyses. Importantly, there was no difference in sample characteristics between those lost to attrition in the childhood follow-up.[17] In the measure of depression, the items predominantly assessed cognitive symptoms. Postnatal research points to a specific association between inflammation and somatic symptoms; as such, it is possible that a measure inclusive of somatic and cognitive symptoms would reveal stronger associations with PNMI.[57,58] Additionally, this study lacks information about maternal mental health during pregnancy. However, we can confirm from *DSM* diagnoses circa 1960, that there was low incidence of serious mental illness (schizophrenia) during pregnancy. Future studies should aim to use well-validated, multimodal assessments of maternal and offspring psychiatric symptomatology.

Conclusions

The results of this study provide preliminary insight into developmental pathways by which PNMI increases risk for depressive symptomatology in adolescent offspring. Additionally, our results underscore that offspring sex and timing of exposure are important factors to consider in the fetal origins of adolescent depression. Often studies examining associations between prenatal adversities and offspring psychopathology identify small effects; however, the confluence of many

environmental and genetic hits across development are crucial in estimating risk for psychopathology.[59] Future exploration of the trajectory from PNMI to risk for adolescent psychopathology may identify intermediate phenotypes that serve as opportunities for early intervention. Recent studies demonstrate that sequelae related to PNMI are evident as early as infancy, including negative affect,[60] heightened stress reactivity,[61] and poor cognitive performance.[62] Replication and expansion of these models using current cohorts, psychological assessments, and comprehensive demographic and early life adversity data could be used to inform a cascade model of adolescent affective disorders via other behavioral changes across the lifespan, beginning in utero.[63] It is likely that PNMI alters fetal neurodevelopment, impacting behavior proximal to birth, generating transactional, developmental changes increasing risk for later symptomatology.

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