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Maternal Immune Activity During Pregnancy and Socioeconomic Disparities in Children's Self-Regulation

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Abstract

Maternal immune activity during pregnancy has been associated with risk for psychiatric disorders in offspring, but less is known about its implications for children's emotional and behavioral development. This study examined whether concentrations of five cytokines assayed from prenatal serum were associated with socioeconomic status (SES) and racial disparities in their offspring's self-regulation abilities. Participants included 1,628 women in the Collaborative Perinatal Project (CPP). Seven behavioral items conceptually related to self-regulation were rated by CPP psychologists when children were 4 years old. Concentrations of interleukin (IL)-1 β , IL-6, IL-8, tumor necrosis factor (TNF)- α , and IL-10 were assessed. Covariates included child sex and mother's age, psychiatric disorders, and medical conditions during pregnancy. There were

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significant SES differences in child self-regulation, with higher SES children scoring higher on self-regulation ($\beta = .18$, 95% CI [.11, .25]), but no racial differences. The concentration of IL-8 in maternal serum was associated with higher child self-regulation, $\beta = .09$, 95% CI [.02, .16]. In mediation analyses, variation in maternal IL-8 contributed to the association between family SES and child self-regulation ($\beta = .02$, 95% CI [.003, .030]), explaining about one-tenth of the SES disparities. This study suggests pregnancy as an early sensitive period and maternal immune activity as an important context for child development.

Keywords

Gestational cytokines; inflammation biomarkers; racial disparity; self-regulation; socioeconomic inequality

1. Introduction

Maternal immune activity during pregnancy is thought to be involved in children's neurodevelopment and long-term risk for psychiatric disorders. Concentrations of maternal interleukin-8 (IL-8), IL-6, IL-1 β , tumor necrosis factor- α (TNF- α), and/or IL-10 during pregnancy have been associated with elevated risk for schizophrenia, autism, major depressive disorder, and lower cognition in children (e.g., Allswede, Yolken, Buka, & Cannon, 2020; Jones et al., 2017; Brown et al., 2004; Buka et al., 2001; Goldstein et al., 2014; Gilman et al., 2016; Rasmussen et al., 2019). However, there are also studies that show a beneficial role of IL-8 or IL-6 in children's neurocognitive development (e.g., Ghassabian et al., 2018; Gilman et al., 2017; Spann et al., 2018).

Less is known about the extent to which immune activity during pregnancy relates to children's behavioral and emotional development. Recently, higher gestational IL-6 and TNF- α were found to be associated with either worse impulse control in toddlers (Graham et al., 2018) or negative affect in infants (Gustafsson et al., 2018), and higher IL-8 was linked to more externalizing symptoms in 9–11-year-old children (Mac Giollabhui et al., 2019). There was also a recent study (Dozmorov et al., 2018) showing that maternal IL-1 β , IL-6, IL-8, and TNF- α were not associated with preschool children's executive functions (e.g., inhibitory control and attention, cognitive flexibility). We extended these studies by examining whether the prenatal immune activity of mothers was associated with the development of children's behavioral functioning, operationalized here as their self-regulation ability.

Self-regulation refers to the ability to regulate (e.g., control, modulate, inhibit, initiate) one's attention, emotion, and behavior in adaptive ways to guide goal-directed activities (Zhou, Chen, & Main, 2012; McCoy, 2013). The two frameworks for studying self-regulation (Zhou et al., 2012) are *effortful control* in temperament research, focusing on inhibition of emotion-driven behavioral responses, and *executive function* in cognitive neuroscience and clinical psychology, focusing on inhibition of cognitive responses. Self-regulation has a pronounced influence on a variety of developmental and health outcomes across the life course, including academic achievement (McClelland & Wanless, 2012), psychological

well-being (Wrosch, Scheier, Miller, Schulz, & Carver, 2003), economic success, and overall health (Moffitt et al., 2011).

From a bioecological perspective (McCoy, 2013), children's development of self-regulation takes place within the context of multiple systems, from neurological to cultural. Family socioeconomic status (SES) and parents' race/ethnicity are two important contexts for child development, as illustrated by the frequent observation of SES and racial disparities in child's self-regulation. Specifically, children from lower SES and racial minority (e.g., Black) families tend to have lower scores on measures of self-regulation (e.g., Garcia, Sulik, & Obradovi, 2018; Nesbitt, Baker-Ward, & Willoughby, 2013; Piotrowski, Lapierre, & Linebarger, 2013) than higher SES and White children.

There is also some evidence for SES and racial differences in maternal immune activity during pregnancy, suggesting the possibility that perturbations in gestational immune activity may (in part) contribute to understanding SES and racial disparities in child self-regulation (Barnes et al., 2016). This evidence is mixed, however, because the nature of SES and racial differences in biomarkers of immune activity varies across studies. Some studies found that lower SES or Black women had higher concentrations of circulating cytokines, such as IL-1 β , IL-6, TNF- α , and IL-10 (e.g., Dutt, Raker, & Anderson, 2015; Steptoe, Owen, Kunz-Ebrecht, & Mohamed-Ali, 2002); yet others found that they had lower levels IL-6, IL-8, TNF- α , and IL-10 (e.g., Gilman et al., 2017; Ryckman, Williams, Krohn, & Simhan, 2008) than higher SES or White women. More work is thus needed to determine the nature and magnitude of immune marker differences during pregnancy according to SES and racial status and their implications for child development. The mediating role of maternal immunity in the effects of SES and race on offspring's self-regulation should also be explored (Goldstein, Hale, Foster, Tobet, & Handa, 2019; Goldstein, Handa, & Tobet, 2014).

In this study, we examined associations between maternal immune activity during pregnancy and young children's self-regulation and assessed whether gestational immune activity contributes to SES disparities in children's behavioral development. To the extent feasible in our study sample, we also determined whether prenatal immune differences might contribute to racial (Black vs. White) disparities in child's self-regulation. We focused on prenatal levels of four pro-inflammatory (IL-1 β , IL-6, IL-8, and TNF- α) cytokines and one anti-inflammatory immune molecule (IL-10) that are coactivators of hypothalamic-pituitary-adrenal (HPA) axis function. These cytokines play a role in signaling along the stress-immune pathways that influence fetal brain development (e.g., O'Connor, O'Halloran, & Shanahan, 2000). Given that these pathways may differ between males and females (Gilman et al., 2016; Goldstein et al., 2014; Mac Giollaibhui et al., 2019), we also explored whether child sex moderated the association between each gestational cytokine and child self-regulation. Notably, building upon existing work (e.g., Gilman et al., 2017) which suggested the potential mediating role of gestational IL-8 for SES differences in infant neurodevelopment, we were particularly interested in examining if such patterns continued into early childhood and on children's behavioral development.

2. Method

2.1. Participants

The study sample included 1,628 women with singleton pregnancies (1959–1966) in the Massachusetts (Boston) and Rhode Island (Providence) cohorts of the Collaborative Perinatal Project (CPP). Mothers who provided blood samples for the immunoassays and their offspring were included. Informed consent was obtained from all mothers before collecting maternal serum samples during pregnancy and from mothers for behavioral assessments of offspring when they were age 4. Compared to all CPP participants from the Boston/Providence cohorts (12% Black and 86% White; mean SES of 58.5), the study sample had similar racial distributions (12% Black and 88% White) and slightly lower family SES (mean of 55.3).

2.2. Measures

Child self-regulation.—Behavioral characteristics were assessed by trained psychologists when children were 4 years old and mothers or caregivers were not present. The examining psychologists observed and rated children's behavior during a standard cognitive testing, and thus the situational context was relatively specific and standardized (Kubzansky, Martin, & Buka, 2004). Seven of the items administered were conceptually related to attention, emotion, and behavior regulation or control (e.g., emotional lability, over-reactivity, hyperactivity, distractibility, perseveration, inappropriate behavior and impulsivity) and used to construct self-regulation. The items (some were reverse-coded) were rated on a scale of 1 (e.g., no effort to reach a goal) to 5 (e.g., compulsive absorption with task), with higher scores reflecting higher ability of children to regulate or control their attention, emotion, or behavior (see Appendix). The seven items were subjected to confirmatory factor analysis and found to load on a single latent factor which had adequate internal consistency (Cronbach's $\alpha = .76$).

Gestational cytokines.—Serum samples acquired from mothers during the second and third trimesters of pregnancy were obtained from the NIH repository. Concentrations of five maternal cytokines (IL-1 β , IL-6, IL-8, TNF- α , and IL-10) were assessed by multiplexed, bead-based immunoassays (Milliplex human cytokine panel MP5HCYTO-60K; Millipore) on a Luminex 3D™ detection platform (Luminex Corporation) (Vignali, 2000). Previous work using samples stored under similar conditions and for a similar length of time (> 40 years) demonstrated the long-term detectability of these cytokines (Gilman et al., 2016; Goldstein et al., 2014). Assay sensitivities ranged from 0.1 to 0.4 pg/ml. We estimated cumulative concentration of inflammatory markers during the second and third trimesters of each pregnancy. This was accomplished by fitting linear piecewise mixed models for each cytokine that included a pregnancy-level random intercept. Parameters from these models were used to define two lines joined together by a knot between 2nd and 3rd trimesters; the area under these lines was used to quantify the cumulative concentration or exposure to each cytokine across the second and third trimesters (Ghassabian et al., 2018).

Demographic measures.—Information on maternal age and race was collected from women during study enrollment by in-person interview. Participants also reported on the

education and occupation of the head of the household and total family income; these data were used to compute a composite index of family SES based on methods developed by the U.S. Census Bureau (Myrianthopoulos & French, 1968). The composite index reflected the cumulative percentage distribution of parental education, parental occupation, and family income and could theoretically range from 0 to 100. Higher percentage scores represented higher SES.

Clinical measures.—Women reported on their history of treatment for psychiatric disorders. Obstetric diagnostic records were used to construct two summary measures of medical conditions suggestive of the presence of elevated maternal immune activation. The first of these summary measures represents common conditions associated with acute inflammatory responses, primarily including infections during pregnancy (e.g., kidney, ureter, bladder infection, fever, positive urine culture, pyuria, vaginitis, viral and bacterial infectious diseases, bacteriuria or receipt of an attenuated live vaccine). The second summary measure includes conditions associated with chronic inflammation (e.g., diabetes mellitus, hypothyroidism, hyperthyroidism, bronchial asthma, rheumatic fever, preeclampsia). Data regarding these conditions were obtained from diagnostic summaries completed by study physicians at the time of enrollment, during pregnancy, and at the end of the pregnancy.

2.3. Analysis Plan

Confirmatory factor analysis (CFA) was first conducted to examine whether the seven items were best represented by one general latent factor of self-regulation or three sub-factors reflecting attentional, emotional, and behavioral dimensions of self-regulation. The mean- and variance-adjusted weighted least squares (WLSMV) estimator was used to conduct CFA, which treated the 5-point self-regulation items as categorical/ordinal indicators instead of continuous data. Structural equation modeling (SEM) was then used to examine associations of family SES, race, and gestational cytokines with child self-regulation and the mediating role of cytokines in the associations of race and SES with child self-regulation. Model fits were assessed by the Comparative Fit Index (CFI) and root mean square error of approximation (RMSEA) (Bentler & Bonett, 1980; Hu & Bentler, 1998). An adequate model fit is indicated by CFI greater than 0.90 and RMSEA less than 0.08 (Hu & Bentler, 1998). For the mediation analyses, we adopted a bootstrapping approach that generated bias-corrected confidence intervals for the direct and indirect effects by resampling 5,000 random samples (Hayes, 2009). The null hypothesis of no effect is rejected if the confidence interval does not contain 0. The overall missing data rate was less than 6%, handled by WLSMV or full-information maximum likelihood (FIML) estimation in *Mplus* version 8.

3. Results

Table 1 summarizes the sample characteristics and descriptive statistics of the main study variables. In total, 56% of the participating children were female and 88% of the participating mothers were White. About 12% of the mothers had psychiatric illness, 45% had infection, and 16% had chronic inflammatory conditions during pregnancy. Maternal mean age at enrollment was 25 years old, and nearly all mothers had one or more prior

pregnancies. The sample exhibited considerable diversity of socioeconomic characteristics, with family SES ranging from 3 to 93.

3.1. Factor Structure of Latent Child Self-Regulation

A one-factor CFA model was first specified in which all items loaded on a general construct of child self-regulation, which achieved adequate model fit after adding several residual correlations, χ^2 (df = 6, N = 1384) = 10.96, p = .090, RMSEA = .024, and CFI = .999. A correlated three-factor CFA model was then estimated where attention, emotion, and behavior self-regulation were specified as three separate dimensions of child self-regulation. The three-factor solution also achieved adequate model fit after adding several residual correlations, χ^2 (df = 5, N = 1384) = 8.96, p = .111, RMSEA = 0.024, and CFI = .999. All items had standardized factor loadings larger than .40. Comparisons of the two CFA models indicated that the one-factor model fit the data as well as the three-factor model, χ^2 (df = 1, N = 1384) = 1.98, p = .159. For parsimony, the one-factor model was retained. Further analyses tested the measurement equivalence of the one-factor model across the two racial groups. We found that the measurement equivalent model (i.e., equal factor loadings) had significantly better model fit than the unconstrained model (i.e., factor loadings allowed to differ across groups), χ^2 (df = 6, N = 1382) = 38.74, p < .001, supporting the analysis of the self-regulation construct in both White and Black children.

3.2. Overall Effects of Family SES and Race on Child Self-Regulation

Children from higher SES families had considerably higher self-regulation ability at age 4, β = .18, 95% CI [.11, .25] – approximately one third of a standard deviation (.60) difference in self-regulation for each standard deviation increase in SES. This overall effect model included all covariates (child sex, maternal age, maternal psychiatric illness, mothers' infections and medical conditions associated with chronic inflammation during pregnancy). Among the covariates, maternal age (β = .09, 95% CI [.03, .15]) and infections (β = -.08, 95% CI [-.15, -.02]) during pregnancy were significantly associated with child self-regulation at age 4. Older mothers and mothers who did not have infections during pregnancy tended to have children with higher self-regulation. There was no difference between Black and White children in self-regulation, β = -.03, 95% CI [-.09, .04].

3.3. SES and Racial Disparities in Maternal Gestational Cytokines

The next step of analysis addressed both SES and racial differences in maternal immune activity during pregnancy. In an analysis including maternal age, child sex, race, and SES (but not maternal psychopathology and medical conditions which might have occurred subsequent to prenatal sample collection), higher SES mothers had higher concentrations of IL-8, β = .17, 95% CI [.13, .22], but not other cytokines. Black mothers had significantly lower concentrations of two cytokines than White mothers: for IL-8, β = -.06, 95% CI [-.10, -.01], and for TNF- α , β = -.06, 95% CI [-.10, -.01]. There was also a sex difference in TNF- α such that mothers with female offspring had lower TNF- α , β = -.06, 95% CI [-.11, -.02] (Table 2).

3.4. Effects of Gestational Cytokines on Child Self-Regulation

Finally, we proceeded with analyses of the associations between maternal cytokines and children's self-regulation, fitting a separate model for each cytokine. IL-8 was positively associated with child self-regulation, $\beta = .11$, 95% CI [.05, .18]. None of the other cytokines (IL-1 β , IL-6, TNF- α , or IL-10) were associated with child self-regulation (Table 3). When family SES, maternal race, and all covariates (i.e., child sex, and mother's age, psychiatric illness, infections, and chronic inflammatory conditions) were incorporated in the models, results were unchanged. The adjusted SEM model for IL-8 had good model fit, $\chi^2 (55, N = 1628) = 211.75$, $p < .001$, RMSEA = .042, and CFI = .979, and showed that IL-8 remained significantly associated with child self-regulation, $\beta = .09$, 95% CI [.02, .16]. The associations between gestational cytokines and child self-regulation did not vary by child sex.

3.5. Mediating Role of Gestational IL-8

Because IL-8, but not other cytokines, was significantly associated with child self-regulation, the mediating role of maternal IL-8 in both SES and racial disparities of child development was further tested. One would typically not expect there to be mediation involving race given the absence of racial differences in self-regulation. However, the absence of race differences does not preclude indirect effects (Hayes, 2009). Bootstrapping analysis results showed that variation in maternal IL-8 contributed to the association between family SES and child self-regulation. That is, mothers from lower SES families had lower levels of gestational IL-8, which in turn was associated with lower self-regulation in children ($\beta = .02$, 95% CI [.003, .030]). There remained a direct association of SES with child self-regulation, $\beta = .16$, 95% CI [.09, .24] (Figure 1). In terms of magnitude, about one-tenth ($.02 / (.02 + .16) = 11\%$) of SES disparities in child self-regulation was associated with SES differences in concentrations of IL-8. Mediation analyses did not reveal an indirect association between race and child self-regulation through gestational IL-8 ($\beta = -.01$, 95% CI [-.013, .000]).

4. Discussion

This study examined SES and racial differences and the role of maternal immune activity in children's self-regulation abilities. We found SES and racial differences in concentrations of IL-8 and/or TNF- α in maternal serum drawn during pregnancy. Only IL-8, however, was associated with differences in children's self-regulation abilities at age 4, which partly contributed to socioeconomic disparities in child self-regulation. Specifically, mothers from lower SES families had lower levels of IL-8 that in turn partly explained why children from lower SES families had lower levels of self-regulation.

We found robust total, direct, and indirect (through IL-8) SES differences in child self-regulation, consistent with previous studies (e.g., Piotrowski et al., 2013). Low SES mothers are likely to experience heightened prenatal stress that affected children's early self-regulation development (Korja, Nolvi, Grant, & McMahon, 2017; Lefmann, Combs-Orme, & Orme, 2017). Moreover, children in low-income homes may have fewer resources available to promote and enable practice of self-regulatory skills (Sektman et al., 2010). The

findings may also reflect the links among low-income environment, alterations in prefrontal cortex functioning and the cognitive processes underlying self-regulation (Kishiyama et al., 2009).

At variance with some previous studies (e.g., Garcia et al., 2018), we did not find racial differences in child self-regulation. This is perhaps due to differences in measurements (e.g., computer-based tasks versus behavioral observations), contexts (e.g., classroom versus standard laboratory setting), and statistical power (i.e., we had a relatively small proportion of Black children). We did find that Black mothers had lower concentrations of IL-8 and TNF- α during pregnancy, consistent with some previous studies (e.g., Ryckman et al., 2008) but not others (e.g., Dutt et al., 2015). One hypothesis is that such racial differences in cytokine concentrations are due in part to racial differences in allele frequencies within genes that promote or inhibit the production of cytokines (Hajeer & Hutchinson, 2001; Pine et al., 2016; Hull, Thomson, & Kwiatkowski, 2000; Van Dyke et al., 2009). It is most likely the case, though, that race differences in concentrations of IL-8 and TNF- α are influenced by the same social factors contributing to SES differences in IL-8. Given that existing data in the literature are sparse and have yielded inconsistent findings, well-designed epidemiologic studies are needed to explore racial differences in maternal cytokines during pregnancy and their implications for maternal health and child development.

Concentrations of IL-8 partly accounted for SES disparities in child self-regulation. To the extent that low family SES might precipitate the mother's ability to respond adaptively to stressful conditions, stress-induced elevations of glucocorticoids may be exaggerated, resulting in greater immunosuppression and lower concentrations of IL-8 (Gilman et al., 2017; Goldstein, 2019). The finding that low IL-8 during pregnancy is associated with poor child self-regulation is consistent with some previously reported associations of higher IL-8 with positive child outcomes, such as neurocognitive functioning and verbal abilities (Ghassabian et al., 2018; Gilman et al., 2017; Dozmorov et al., 2018). Concentrations of maternal IL-8 may play a role in normal uterine and placental physiology (Maldonado-Pérez et al., 2009) and influence fetal neurodevelopment processes that underlie the offspring's later self-regulation ability. For instance, deficits in IL-8 signaling may disrupt the normal trafficking of neuronal processes and the formation of appropriate synaptic contacts during central nervous system development, leading to emotional and behavioral disturbances in the offspring (Gilman et al., 2017; Semple, Kossmann, & Morganti-Kossmann, 2010).

We did not observe any associations between other examined cytokines (IL-1 β , IL-6, TNF- α , and IL-10) and children's self-regulation. Findings regarding the associations between gestational levels of maternal cytokines and offspring development have been mixed. Our result was consistent with studies that reported a lack of significant associations between IL-1 β , IL-6, TNF- α , or IL-10 and cognitive functioning or autism risk (Dozmorov et al., 2018; Goines et al., 2011) but inconsistent with those who either found higher maternal prenatal IL-6, IL-1 β , IL-8, TNF- α , or IL-10 associated with higher risk for schizophrenia and decreased cognitive functions (Dozmorov et al., 2018; Goldstein et al., 2014; Jones et al., 2017) or IL-6 associated positively with offspring cognitive development (Spann, Monk, Scheinost, & Peterson, 2018). Several factors may explain the inconsistency of associations between maternal gestational cytokines and offspring outcomes. The effects of individual

cytokines on child development may play different roles in shaping variability in normal child development than in risk for neuropsychiatric disorder. The lack of population norms for establishing clinical ranges of immune markers, particularly across all gestational periods, and analytic differences across studies, also make it challenging to interpret apparently conflicting results across studies regarding the direction of associations between inflammatory cytokines and offspring outcomes. For IL-6 in particular, it is part of both pro-inflammatory and anti-inflammatory pathways, depending on the context, and a prenatal imbalance of pro- and anti-inflammatory signaling may contribute to changes in offspring development (Spann et al., 2018). Moreover, given feedback loops between the immune system and the HPA axis, it may ultimately be necessary to measure glucocorticoids along with immune markers in order to understand why higher or lower concentrations of specific markers appear to be protective in some circumstances and adverse in others (Cain & Cidlowski, 2017). Of equal importance is to identify factors that create vulnerability for certain offspring after exposure to maternal immune disruptions during pregnancy, including the role of offspring adaptive or resilient neurodevelopmental responses.

This study had several strengths, including a prospective, longitudinal design with a large sample size. A prospective examination ensures clear temporal precedence of exposure to maternal inflammation relative to child developmental outcomes. The sample size of over 1600 provided increased power to detect associations involving immune markers during pregnancy compared with many previous studies. In addition, we assessed child outcomes in a standardized context and derived a latent measure of children's self-regulation ability, allowing comparability across study participants and reducing measurement error. Our findings suggest that maternal immune activity during pregnancy may be a potential mechanism for the impact of family SES at birth and child development in early childhood.

Several study limitations should be noted. The CPP samples were collected between 1959 and 1966, thus, analytes might be subject to degradation. Cytokine degradation might have attenuated associations and could be one explanation for the lack of observed associations of the other four cytokines with child development. However, cytokine concentrations in the CPP samples are within the same ranges as those in samples obtained from participants in more recent pregnancy cohorts (Cheslack-Postava et al., 2017; Ferguson, Meeker, McElrath, Mukherjee, Cantonwine, 2017). In addition, our measure of child's self-regulation based on behavioral observation during cognitive testing may be subjected to examiner bias or influenced by fatigue associated with completing the cognitive tasks. We do not have information about the racial and SES status of the psychologists or over what period of time while completing the tasks did the psychological observation take place. Thus, we cannot evaluate how much the bias could potentially affect the rating of child self-regulation. Finally, we did not have a sufficient number of cytokine samples within each trimester from each pregnancy to conduct trimester-specific analyses of cytokines (e.g., Allswede et al., 2020; Mac Giollabhui et al., 2019), which we know is important to consider (Meyer et al., 2006) and also critical for identifying sex effects (Goldstein, 2019).

5. Conclusions

In summary, we found SES, but not racial, differences in child self-regulation at age 4. Moreover, we found both SES and racial differences in mothers' gestational IL-8 which was in turn associated with individual differences in child self-regulation. These results provide evidence for the possible contributing role of maternal immune activity during pregnancy to the SES differences in offspring's development (i.e., attention, emotion, and behavior regulation). The findings point to the possibility that intergenerational transmission of socioeconomic disparities is partly accounted for by gestational immune imbalance. Circulating concentrations of cytokines in pregnant mothers (associated with a variety of physical, psychological, social or chemical exposures) may have important implications for children's neurocognitive, emotional, and behavioral development in early childhood, as has also been shown for offspring's lifetime risk of psychopathology.

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Appendix

Table A.

Behavioral Items Used to Construct Child Self-Regulation

Items	1	2	3	4	5
1. Duration of attention span	Attends to tasks very briefly (2.5)	Spends short time with tasks (13.7)	Spends adequate amount of time on tasks (81.0)	Spends more than average time on tasks (2.6)	Highly perseverative (0.1)
2. Goal orientation	No effort to reach a goal (0.9)	Briefly attempts to achieve goal (14.4)	Able to keep goal or direction in mind (80.8)	Keeps goal and questions in mind (3.7)	Compulsive absorption with task (0.1)
3. Response to directions	Unwilling or unable to follow specific directions (1.7)	Some responsiveness to directions (13.7)	Responds to directions; some self-initiative and spontaneity (75.8)	Shows very little deviation from examiner's directions (8.0)	Completely dependent upon specific directions (0.9)
4. Degree of Irritability (R)	Extremely phlegmatic (2.0)	Rarely annoyed or disturbed by any situation (9.1)	Normally reactive (71.6)	Frequently irritable and fretful (16.2)	Extremely irritable and fretful; over-reacts markedly (1.2)
5. Emotional reactivity (R)	Extremely flat; no change in facial expression (2.0)	Somewhat flat; little change in emotional tone (10.3)	Normal responsiveness; affect appropriate to situation (74.8)	Mood more variable than average (11.6)	Extreme instability of emotional responses; marked emotional lability (1.4)
6. Level of activity (R)	Extreme inactivity and passivity; placid, sluggish (1.3)	Little activity; content to sit still most of the time (12.6)	Normal amount of activity (72.5)	Unusual amount of activity and restlessness (12.9)	Extreme over-activity and restlessness; can't sit still (0.7)

Items	1	2	3	4	5
7. Nature of activity (R)	Extreme rigidity; unable to shift activity or approach to task (0.7)	Some rigidity (4.9)	Flexible behavioral patterns; activity appropriate to different situations (87.5)	Behavior frequently impulsive (6.5)	Extremely impulsive; explosive and uncontrolled behavior (0.4)

Note: R = Reverse-coded. Columns two to six represent the five response categories for each item. Numbers in the parenthesis after each item represent the percentage of children who endorsed such behavior ($N = 1,384$)

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- Maternal immune activity during pregnancy influences offspring's risk for psychiatric disorders
- Effects of maternal cytokines during pregnancy on children's behavioral development are unknown
- We found no racial but significant SES differences in child self-regulation
- Maternal IL-8 partly mediated socioeconomic disparities in child self-regulation
- Trimester-specific effects of maternal cytokines need to be studied

Figure 1.

Family SES, Maternal Race, Gestational IL-8 During Pregnancy, and Child Self-Regulation.

Note: Standardized path coefficients [and their 95% confidence intervals in the bracket] are presented. R = Reverse-coded. $*p < .05$. $***p < .001$.

Table 1

Descriptive Statistics for Main Study Variables

		Overall (N=1628)	Black (n=187)	White (n=1438)
Child sex	girls	909 (55.8%)	108 (57.8%)	799 (55.6%)
Psychiatric illness	yes	200 (12.3%)	22 (11.8%)	177 (12.3%)
Maternal infection	yes	735 (45.1%)	85 (45.5%)	649 (45.1%)
Chronic conditions	yes	259 (15.9%)	29 (15.5%)	229 (15.9%)
Mother age, years	Mean (<i>SD</i>)	25.04 (5.78)	24.22 (5.42)	25.14 (5.82)
	Range	14–45	15–40	14–45
Family SES	Mean (<i>SD</i>)	55.32 (19.82)	47.01 (21.48)	56.39 (19.34)
	Range	3–93	5–93	3–93
IL-1 β	Mean (<i>SD</i>)	3.80 (1.40)	3.67 (1.45)	3.82 (1.40)
	Range	0.71–9.66	0.75–8.02	0.71–9.66
IL-6	Mean (<i>SD</i>)	3.71 (1.63)	3.72 (1.34)	3.70 (1.12)
	Range	0.72–10.49	0.78–9.36	0.72–10.49
IL-8	Mean (<i>SD</i>)	6.61 (1.63)	6.24 (1.73)	6.66 (1.61)
	Range	2.47–14.44	2.47–14.44	2.61–13.33
IL-10	Mean (<i>SD</i>)	4.22 (0.78)	4.14 (0.82)	4.23 (0.77)
	Range	1.37–9.90	1.55–8.18	1.37–9.90
TNF- α	Mean (<i>SD</i>)	4.80 (0.42)	4.73 (0.51)	4.81 (0.41)
	Range	1.55–7.66	1.55–6.58	1.91–7.66
Child	Mean (<i>SD</i>)	0.01 (0.54)	−0.05 (0.54)	0.02 (0.55)
Self-Regulation	Range	−2.46–2.18	−1.65–1.40	−2.46–2.18

Note: Natural logarithm transformed cumulative cytokine concentrations were used in the analysis and presented in this table. Latent child self-regulation descriptive statistics were based on saved factor scores from the final confirmatory factor analysis model.

Table 2

Associations of Race and Family SES with Gestational Cytokines during Pregnancy

	IL-1 β			IL-6			IL-8			IL-10			TNF- α		
	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI	
Race	-.03	[-.08, .01]	.01	[-.04, .06]	-.06	[-.10, -.01]	-.03	[-.08, .02]	-.06	[-.10, -.01]					
Family SES	.05	[-.003, .09]	.03	[-.03, .08]	.17	[.13, .22]	.05	[-.001, .10]	.02	[-.03, .07]					
Child Sex	-.01	[-.06, .03]	-.02	[-.06, .03]	-.03	[-.08, .02]	-.02	[-.07, .02]	-.06	[-.11, -.02]					
Mother Age	-.01	[-.06, .03]	.03	[-.02, .08]	.02	[-.03, .07]	-.02	[-.07, .03]	.04	[-.01, .09]					

Note: Regression models tested whether race and family SES predicted each gestational cytokine. Child sex and mother age were included as covariates, but not maternal psychiatric disorders and medical conditions, due to temporal considerations. Bold standardized coefficients were statistically significant ($p < .05$).

Table 3

Associations between Gestational Cytokines and Child Self-Regulation

	Child Self-Regulation (Unadjusted Models)		Child Self-Regulation (Adjusted Models)	
	β	95% CI	β	95% CI
IL-1 β	.004	[−.06, .07]	−.002	[−.07, .06]
IL-6	.05	[−.01, .07]	.05	[−.02, .12]
IL-8	.11	[.05, .18]	.09	[.02, .16]
IL-10	−.02	[−.09, .04]	−.04	[−.10, .03]
TNF- α	.03	[−.05, .11]	.02	[−.06, .10]

Note: Standardized path coefficients and their 95% confidence intervals (CI) are presented. Bold coefficients are statistically different from 0. In the adjusted models, maternal race, family SES, child sex, maternal age, maternal psychiatric conditions, maternal infection, and other medical conditions associated with chronic inflammation were all in the models.