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Early inflammatory measures and neurodevelopmental outcomes in preterm infants

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Abstract

Background: Inflammation may be an important predictor of long-term neurodevelopment in preterm infants. The identification of specific inflammatory biomarkers that predict outcomes is an important research goal.

Objectives: The purpose of this analysis was to identify associations between an early measure of inflammation and neurodevelopment in very preterm infants and to identify differences in the relationship between inflammation and neurodevelopment based on infant sex and race.

Methods: We conducted a secondary analysis of data from a randomized controlled trial of a caregiving intervention for preterm infants born less than 33 weeks post-menstrual age. Plasma was collected with a clinically-indicated lab draw by neonatal intensive care unit nurses and analyzed by multiplex assay for cytokines, chemokines, and growth factors. Neurobehavior was assessed by research nurses at the time of discharge from the neonatal intensive care unit using the motor development and vigor and alertness/orientation clusters from the Neurobehavioral Assessment of the Preterm Infant. Neurodevelopment was assessed at six months corrected age by the developmental specialist in the hospital's neonatal follow-up clinic using the Bayley Scales of Infant Development, 3rd Edition. We used linear regressions to estimate the effect of cytokine levels on neurodevelopment and allowed the effects to differ by infant sex and race.

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The authors have no conflicts of interest to report.

Ethical Conduct of Research: The study was approved by the Cincinnati Children's Hospital Medical Center (Study ID: 2011–0871) and The Ohio State University (Study Number: 2015H0347).

Clinical Trial Registration: ClinicalTrials.gov, NCT01577615, Trial Registered April 2012, Date of First Enrollment, May 2012, https://clinicaltrials.gov/ct2/show/NCT01577615

Results: In a sample of 62 preterm infants with discharge neurobehavioral assessments and a sample of 40 preterm infants with six month neurodevelopmental assessments, we found inconsistent associations between single-timepoint inflammatory measures and neurobehavior or neurodevelopment in analyses of the total sample. However, regressions with interactions revealed effects for multiple inflammatory measures on early neurobehavior and neurodevelopment that differed by infant sex and race.

Discussion: Although early single-timepoint measures of inflammation may be insufficient to predict neurodevelopment for all preterm infants, the effect of inflammation appears to differ by infant sex and race. These demographic factors may be important considerations for future studies of inflammation and neurodevelopment as well was the development of future interventions to optimize outcomes.

Keywords

preterm infant; inflammation; neurodevelopment; neurobehavior; cytokine

Compared to term-born infants, infants born before 37 weeks post-menstrual age (PMA) have poorer neurodevelopmental outcomes (Ionio et al., 2016). Those born very preterm (i.e. less than 32 weeks PMA) experience the most significant adverse long-term effects, with more than 80% requiring early intervention (Clements, Barfield, Ayadi, & Wilber, 2007) and 40–75% requiring special education services (Carter & Msall, 2018) to mitigate the neurodevelopmental consequences of their early birth. Common causative factors of neurodevelopmental impairment in preterm infants include hypoxemia during the neonatal period (Poets et al., 2015), critical illness (Cassiano, Gaspardo, & Linhares, 2016), extended length of hospital stay (Subedi, DeBoer, & Scharf, 2017), and neonatal stress exposure (Cong et al., 2017). In addition to clinical factors, researchers have identified demographic characteristics, including male sex and non-White race, as predictors of poorer neurodevelopment in preterm infants (Linsell, Malouf, Morris, Kurinczuk, & Marlow, 2015).

Early inflammation may also be an important and potentially modifiable cause of neurodevelopmental impairment in preterm infants (Bennet et al., 2018). Circulating cytokines affect the brain by activating receptors on the vascular endothelium and causing damage to the blood-brain barrier that allows for their direct transport into the brain parenchyma (Volpe, Kinney, Jensen, & Rosenberg, 2011). These inflammatory signals can be propagated by resident immune cells in the brain parenchyma and damage developing neurons and oligodendrocyte precursors (Hagberg & Mallard, 2005; Volpe et al., 2011). Researchers have measured circulating cytokines in preterm infants and have found that compared to those with lower levels, infants with higher levels of inflammatory cytokines, such as interleukin (IL)-8, tumor necrosis factor-alpha (TNF-α), IL-6, and IL-1β, develop more short and long-term impairments in cognitive and motor functioning (Nist & Pickler, 2019). However, researchers have found conflicting results that appear to depend on the study sample, timing of the cytokine measurement, and outcome measure.

The purpose of this analysis was to determine whether neonatal inflammation, measured in the first three weeks of life by theoretically selected plasma cytokines, chemokines, and growth factors, was associated with short-term neurodevelopment in preterm infants. The

analysis was based on a model of neurodevelopmental risk and protection that posits, in part, that early exposure to inflammatory agents such as cytokines, may predispose a preterm infant to poor neurodevelopmental outcomes (Pickler, McGrath, et al., 2010). The aims of this exploratory analysis were (1) to determine the association between neonatal inflammation and neurodevelopment, and (2) to determine the extent to which infant sex and/or infant race moderate the relationship between neonatal inflammation and neurodevelopment.

Methods

Patterned Feeding Experience Trial (PEPI)

Data for this analysis were collected as part of a larger randomized controlled trial (Patterned Experience for Preterm Infants; PEPI) designed to examine the effects of a patterned feeding and caregiving experience on neurobehavioral organization at the transition to oral feedings, discharge from the neonatal intensive care unit (NICU), and at two months corrected age; neurodevelopment at six months corrected age; and clinical outcomes including the length of NICU stay and achievement of oral feeding milestones (Pickler, Wetzel, Meinzen-Derr, Tubbs-Cooley, & Moore, 2015). Participants in the PEPI trial included 120 infants born less than 33 weeks PMA and hospitalized in one of two NICUs in a large Midwest city. Infants were randomized to the intervention group, in which they received a tactile intervention during gavage and oral feedings, or to standard feeding care. Because the trial focused on a feeding intervention, only infants born younger than the expected onset of oral feeding (~33–34 weeks) were enrolled. Neurobehavioral organization was measured at the transition to oral feedings, NICU discharge, and at 2 months corrected age (48 weeks PMA) using the Neurobehavioral Assessment of the Preterm Infant, Revised 2nd Edition (NAPI; Korner, Brown, Thom, & Constantinou, 2000). Neurodevelopment was measured at six months corrected age using the Bayley Scales of Infant Development, Third Edition (BSID-III; Bayley, 2006). Infants were excluded if they had gastrointestinal, craniofacial, cardiovascular, neuromuscular, or genetic defects. Approval for the study was provided by the Institutional Review Board, Cincinnati Children's Hospital Medical Center (2011–0871) and The Ohio State University (2015H0347); the trial was registered at ClinicalTrials.gov (NCT10577615). All parents provided written informed consent prior to enrollment of infants in the study.

Sample

Data for this analysis included only those participants who (1) had cytokine measures, (2) survived to discharge from the NICU, (3) had outcome measure (i.e. discharge NAPI or six-month BSID-III), and (4) had no late diagnosis of metabolic disorder or congenital or chromosomal anomaly.

Measures

Demographic and clinical data.—Demographic data including infant sex and PMA at birth and maternal clinical data (e.g. pregnancy complications, maternal medications) were collected from the infant's electronic health record at the time of enrollment in the clinical

trial. Infant clinical data were collected prospectively after enrollment and throughout the infant's hospitalization.

Immunologic measures.—Immunologic measures were selected on the basis of theoretical and empirical data suggesting the importance of the selected measures to neurologic outcomes in preterm infants (Pickler, Brown, et al., 2010). During the first three weeks of life, and prior to the start of the caregiving intervention (i.e. baseline), 500μL of whole blood was collected with a clinically-indicated blood draw for the measurement of plasma cytokines (IL-6, IL-10, IL-1 receptor antagonist [RA], TNF-α), chemokines (IL-8, monocyte chemoattractant protein [MCP]-1), and growth factors (granulocyte colony stimulating factor [GCSF], and granulocyte macrophage colony stimulating factor [GMCSF]). Plasma was separated by centrifugation, and all specimens were aliquoted immediately, frozen, and stored in a − 80 °C freezer until analysis. Samples were analyzed using the Luminex Human Multiplex (Millipore, Billerica, MA) according to the manufacturer's protocol. Briefly, beads were incubated first with diluted standards or samples and then with biotinylated detector antibodies. They were washed twice in phosphate-buffered saline and incubated for 30 minutes at room temperature. Each measurement was taken in duplicate. Standard curves were generated using the reference cytokine concentrations supplied by the manufacturer. Raw data (mean fluorescent intensity) were analyzed using manufacturer software to obtain concentration values. Concentrations were expressed in picograms per milliliter (pg/ml).

Neurobehavioral and neurodevelopmental assessments.—Infant neurobehavior was measured using the NAPI, a norm-referenced assessment for infants between 32 and 40 weeks PMA (Korner et al., 2000). The NAPI consists of 71 test items administered in an invariant sequence and scored as seven "clusters" – scarf sign, motor development and vigor (MDV), popliteal angle, alertness/orientation (AO), cry quality, irritability, and percent asleep ratings. Compared to other developmental assessments for preterm infants, the NAPI has adequate reliability, excellent content validity, and adequate construct and criterion validity (Noble & Boyd, 2012). NAPI scores significantly discriminate between extremely low birthweight infants and very low birthweight infants and are correlated with developmental assessment outcomes at 18 and 30 months corrected age (Constantinou, Adamson-Macedo, Mirmiran, Ariagno, & Fleisher, 2005). Converted cluster scores for the AO and MDV clusters measured at the time of discharge from the NICU were used as outcome measures for this analysis. Compared to other NAPI clusters, AO and MDV are each comprised of multiple assessments and provide the greatest opportunity for measure variance.

The BSID-III, a comprehensive measure of cognitive, motor, language, and socioemotional development for children between birth and 4 years of age (Bayley, 2006), was used to measure neurodevelopment. BSID-III scores discriminate between children born preterm and those born at term, and cognitive and language subscales measured in children born preterm are highly correlated with intelligence quotients at 4 years of age (Bode, D'Eugenio, Mettelman, & Gross, 2014). A recent meta-analysis revealed that BSID cognitive and language subscale scores are highly correlated with intelligence scores at school-age and

that BSID motor subscale scores are moderately correlated with later motor function (Luttikhuizen dos Santos, de Kieviet, Konigs, van Elburg, & Oosterlaan, 2013). For this analysis, we used raw and composite BSID cognitive scores, raw fine and gross motor scores, composite motor scores, and composite language scores measured at 6 months corrected age as outcome measures.

Statistical Analysis

To determine the effect of inflammation on neurodevelopment, data were analyzed using linear regression models with Huber-White sandwich variance estimators, controlling for PMA at birth, day of life (DOL) of blood collection for cytokine analysis, and infant age at the time of neurobehavioral/neurodevelopmental assessment. Analyses were repeated to include interactions with infant sex (male vs female) and, subsequently, race (White vs non-White). We also included PMA at birth, day of life (DOL) of blood collection for cytokine analysis, and infant age at the time of neurobehavioral/neurodevelopmental assessment as covariates in the interaction models. Due to high correlations among inflammatory biomarkers (Takahashi et al., 2010) that preclude the inclusion of multiple cytokines in the same statistical model, we analyzed the effect of each of the eight cytokines individually. We used standardized regression coefficients to facilitate interpretation of the data so that all reported coefficients represent the mean change in outcome per one standard deviation increase in the cytokine. All analyses were conducted using STATA (version 13). For this exploratory analysis, significance was set at $\alpha = .05$.

Results

Of the 120 participants enrolled in the trial, 54 were excluded from the cytokine analysis because no blood was collected for the measurement of cytokines ($n = 47$), the participant expired prior to discharge or was diagnosed with a metabolic disorder after enrollment ($n = 3$), or no neurodevelopmental outcomes were measured ($n = 4$). Of the 66 participants who were eligible for analysis, NAPI outcomes were available for 62 participants, and BSID-III outcomes were available for 40 participants (Supplement Digital Content, Figure 1). Median PMA at birth was approximately 30 weeks in both samples (Table 1). Slightly more males than females were included in the sample for BSID-III outcomes (60% male) and the majority of infants were White. Additional demographic characteristics are available in Table 1.

Cytokine Associations with Neurodevelopment

For the entire sample of infants, we found very few cytokine associations with neurodevelopment, controlling for PMA at birth, blood draw DOL, and infant age at the time of outcome assessment. We found that for every one standard deviation increase in IL-8, there was an average 2.97 (95% CI [0.50, 5.19], $p = .019$) point increase in NAPI AO. Conversely, we found that for every one standard deviation increase in IL-1RA and GCSF, there was an average 4.91 (95% CI [−7.69, −1.89], $p = .002$) and 1.23 (95% CI [−1.70, −0.75], $p < .0005$) point decrease in NAPI MDV and BSID-III raw gross motor score, respectively.

Moderation of Outcomes by Infant Sex

When interactions with infant sex were included in the models, we found associations between a few cytokines and NAPI or BSID-III outcomes in males, controlling for PMA at birth, blood draw DOL, and age at time of NAPI or BSID-III assessment. Among males, increasing levels of IL-8 were associated with better scores on the NAPI AO (see Table 2). For BSID-III assessments performed at 6 months corrected age, we found that increasing levels of GCSF were associated with poorer raw gross motor scores (see Table 3). There were no other significant associations for males.

In contrast to males for whom there were few associations between cytokines and neurodevelopment, we found associations for multiple cytokines and NAPI or BSID-III outcomes in females, controlling for PMA at birth, blood draw DOL, and age at the time of NAPI or BSID-III assessment. We found a significant negative effect for IL-8 and IL-1RA on NAPI MDV in females (see Table 2). Increasing levels of these cytokines were associated with poorer scores on the NAPI MDV. For BSID-III assessments performed at 6 months corrected age, we found that increasing levels of TNF-α were associated with poorer raw cognitive, fine motor, and composite cognitive scores (see Table 3). In addition, increasing levels of GCSF were associated with poorer raw gross motor and composite language scores. Similarly, increasing levels of IL-6 were associated with poorer composite cognitive, composite language, and composite motor scores in females. Increasing levels of MCP-1 were associated with poorer composite language and composite motor scores in females. Of the included cytokines, GCSF had the largest negative effect on neurodevelopment in females. BSID-III composite language scores decreased an average of 13.21 points (95% CI [−21.7, −5.28], $p = .002$) for every one standard deviation increase in GCSF. There were no cytokines for which higher levels were associated with better NAPI or BSID-III outcomes in females.

Moderation of Outcomes by Infant Race

When interactions with infant race were included in the models, we found associations between a few cytokines and NAPI or BSID-III outcomes in Whites, controlling for PMA at birth, blood draw DOL, and age at the time of NAPI or BSID-III assessment. Among Whites, increasing levels of IL-8 were associated with better NAPI AO scores, whereas increasing levels of IL-1RA were associated with poorer NAPI MDV scores (see Table 4). For BSID-III assessments performed at 6 months corrected age, higher levels of GCSF were associated with lower raw cognitive scores and raw gross motor scores (see Table 5). There were no other significant findings for Whites.

We found multiple associations between cytokines and NAPI or BSID-III outcomes among non-Whites, controlling for PMA at birth, blood draw DOL, and age at the time of NAPI or BSID-III assessment. Among non-Whites, increasing levels of IL-8, IL-10, and IL-1RA were associated with lower NAPI AO scores, and increasing levels of IL-8 and IL-1RA were associated with lower NAPI MDV scores. Only higher levels of TNF-α were associated with better NAPI MDV scores among non-Whites (see Table 4). Similarly, multiple cytokines were associated with poorer BSID-III scores among non-Whites (see Table 5). Increasing levels of IL-10 were associated with poorer performance in all assessed BSID-III domains.

Additionally, higher levels of IL-6 and GCSF were associated with lower composite language scores among non-Whites. Higher levels of MCP-1 among non-Whites were associated with poorer composite language and composite motor scores. The largest effect was noted for IL-10 on composite motor scores among non-Whites. For each one standard deviation increase in IL-10, BSID-III composite motor scores decreased an average of 18.92 points (95% CI [−28.55, −9.3], $p < .0005$). There were no cytokines for which higher levels were associated with improved outcomes in non-Whites.

Discussion

The purpose of this analysis was to determine whether early measures of neonatal inflammation using select plasma cytokines, chemokines, and growth factors, were associated with short-term neurobehavioral or neurodevelopmental outcomes in preterm infants. We further sought to determine if there were important modifiers of these relationships. The results build on the growing body of literature describing the effect of inflammation on preterm infant neurodevelopment, as we found a number of differences in the association between the cytokines and neurodevelopment based on infant sex and race.

As single-timepoint measures, there were no cytokines that were consistently associated with neurodevelopment in all groups of infants in our study. We found only associations between IL-8, IL-1RA, and GCSF and specific domains of neurobehavior or neurodevelopment for the entire sample. Other researchers have found that early measures of inflammation, including IL-6, TNF-α, and IL-8, are associated with poorer neurodevelopment in preterm infants, but these findings are inconsistent across studies and may depend on the timing of such measures and the specific neurodevelopmental outcome (e.g. motor, cognitive, behavioral; Nist & Pickler, 2019). Although some researchers have found that early measures of inflammation predict neurodevelopment (Carlo et al., 2011; Hansen-Pupp et al., 2008), sustained inflammation may be a better predictor of neurodevelopment than single, early measures (Korzeniewski et al., 2014; Leviton et al., 2016). Researchers have reported that chronic inflammation, defined by high levels of inflammatory measures at two or more timepoints, predicts structural abnormalities in the brain (Korzeniewski et al., 2015), cerebral palsy (Korzeniewski et al., 2015; Kuban et al., 2014), and cognitive impairment (Kuban et al., 2017).

To develop targeted interventions to mitigate the effects of inflammation, it is important to first identify how the effect of inflammation might be influenced by non-modifiable demographic characteristics. Therefore, we included interactions with infant sex and race in our analysis. While we found very few associations between our measured cytokines and neurodevelopment before examining interactions with infant sex and race, the inclusion of these interactions revealed potentially important findings to guide future research and intervention development. For example, higher levels of IL-8 were associated with poorer NAPI scores, but this relationship was only true for females. Similarly, higher levels of TNF-α were associated with lower scores on some BSID-III subscales, but this relationship was also true only for females. We found no associations between IL-10 and neurodevelopment in the models without interactions, but the interaction models revealed associations between IL-10 and multiple BSID-III outcomes among non-Whites.

Our analysis revealed several cytokines that might be useful as early predictors of neurodevelopment in females. TNF-α and IL-6, along with GCSF and MCP-1 to a lesser extent, predicted poorer neurodevelopment across multiple domains among females at six months corrected age, but there were no cytokines that consistently predicted outcomes in males. Sex hormones differentially affect the development of neuroimmune cells (i.e. microglia) and neural circuits in the immature brain, resulting in disparate microglia-mediated neuroimmune responses to inflammatory stimuli (Osborne, Turano, & Schwarz, 2018). Early life peripheral innate immune responses may also be sex-specific (Rana, Aavani, & Pittman, 2012). Thus, the combination of differences in brain and immune system development and responses between the sexes could account for the sex-specific findings from our study. Similar to our findings, Varner et al. (2020) reported that polymorphisms of the IL-6 gene were associated with neurodevelopmental impairment in females but not males. However, very few studies have been designed to examine sex-specific associations between cytokines and neurodevelopment.

Our analysis also revealed relationships between inflammation and neurodevelopment that differed by race. While higher levels of IL-10 were associated with poorer outcomes across all measured domains of neurodevelopment at six months corrected age among non-Whites, this was not true for Whites. Few studies have examined differences in immune function and neurodevelopment by race. The majority of studies in this area have focused on maternal immune function and the occurrence of preterm birth. Researchers have found distinct cytokine patterns in amniotic fluid, maternal blood, and fetal/cord blood associated with preterm birth that differ between White and African-American populations (Brou et al., 2012). Amniotic fluid levels of IL-6 (Menon, Camargo, Thorsen, Lombardi, & Fortunato, 2008), IL-1β (Brou et al., 2012), TNF-α (Brou et al., 2012), and IL-8 (Menon, Williams, & Fortunato, 2007) and their associations with preterm birth have been differentially reported for White and African-American women. However, we could find no studies that examined interactions between infant cytokine levels and race on neurodevelopmental outcomes.

The reasons for different associations between cytokine levels and neurodevelopment for males and females or Whites and non-Whites in our study are unclear. There may be genetic, demographic, or other factors that account for the differences observed between groups. These findings underscore the importance of examining interactions with sex and race in studies of preterm infants rather than simply controlling for these factors in the statistical analysis. Such factors may be important in the development of future interventions to optimize outcomes.

Limitations

There are several limitations of our analysis. First, we were able to obtain only a single, early-life measure of cytokines, chemokines, and growth factors. Thus, we cannot determine the duration of inflammation for each infant, which may be important in predicting subsequent brain injury and neurodevelopment. Second, our sample was small and we did not control for multiple comparisons in our analysis. This study was an exploratory analysis of secondary data that aimed to provide preliminary guidance to the design of future studies of inflammation and neurodevelopment in preterm infants. Finally, based on the

demographics of our sample, we were only able to dichotomize race into White and non-White. Studies with larger, more diverse samples could examine race in greater detail.

Future Directions

Our findings provide a foundation to guide the design of future studies on the effect of inflammation on neurodevelopment in preterm infants. To build on this work, future studies could include longitudinal measures of inflammation to better discriminate between transient and sustained inflammation, for which there may be different effects. In addition, we have shown that infant sex and race are important moderators of the relationship between inflammation and neurodevelopment. While researchers occasionally control for infant sex in their analyses, they rarely examine interactions with infant sex or race (Nist & Pickler, 2019). Additional research is needed to describe the differences in inflammation-mediated effects between males and females and between Whites and non-Whites, as this information may be critical in designing future interventions to meet the unique needs of individual infants.

Conclusion

Inflammation may cause injury to the developing brain and is associated with neurodevelopmental impairment in preterm infants. Future studies examining repeated measures of inflammatory measures as predictors of subsequent neurodevelopment are needed. Moreover, the association of cytokines with neurodevelopment in preterm infants appears to differ based on infant sex and race. Examination of interactions with infant sex and race will be critical to future studies of inflammation and neurodevelopment and the development of future nursing interventions to optimize outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Participant Characteristics

	NAPI Sample (n=62) *n* (%)	BSID-III Sample (n=40) *n* (%)
Male sex (*n*, %)	31 (50%)	24 (60%)
White race (*n*, %)	35 (56.5%)	25 (62.5%)
	Median (Min-Max)	**Median (Min-Max)**
PMA at birth (weeks)	30.3 (25–32.9)	29.6 (25.6–32.9)
Age at outcome assessment	36.4 (33.4–42.4) weeks[a]	6.3 (5.6–8) months[b]
Postnatal age at blood draw (days)	5 (1–13)	5.5 (3–13)
IL-6 (pg/mL)	10.4 (0.96–251.9)	19.7 (1.2–251.9)
IL-10 (pg/mL)	5.7 (0.6–97.3)	6.5 (0.75–97.3)
IL-1RA (pg/mL)	105.8 (8.3–2200)	122.1 (10–2200)
TNF-α (pg/mL)	33.5 (10.6–107.4)	35.2 (12.9–107.4)
IL-8 (pg/mL)	64.3 (12.5–1216)	78.8 (15.9–1216)
MCP-1 (pg/mL)	1040.4 (176–8907.2)	1114.4 (176–10000)
GCSF (pg/mL)	108.9 (27.5–7000)	116.4 (34.1–7000)
GMCSF (pg/mL)	6.2 (0.7–29.7)	6.4 (2.3–29.7)

Note.

[a] PMA in weeks;

[b] Age in months, corrected for degree of prematurity, and based on a 30-day month;

PMA, post-menstrual age; NAPI, Neurobehavioral Assessment of the Preterm Infant; BSID-III, Bayley Scales of Infant Development, 3rd Edition; pg/mL, picograms per milliliter; IL, interleukin; RA, receptor antagonist; TNF-α, tumor necrosis factor-alpha; MCP, monocyte chemoattractant protein; GCSF, granulocyte colony stimulating factor; GMCSF, granulocyte macrophage colony stimulating factor.

Table 2.

Significant Findings for NAPI Outcomes Moderated by Infant Sex

		Coefficient	95% CI	*p*-value
NAPI AO	TNF-α			
	Interaction	8.38	0.28, 16.57	.043
	Effect for females	−4.28	−9.68, 1.12	.12
	Effect for males	4.10	−1.40, 9.68	.14
	MCP-1			
	Interaction	6.93	0.51, 13.34	.035
	Effect for females	−3.59	−7.95, 0.92	.12
	Effect for males	3.59	−1.59, 8.47	.18
	IL-8			
	Interaction	9.45	2.78, 16.12	.006
	Effect for females	−5.37	−11.49, 0.74	.084
	Effect for males	4.08	1.85, 6.30	<.0005
NAPI MDV	IL-8			
	Interaction	4.08	−1.39, 9.64	.14
	Effect for females	−5.37	−10.19, −0.43	.033
	Effect for males	−1.13	−3.34, 1.11	.32
	IL-1RA			
	Interaction	0.71	−5.91, 7.09	.84
	Effect for females	−5.08	−7.69, −2.31	<.0005
	Effect for males	−4.37	−10.64, 2.19	.19

Note. Table contains standardized regression coefficients. NAPI = Neurobehavioral Assessment of the Preterm Infant; AO = alertness/orientation; MDV = motor development and vigor; CI = confidence interval; TNF-α = tumor necrosis factor-alpha; MCP = monocyte chemoattractant protein; IL = interleukin, RA = receptor antagonist.

Table 3.

Significant Findings for BSID Outcomes Moderated by Infant Sex

		Coefficient	95% CI	*p*-value
Raw cognitive score	TNF-α			
	Interaction	2.05	−0.73, 4.84	.14
	Effect for females	−2.42	−4.66, −0.02	.049
	Effect for males	−0.28	−1.82, 1.27	.71
Raw fine motor score	TNF-α			
	Interaction	2.23	0.45, 3.91	.016
	Effect for females	−2.05	−3.72, −0.52	.011
	Effect for males	0.07	−1.28, 1.43	.92
Raw gross motor score	GCSF			
	Interaction	1.13	−0.41, 2.64	.15
	Effect for females	−2.17	−3.58, −0.85	.002
	Effect for males	−1.13	−1.79, −0.43	.002
Composite cognitive score	IL-6			
	Interaction	4.26	−4.49, 12.95	.33
	Effect for females	−5.09	−8.79, −1.06	.014
	Effect for males	−0.79	−8.33, 6.48	.83
	TNF-α			
	Interaction	8.19	−1.40, 17.69	.092
	Effect for females	−8.57	−16.20, −1.10	.026
	Effect for males	−0.45	−5.59, 4.84	.86
Composite language score	IL-6			
	Interaction	10.18	1.34, 18.50	.025
	Effect for females	−6.94	−12.03, −2.08	.007
	Effect for males	2.91	−4.39, 10.18	.42
	GCSF			
	Interaction	14.15	5.28, 22.64	.003
	Effect for females	−13.21	−21.70, −5.28	.002
	Effect for males	0.17	−2.08, 2.36	.88
	MCP-1			
	Interaction	8.47	−1.82, 18.47	.1
	Effect for females	−8.21	−15.91, −0.41	.04
	Effect for males	0.21	−5.64, 6.16	.94
Composite motor score	IL-6			
	Interaction	8.33	−6.01, 22.20	.24
	Effect for females	−6.48	−10.64, −2.54	.002
	Effect for males	1.71	−12.03, 15.26	.8
	TNF-α			
	Interaction	9.50	0.13, 18.99	.047
	Effect for females	−6.14	−13.59, 1.38	.11

		Coefficient	95% CI	*p*-value
	Effect for males	3.54	−2.79, 9.68	.26
	MCP-1			
	Interaction	10.01	−2.46, 22.58	.11
	Effect for females	−7.18	−14.62, −0.05	.049
	Effect for males	2.82	−6.93, 12.57	.57

Note. Table contains standardized regression coefficients. BSID = Bayley Scales of Infant Development; CI = confidence interval; TNF-α = tumor necrosis factor-alpha; GCSF = granulocyte colony stimulating factor; IL = interleukin; MCP = monocyte chemoattractant protein.

Table 4.

Significant Findings for NAPI Outcomes Moderated by Infant Race

		Coefficient	95% CI	*p*-value
NAPI AO	IL-8			
	Interaction	−12.42	−18.53, −5.75	<.0005
	Effect for Whites	5.19	2.78, 7.60	<.0005
	Effect for non-Whites	−7.23	−12.97, −1.37	.016
	IL-10			
	Interaction	−13.11	−20.58, −5.81	.001
	Effect for Whites	0.42	−1.48, 2.32	.67
	Effect for non-Whites	−12.78	−20.09, −5.48	.001
	IL-1RA			
	Interaction	−11.23	−15.37, −7.09	<.0005
	Effect for Whites	−0.30	−4.20, 3.61	.88
	Effect for non-Whites	−11.82	−13.60, −9.46	<.0005
NAPI MDV	TNF-α			
	Interaction	4.10	−0.24, 8.57	.064
	Effect for Whites	−1.10	−4.47, 2.23	.51
	Effect for non-Whites	3.17	0.07, 6.14	.045
	IL-8			
	Interaction	−7.60	−13.16, −2.04	.009
	Effect for Whites	−0.01	−2.59, 25.95	.99
	Effect for non-Whites	−7.60	−11.86, −3.34	.001
	IL-1RA			
	Interaction	−0.71	−5.26, 3.84	.76
	Effect for Whites	−4.67	−9.46, −0.20	.041
	Effect for non-Whites	−5.38	−7.09, −3.67	<.0005

Note. Table contains standardized regression coefficients. NAPI = Neurobehavioral Assessment of the Preterm Infant; AO = alertness/orientation; MDV = motor development and vigor; CI = confidence interval; IL = interleukin; RA = receptor antagonist; TNF-α = tumor necrosis factor-alpha.

Table 5.

Significant Findings for BSID Outcomes Moderated by Infant Race

		Coefficient	95% CI	*p*-value
Raw cognitive score	GCSF			
	Interaction	0.45	−1.60, 2.55	.66
	Effect for Whites	−0.42	−0.82, −0.01	.047
	Effect for non-Whites	0.04	−2.08, 2.17	.97
	IL-10			
	Interaction	−3.15	−5.31, −1.06	.005
	Effect for Whites	−0.43	−1.44, 0.60	.4
	Effect for non-Whites	−3.65	−5.64, −1.64	.001
Raw fine motor score	IL-10			
	Interaction	−3.82	−5.64, −1.99	<.0005
	Effect for Whites	0.42	−0.55, 1.39	.39
	Effect for non-Whites	−3.32	−5.15, −1.61	.001
Raw gross motor score	GCSF			
	Interaction	−0.35	−2.55, 1.89	.75
	Effect for Whites	−1.23	−1.70, −0.69	<.0005
	Effect for non-Whites	−1.51	−3.77, 0.67	.16
	IL-10			
	Interaction	−3.49	−6.81, −0.15	.041
	Effect for Whites	−0.53	−3.15, 1.99	.68
	Effect for non-Whites	−3.98	−6.64, −1.44	.003
Composite cognitive score	IL-10			
	Interaction	−9.96	−17.60, −2.32	.012
	Effect for Whites	−1.83	−4.98, 1.38	.26
	Effect for non-Whites	−11.79	−18.59, −4.81	.002
Composite language score	IL-6			
	Interaction	−7.86	−14.80, −0.42	.039
	Effect for Whites	1.76	−4.63, 8.33	.59
	Effect for non-Whites	−6.01	−10.64, −1.30	.014
	GCSF			
	Interaction	−12.26	−20.75, −3.40	.007
	Effect for Whites	−0.10	−1.98, 1.79	.92
	Effect for non-Whites	−12.26	−20.75, −3.68	.006
	MCP-1			
	Interaction	−7.95	−13.34, −2.57	.005
	Effect for Whites	−1.03	−5.64, 3.59	.65
	Effect for non-Whites	−8.98	−12.83, −5.39	<.0005
	IL-10			
	Interaction	−12.45	−21.41, −3.49	.008
	Effect for Whites	−0.96	−2.99, 1.13	.35

		Coefficient	95% CI	*p*-value
	Effect for non-Whites	−13.45	−22.41, −4.48	.005
Composite motor score	MCP-1			
	Interaction	−6.93	−16.16, 2.44	.14
	Effect for Whites	0.22	−7.44, 7.95	.96
	Effect for non-Whites	−6.67	−12.57, −0.64	.031
	IL-10			
	Interaction	−18.76	−30.05, −7.64	.002
	Effect for Whites	−0.09	−6.81, 6.64	.98
	Effect for non-Whites	−18.92	−28.55, −9.30	<.0005

Note. Table contains standardized regression coefficients. BSID = Bayley Scales of Infant Development; CI = confidence interval; GCSF = granulocyte colony stimulating factor; IL = interleukin; MCP = monocyte chemoattractant protein.