

# Associations of Maternal Prenatal Stress and Depressive Symptoms With Childhood Neurobehavioral Outcomes in the ECHO Cohort of the NICHD Fetal Growth Studies: Fetal Growth Velocity as a Potential Mediator

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**Objective:** Maternal prenatal stress and mood symptoms are associated with risk for child psychopathology. Within the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Fetal Growth Studies (ECHO-FGS), a racially and ethnically diverse cohort, we studied associations between prenatal stress and depressive symptoms with child neurobehavior, and potential mediation by fetal growth velocity (FGV) in low-risk pregnancies.

**Method:** For 730 mother–child pairs, we had serial ultrasound measurements, self-reports of prenatal stress and depression, observations of child executive functions and motor skills from 4 to 8 years, and maternal reports of child psychiatric problems. We tested associations between prenatal stress and depressive symptoms with child neurobehavior in regression analyses, and associations with FGV in mixed effect models. Post hoc we tested severity of prenatal symptoms; FGV at 25<sup>th</sup>, 50<sup>th</sup>, and 75<sup>th</sup> percentiles; and moderation by biological sex and by race and ethnicity.

**Results:** Prenatal stress and depressive symptoms were associated with child psychiatric problems, and prenatal depressive symptoms with decrements in executive functions and motor skills, especially in biological male children. Neither prenatal stress nor depressive symptoms were associated with FGV.

**Conclusion:** In one of the largest cohorts with observed child outcomes, and the first with broad representation of race and ethnicity in the United States, we found that prenatal stress and depressive symptoms were associated with greater reports of child psychiatric symptoms. Only prenatal depressive symptoms were associated with observed decrements in cognitive abilities, most significantly in biological male children. Stress during low-risk pregnancies may be less detrimental than theorized. There was no mediation by FGV. These findings support the need to attend to even small changes in prenatal distress, as these may have long-lasting implications.

**Key words:** prenatal stress, neurodevelopment, neurobehavior, psychiatric problems, fetal growth velocity

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**M**aternal stress and depressive symptoms during pregnancy are associated with a range of adverse neurobehavioral outcomes in offspring extending throughout childhood, particularly including attention, emotion, and behavior problems.<sup>1</sup> In a prenatal cohort, O'Donnell *et al.*<sup>2</sup> demonstrated that higher levels of

prenatal depression and anxiety were associated with a 2-fold increased risk of child behavioral and emotional problems. Similarly, Szekely *et al.*<sup>3</sup> replicated findings across 3 prenatal cohorts to demonstrate that prenatal affective problems were associated with child psychopathology. Anxiety during pregnancy has also been associated with

decrements in executive functions,<sup>4</sup> and prenatal stress with compromised motor skills.<sup>5</sup> There are no prenatal programming studies to date that have examined both psychiatric outcomes and cognitive abilities within the same cohort, despite the fact that they are highly related.<sup>6-8</sup> Although integral to establishing associations between prenatal adversity and child neurobehavior, previous cohort studies are predominantly homogeneous in terms of race and ethnicity, most often rely on maternal report of child outcomes, and do not identify maternal prenatal mood effects prior to postpartum environmental influences.<sup>2,3</sup>

We address these gaps using data from the Environmental Influences on Child Health Outcomes cohort of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Fetal Growth Studies (ECHO-FGS), a cohort with a broad representation of the racial and ethnic diversity in the United States.<sup>9</sup> ECHO-FGS gathered self-reports of prenatal stress and depressive symptoms, and observations of children's executive functions and motor skills at ages 4 to 8 years, in addition to maternal reports of child psychiatric problems and ultrasound measures of fetal growth velocity (FGV).

Maternal prenatal stress and affective disorders are risk factors associated with cognitive deficits throughout childhood.<sup>10</sup> Cognition is a domain of behavioral and neurological health that encompasses executive functions and motor skills.<sup>11</sup> Executive functions, which are top-down cognitive modulations of goal-directed activity, include inhibitory control/sustained attention, cognitive flexibility, and working memory.<sup>11</sup> These functions enable children to better control thoughts, feelings, and behaviors; facilitate their ability to learn, problem solve, plan, and complete tasks; and increase social and academic success.<sup>12</sup> The development of executive functions, largely substantiated by neural circuits in the prefrontal cortex,<sup>12</sup> emerges in infancy, grows rapidly from 2 to 5 years, and can be assessed using standardized observational measures.<sup>11</sup> Maternal prenatal depression has been associated with decreases in cognitive development as early as 18 months,<sup>13</sup> and prenatal anxiety with impaired working memory at 8 years.<sup>4</sup> Pregnancy-related anxiety has been associated with impaired working memory at 6 to 9 years, along with impaired inhibitory control in biological female children.<sup>14</sup>

Executive functions can be better understood when studied in conjunction with motor skills; both sets of abilities co-develop in bidirectional and reciprocal ways.<sup>12</sup> Children with better motor skills show more mature white matter patterns within motor pathways, and the structural variation in these pathways partially accounts for variability in motor performance associated with early learning.<sup>15</sup> Prenatal stress has been associated with delays in

fine and gross motor skills from early childhood to adolescence, with greater delays among children whose mothers experience stress in late pregnancy.<sup>5,16</sup> Fine motor skills are associated with literacy and mathematics, whereas gross motor skills are associated with social and behavioral outcomes.<sup>12</sup> In infancy, there are data to suggest that biological male infants have greater delays in motor skills than biological female infants when exposed to prenatal depression.<sup>17</sup> In children 5.5 years old, prenatal stress has been associated with decreased bilateral coordination and visual motor integration, again especially in biological males children.<sup>13</sup> Impairments in motor development have been demonstrated in both biological sexes when maternal stress exposure occurs later in pregnancy.<sup>18,19</sup> Not yet conclusive, there are data to suggest that children exposed to prenatal stress continue to demonstrate delays in motor skills at 10, 14, and 17 years of age.<sup>5</sup>

Decrements in executive functions and motor skills are strongly associated with childhood psychopathology, which highlights the possibility of shared etiological influences.<sup>6-8</sup> Deficits in executive functions are associated with general psychopathology, including anxiety, depression, oppositional defiant disorder, attention-deficit/hyperactivity disorder (ADHD), and autism spectrum disorder (ASD). Deficits in motor skills appear to be associated more specifically with ADHD, learning disorders, and ASD.<sup>6-8,20</sup> Neurobehavioral development encompasses multiple inter-related domains of functioning, and research that considers each of these domains is needed to establish a more nuanced and integrated understanding of how maternal prenatal stress and mood disturbances relate to children's mental health and well-being.<sup>12</sup>

Prenatal affective problems have been associated with childhood cognitive deficits and psychopathology<sup>2,3</sup>; however, there is a lack of direct evidence to support prenatal programming at the time at which it is hypothesized to occur.<sup>21</sup> We included FGV as a potential mediator of the association between prenatal stress and depressive symptoms with child neurobehavior. Prenatal stress has been associated with various proxy measures of FGV (eg, birth weight, gestational age)<sup>22</sup> (although a previous study reports contrasting results<sup>23</sup>), which in turn have been associated with increased risk for child psychopathology,<sup>10,21,24</sup> particularly for ADHD.<sup>25</sup> When FGV of estimated fetal weight is <5<sup>th</sup> percentile, this estimate is more highly associated with low birth weight than with fetal size.<sup>24</sup> Whether prenatal stress is associated with poor FGV, or whether FGV mediates the association between prenatal stress or depressive symptoms and child neurobehavior, has yet to be determined.

Although there is evidence that prenatal stress and mood symptoms are associated with variations in child

neurobehavior, these findings have not been clearly established in a racially and ethnically diverse sample; nor is there clear evidence to suggest that this effect is programmed prior to birth.<sup>21</sup> Our goal was to determine whether prenatal stress and depressive symptoms during otherwise low-risk pregnancies would be associated with multiple domains of child neurobehavior, both observed and maternal-reported, in a racially and ethnically diverse sample, and, if so, whether these associations would be mediated by FGV. The domains included the following: (1) decrements in executive functions, (2) delays in motor skills, and (3) increased psychiatric problems. In addition, we investigated whether our findings would differ by biological sex, given evidence for sex differences,<sup>26</sup> or by self-reported race and ethnicity, given evidence that a number of studies and measures that assess child mental health lack cross-cultural validity.<sup>27</sup>

## METHOD

The Eunice Kennedy Shriver NICHD Fetal Growth Studies recruited 2,334 women with low-risk singleton pregnancies from 12 community and perinatal centers across the United States from 2009 to 2013. The study established fetal growth standards using a sample with a broad representation of self-reported race and ethnicity.<sup>9,28</sup> Eligibility criteria were maternal age 18 to 40 years at delivery, pregravid body mass index (BMI) between 19.0 and 29.9, and no confirmed or suspected congenital, structural, or chromosomal anomalies. Exclusion criteria were maternal cigarette smoking, illicit drug use, consumption of at least one alcoholic drink per day, conception with reproductive drugs or technology, history of chronic medical conditions, psychiatric disorder currently requiring medication, and past pregnancy complications (ie, gestational diabetes, severe preeclampsia, miscarriage, stillbirth, preterm delivery, low birth weight). ECHO-FGS is a follow-up study of 1,116 mother–child pairs initially recruited for the NICHD Fetal Growth Studies; only 10 of the 12 sites continued to participate in the follow-up study that assessed children from 2017 to 2019 when they were 4 to 8 years of age. Our study included 730 (of the 1,116) mother–child pairs, based on the availability of serial antenatal ultrasound measurements of fetal growth, maternal self-report of prenatal stress and depressive symptoms, standardized observations of child executive functions and motor skills, and maternal reports of child psychiatric problems.

### Prenatal Stress and Depressive Symptoms Measures

The Perceived Stress Scale (PSS)<sup>29</sup> measured perceived stress over the past month, and the Edinburgh Postpartum

Depression Scale (EPDS)<sup>30</sup> measured depressive symptoms over the past week. The PSS and EPDS were administered 6 times throughout pregnancy (ie, 16–22, 24–29, 30–33, 34–37, 38–41 weeks' gestation). The PSS included 10 items rated on a 5-point Likert scale, with higher scores indicating greater stress (range, 0–40). The EPDS included 10 items rated on a 4-point Likert scale, with higher scores indicating greater depressive symptoms. Prenatal stress was summed and averaged at each time point; the 6 average scores were summed and averaged as the final score. The same procedure was repeated for prenatal depressive symptoms. Trimester-specific effects were not considered, as scores did not vary significantly across gestation, which is typical of a community-based sample.<sup>31</sup>

### Child Neurobehavior Measures

Neurobehavioral outcomes were assessed between age 4 and 8 years and included standardized (1) observations of executive functions, (2) observations of motor skills, and (3) maternal reports of psychiatric problems.

*Executive Functions and Motor Skills.* To assess executive functions and motor skills, we used the NIH Toolbox for Assessment of Neurological and Behavioral Function (NIH-TB), a standardized observational measure of executive functions (ie, inhibitory control/sustained attention, working memory, cognitive flexibility) and motor skills (ie, dexterity dominant, dexterity nondominant, strength, balance).<sup>32</sup> Raw scores were converted to *t* scores. Each outcome variable was summed and averaged as an overall score and analyzed as a continuous variable. Higher scores indicated greater cognitive abilities, and lower scores indicated decrements.

*Psychiatric Problems.* To assess psychiatric problems, the Child Behavior Checklist (CBCL)<sup>33</sup> and the Social Communication Questionnaire (SCQ)<sup>34</sup> are standardized questionnaires of child psychiatric problems. We used the CBCL to assess maternal reports of attention problems, oppositional defiant problems, conduct problems, anxiety problems, and depression problems. Raw scores on the CBCL were converted to *t* scores. Each outcome variable was summed and averaged as an overall score, and assessed as continuous with greater scores indicating greater problems.<sup>33</sup> The SCQ was used to assess symptoms of ASD. The SCQ-Current was used when children were 4 to 5 years of age, and the SCQ-Lifetime was used when children were  $\geq 6$  years. The outcome variable was summed and averaged as an overall score, and assessed as a continuous score with greater scores indicating greater symptoms of ASD.<sup>35</sup>

### Fetal Growth Velocity Assessment

A model to compute FGV percentiles throughout gestation has previously been developed.<sup>24</sup> The FGV calculations included serial measures of fetal growth divided by gestational age, measured at 16 to 22, 24 to 29, 30 to 33, 34 to 37, and 38 to 41 weeks' gestation. FGV was first calculated for individual biometric parameters (ie, head circumference, abdominal circumference, femur length) to create 5<sup>th</sup>, 10<sup>th</sup>, 50<sup>th</sup>, 90<sup>th</sup>, and 95<sup>th</sup> percentiles by maternal self-reported race and ethnicity, based on prior studies showing race and ethnicity differences in FGV.<sup>9,36</sup> FGV for estimated fetal weight was then calculated by adding the individual biometric parameters (ie, a calculation that includes FGV for head circumference, abdominal circumference, and femur length).<sup>37</sup> FGV norms for NICHD Fetal Growth Studies have previously been published.<sup>24</sup> FGV for estimated fetal weight, a continuous measure with 5 time points, was considered as a mediator of associations between prenatal stress and depressive symptoms with child neurobehavior.

### Covariates

Information on maternal age, pregravid BMI, education background, income, prenatal social support, maternal stress and depressive symptoms at the time of child neurobehavioral assessment, fetal exposure to secondhand smoke, biological sex, maternal self-reported race and ethnicity, mode of delivery, and gestational age at birth were gathered during pregnancy and subsequent study visits. Sociodemographic information was reported on a Maternal Questionnaire designed for this study. Educational background was subdivided into 5 categories, and income was adjusted for household family size with the Square Root Scale (ie, divided by the square root of the number of individuals per household, divided into quintiles).<sup>3,38</sup> Social support was reported on the Enhancing Recovery in Coronary Heart Disease Patients Social Support Instrument (ESSI). We used 6 items from the ESSI rated on a 5-point Likert scale (ie, range, 0-30), with higher scores indicating greater social support.<sup>39</sup> Maternal stress and depressive symptoms at time of child assessment were self-reported on the same PSS and EPDS scales used in the perinatal period.<sup>40</sup> The EPDS has been validated for depression screening in the general population.<sup>41,42</sup> Serum cotinine levels were extracted from maternal blood draws collected at 10 to 13 weeks' gestation to assess fetal exposure to secondhand smoke (ie,  $\geq 0.05$  ng/mL). Possible modes of delivery were spontaneous vaginal delivery, scheduled cesarean delivery without labor, cesarean delivery after trial of labor, or operative vaginal delivery. All covariates were assessed as continuous variables except for

maternal education, income, biological sex, maternal self-reported race and ethnicity, and mode of delivery, which were inherently categorical.

### Statistical Analysis

We examined the distribution of continuous variables; prenatal stress and depressive symptoms were normally distributed. Balance, dexterity (dominant and nondominant), and child psychiatric problems were skewed and log transformed. Other variables were normally distributed. Any values beyond a 3 interquartile range from the first and third quartiles were considered outliers. They were included in all analyses and then excluded to evaluate the stability of findings. Missing values for covariates were examined and compared to nonmissing values; missing values ranged from 0% to 6%. We performed multiple imputation for missing values using Multivariate Imputation by Chained Equations with 20 imputations.<sup>43</sup> Results were pooled following the Rubin rule.<sup>44</sup> Multiple comparison correction was conducted to control for false discovery rate (FDR).<sup>45</sup> We considered the FDR adjusted *p* values (*q* values)  $< .05$  as statistically significant.

Regression was used to test for associations between maternal prenatal stress and depressive symptoms with child neurobehavior. Mixed effect modeling was used to test associations between maternal prenatal stress and depressive symptoms with FGV. The mixed effect models included FGV as the repeated dependent variable, prenatal stress (or depressive symptoms), and gestational age as the fixed effects, a random intercept, and slope for gestational age. Models were adjusted with covariates.

We planned to conduct a mediation analysis to test the hypothesis that FGV would mediate associations between prenatal stress and depressive symptoms with child neurobehavioral outcomes; however, mediation was not supported, given that neither prenatal stress nor depressive symptoms was associated with FGV.

**Post Hoc Analysis.** We explored whether higher prenatal stress and depressive symptoms were associated with child neurobehavioral outcomes or FGV. Scores on the PSS were dichotomized at  $\geq 85^{\text{th}}$  percentile, and scores on the EPDS at  $\geq 10$  cutoff score.<sup>46</sup> A cutoff score of  $\geq 10$  on the EPDS is commonly used for depression screening with good sensitivity and specificity, and can reduce false-negative results as compared to higher cutoff scores (eg,  $\geq 13$ ), as described in a recent meta-analysis.<sup>46</sup> The regression analyses with child neurobehavioral outcomes and mixed effect analyses with FGV were re-run with dichotomous prenatal stress and depressive symptoms.

We performed exploratory regression analyses to test associations between prenatal stress and depressive symptoms with FGV dichotomized at the 25<sup>th</sup>, 50<sup>th</sup>, and 75<sup>th</sup> percentiles, controlling for covariates. Prenatal stress and depressive symptoms were included as continuous and dichotomous variables. We did not investigate FGV at the 5<sup>th</sup> or 95<sup>th</sup> percentiles, as there were too few observations.

Regression analyses were stratified by biological sex, maternal self-reported race and ethnicity, education, and income. Interactions were formally tested in regression analyses; interaction terms were created to test whether there were associations between prenatal stress and depressive symptoms with child neurobehavioral outcomes, moderated by biological sex, self-reported race and ethnicity, education, or income. Because there were 4 categories for race and ethnicity and 5 categories for education, pairwise comparison tests were performed to identify contrasts between groups (Table S1 and Table S2, available online). Prenatal stress and depressive symptoms were included as both continuous or dichotomous variables, and models were adjusted with covariates. Multiple comparison correction was conducted to control for FDR when models were significant.

## RESULTS

### Demographics

Participant sociodemographic characteristics were representative of a low-risk community-based sample with average levels of prenatal stress (mean = 9.61, SD = 5.39)<sup>31</sup> and low levels of prenatal depressive symptoms (mean = 4.49, SD = 3.18)<sup>47</sup> (Table 1). The cohort demonstrated an average education background and income, and a broad representation of self-reported race and ethnicity in the US population (Table 1).<sup>9,24</sup> However, Hispanic and non-Hispanic Black women had significantly lower educational background and income as compared to Asian/Pacific Islander and non-Hispanic White women (Table 1). Prenatal stress and depressive symptoms were each highly correlated across the first, second, and third trimesters ( $r = 0.67-0.77, p < .001$ ).<sup>31</sup>

### Child Neurobehavioral Outcomes

Higher prenatal stress was associated with greater reports of child psychiatric problems (ie, attention problems, oppositional defiant problems, conduct problems, depression problems), but was not associated with observed child executive functions or motor skills (Table 2). Higher prenatal depressive symptoms were associated with greater reports of child psychiatric problems (ie, attention problems, depression problems) and with decrements in observed child

motor skills (ie, strength), but not with observed child executive functions (Table 2). Prenatal stress and depressive symptoms were not associated with maternal reports of ASD symptoms. After correcting for multiple comparisons to control for FDR, the only association that remained significant was the association between higher levels of prenatal stress and greater reports of oppositional defiant problems ( $\beta = 0.002$ , standard error [SE] = 0.001,  $p = .055$ ).

### FGV Outcomes

Prenatal stress and depressive symptoms were not associated with FGV (Table 3).

### Post Hoc Results

*Dichotomous Prenatal Stress and Depressive Symptoms.* Prenatal stress  $\geq 85^{\text{th}}$  percentile ( $n = 108$ , mean = 19.02, SD = 2.77) was associated with greater reports of child psychiatric problems (ie, attention problems, oppositional defiant problems, conduct problems, depression problems), but not with observed child executive functions or motor skills (Table 2). Prenatal depressive symptoms  $\geq 10$  cutoff ( $n = 50$ , mean = 11.55, SD = 1.76) were associated with greater reports of child psychiatric problems (ie, attention problems, oppositional defiant problems) and with decrements in observed child executive functions (ie, cognitive flexibility), but not with observed delays in child motor skills (Table 2). After correcting for multiple comparisons to control for FDR, associations did not remain significant.

*Dichotomous FGV.* Prenatal stress and depressive symptoms, analyzed as either continuous or dichotomous variables, were not associated with FGV as either a continuous or dichotomous variable (ie, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup> percentiles) (Table 3).

*Moderation by Biological Sex.* There was an association between prenatal depressive symptoms  $\geq 10$  cutoff and decrements in observed child executive functions (ie, inhibitory control/sustained attention) moderated by biological sex ( $F = 5.802$ ,  $df = 646.356$ ,  $p < .05$ ), with a stronger association among males as compared to females ( $\beta = -5.681$ , SE = 2.325,  $p < .05$ ) (Figure 1). There was also an association between prenatal depressive symptoms  $\geq 10$  cutoff and decrements in observed child motor skills (ie, strength) moderated by sex ( $F = 3.966$ ,  $df = 638.601$ ,  $p < .05$ ), also with a stronger association among males as compared to females ( $\beta = -6.005$ , SE = 2.313,  $p < .01$ ) (Figure 1). These associations remained significant after correcting for multiple comparisons to control for FDR.

**TABLE 1 Demographic Characteristics Stratified by Self-Reported Race and Ethnicity**

	Asian/Pacific Islander		Hispanic		Non-Hispanic Black		Non-Hispanic White	
	M (SD)	Frequency (%)	M (SD)	Frequency (%)	M (SD)	Frequency (%)	M (SD)	Frequency (%)
Self-reported race and ethnicity		88 (12.05)		176 (24.11)		239 (32.74)		227 (31.1)
Maternal age at delivery, y***	31.16 (4.54)		28.53 (5.87)		24.82 (5.45)		30.95 (4.19)	
Pregavid BMI***	23.15 (2.90)		26.82 (5.73)		26.33 (5.69)		25.53 (5.25)	
Cotinine exposure, yes***		7 (8.24)		35 (20.83)		135 (57.45)		35 (16.2)
Mode of delivery								
Spontaneous vaginal delivery		52 (59.09)		112 (63.64)		152 (63.60)		140 (61.67)
Scheduled cesarean delivery		9 (10.23)		6 (3.41)		12 (5.02)		11 (4.85)
Cesarean delivery after trial of labor		13 (14.77)		35 (19.89)		29 (12.13)		42 (18.5)
Operative vaginal delivery		14 (15.91)		23 (13.07)		46 (19.25)		34 (14.98)
Gestational age at birth, wk	39.17 (1.65)		39.35 (1.31)		38.99 (1.70)		39.17 (1.47)	
Child biological sex, female		41 (46.59)		89 (50.57)		116 (48.54)		106 (46.70)
Social support	27.11 (3.38)		27.10 (4.09)		27.89 (3.06)		28.62 (1.90)	
Maternal prenatal stress***	9.22 (4.70)		9.31 (5.24)		11.27 (6.00)		8.26 (4.61)	
Maternal prenatal stress ≥85 <sup>th</sup> percentile***		8 (9.09)		21 (12.00)		65 (27.20)		14 (6.17)
Maternal stress at child assessment**	10.96 (6.63)		10.72 (5.71)		11.96 (6.66)		9.95 (5.34)	
Maternal prenatal depressive symptoms**	4.58 (2.91)		4.55 (3.17)		5.08 (3.53)		3.79 (2.76)	
Maternal prenatal depressive symptoms ≥10 cutoff*		5 (5.68)		12 (6.82)		26 (10.88)		7 (3.08)
Maternal depressive symptoms at child assessment	4.54 (3.53)		4.10 (3.57)		4.79 (3.80)		4.35 (3.41)	
Maternal education***								
Less than high school		4 (4.55)		38 (21.59)		37 (15.48)		2 (0.88)
High school/GED		8 (9.09)		35 (19.89)		66 (27.62)		8 (3.52)
Some college or associate degree		11 (12.50)		70 (39.77)		91 (38.08)		44 (19.38)
Undergraduate degree		32 (36.36)		26 (14.77)		28 (11.72)		95 (41.85)
Postgraduate degree		33 (37.50)		7 (3.98)		17 (7.11)		78 (34.36)

(continued)

**TABLE 1 Continued**

	Asian/Pacific Islander		Hispanic		Non-Hispanic Black		Non-Hispanic White	
	M (SD)	Frequency (%)	M (SD)	Frequency (%)	M (SD)	Frequency (%)	M (SD)	Frequency (%)
Annual income adjusted, quintiles***								
First		5 (5.68)		35 (19.89)		91(38.08)		6 (2.64)
≤ \$ 9,999		6 (6.82)		67 (38.07)		66 (27.62)		19 (8.37)
Second		21 (23.86)		20 (11.36)		24 (10.04)		41 (18.06)
\$10,000-29,999		23 26.14)		20 (11.36)		20 (8.37)		90 (39.65)
Third		19 (21.59)		8 (4.55)		11 (4.60)		63 (27.75)
\$ 30,000-49,999		14 (15.91)		26 (14.77)		27 (11.30)		8 (3.52)
Fourth								
\$ 50,000-99,999								
Fifth								
≥ \$ 100,000								
Did not respond								

**Note:** Annual income was adjusted to account for household family size, and divided into quintiles ranging from lowest to highest income groups. Group differences were analyzed using the Kruskal–Wallis test when variables were continuous and the  $\chi^2$  test when variables were categorical. Mean (SD) are bolded; n (%) are not bolded. BMI = body mass index; GED = general education diploma.

\*p < .05; \*\*p < .01; \*\*\*p < .001.

**Moderation by Self-Reported Race and Ethnicity.** There was an association between prenatal stress  $\geq 85^{\text{th}}$  percentile with reports of child oppositional defiant problems ( $F = 3.127$ ,  $df = 469.910$ ,  $p < .05$ ) moderated by maternal self-reported race and ethnicity, such that mothers in the non-Hispanic White group reported greater oppositional defiant problems (Table S1, available online). There was also an association between prenatal depressive symptoms and reports of child anxiety problems ( $F = 4.287$ ,  $df = 462.528$ ,  $p < .01$ ) moderated by race and ethnicity, such that mothers in the non-Hispanic White group reported greater anxiety problems (Table S1, available online). Finally, there were associations between prenatal depressive symptoms  $\geq 10$  cutoff with reports of child anxiety problems ( $F = 7.749$ ,  $df = 465.181$ ,  $p < .001$ ) and depression problems ( $F = 3.945$ ,  $df = 467.536$ ,  $p < .01$ ) moderated by race and ethnicity, such that the non-Hispanic White group reported greater anxiety and depression problems (Table S1, available online). After correcting for multiple comparisons to control for FDR, these associations remained significant.

**Moderation by Education.** There was an association between prenatal stress  $\geq 85^{\text{th}}$  percentile with reports of child depression problems ( $F = 4.338$ ,  $df = 499.632$ ,  $p < .01$ ) moderated by maternal education, such that mothers in lower education groups were more likely to report greater depression problems (Table S2, available online). There was also an association between prenatal depressive symptoms  $\geq 10$  cutoff with reports of child anxiety problems ( $F = 2.897$ ,  $df = 499.368$ ,  $p < .05$ ) moderated by maternal education, such that mothers in the higher education groups were more likely to report greater anxiety problems (Table, S2 available online). Associations remained significant after controlling for FDR.

**Moderation by Income.** Maternal income did not moderate associations between prenatal stress or depressive symptoms with child neurodevelopmental outcomes.

**DISCUSSION**

Our study contributes to the growing evidence that maternal mood disturbances during pregnancy can affect child neurodevelopment, adding observational neurocognitive examinations to maternal reports of child psychiatric problems in a racially and ethnically diverse cohort. We found that prenatal depressive symptoms, but not stress, were associated with observed decrements in child executive functions and motor skills, whereas both prenatal stress and depressive symptoms were associated with maternal reports of child psychiatric problems. FGV was not identified in

**TABLE 2** Associations Between Maternal Prenatal Stress and Depressive Symptoms and Child Neurobehavior

	Prenatal stress			Prenatal depressive symptoms			Prenatal stress $\geq 85^{\text{th}}$ percentile			Prenatal depressive symptoms $\geq 10$		
	$\beta$	SE	<i>p</i>	$\beta$	SE	<i>p</i>	$\beta$	SE	<i>p</i>	$\beta$	SE	<i>p</i>
Inhibitory control/sustained attention	−0.009	0.070	.898	0.103	0.119	.384	0.192	0.993	.847	−0.827	1.333	.535
Cognitive flexibility	−0.114	0.068	.096	−0.163	0.115	.157	−1.694	0.957	.077	−2.540	1.270	.045
Working memory	−0.125	0.086	.145	−0.103	0.147	.484	−2.171	1.202	.071	−1.955	1.720	.256
Dexterity (dominant)	−0.003	0.002	.080	−0.003	0.003	.332	−0.043	0.025	.092	−0.057	0.034	.089
Dexterity (nondominant)	−0.002	0.002	.218	−0.002	0.003	.624	−0.032	0.027	.226	−0.056	0.035	.112
Strength	−0.108	0.075	.149	−0.279	0.125	.026	−1.575	1.060	.137	−2.024	1.415	.153
Balance	0.004	0.004	.340	0.011	0.007	.098	0.117	0.062	.060	0.045	0.084	.593
Attention problems	0.002	0.001	.008	0.003	0.001	.026	0.024	0.011	.032	0.033	0.016	.038
Oppositional defiant problems	0.002	0.001	.002 <sup>a</sup>	0.002	0.001	.159	0.022	0.010	.031	0.041	0.015	.005
Conduct problems	0.001	0.001	.036	0.001	0.001	.271	0.024	0.010	.015	0.026	0.014	.056
Anxiety problems	0.001	0.001	.176	0.002	0.001	.184	0.005	0.010	.625	0.014	0.015	.340
Depression problems	0.002	0.001	.021	0.002	0.001	.037	0.021	0.010	.039	0.018	0.014	.206
Symptoms of ASD	0.008	0.005	.122	0.015	0.009	.105	0.111	0.076	.146	0.092	0.102	.365

**Note:** Results reported are from regression models adjusted with covariates as follows: maternal age, pregravid body mass index, education background, income adjusted for household family size, prenatal social support, maternal stress and depressive symptoms at time of child neurobehavioral assessment, fetal exposure to secondhand smoke, biological sex, self-reported race and ethnicity, mode of delivery, and gestational age at birth. ASD = autism spectrum disorder; SE = standard error.

<sup>a</sup>Remained significant after multiple comparison correction to control for false discovery rate.

these associations as an underlying mechanism of prenatal maternal mood effects prior to birth. These associations varied according to severity of prenatal stress and depressive symptoms, biological sex (with male children more affected) and maternal self-reported race and ethnicity (with women who were non-Hispanic White being more likely to report child internalizing problems).

In our primary set of analyses, only one of our significant associations remained significant after correcting for multiple comparisons. This is to be expected in the context of small effect sizes and a rigorous assessment of outcomes, particularly for neurocognitive development, in that we tested many aspects of executive functions and motor skills using observational methods. Moreover, all of our results had  $\beta$  slopes in the anticipated direction, that is, they confirmed our hypotheses and were consistent with existing studies.

The associations that we demonstrate between prenatal stress and depressive symptoms with maternal reports of child psychiatric problems are consistent with much of the Developmental Origins of Health and Disease (DOHaD) research, in particular, findings by O'Donnell *et al.*<sup>2</sup> and Szekely *et al.*,<sup>3</sup> who showed that prenatal affective problems are associated with reports of child psychopathology. This work was formative in establishing prenatal programming research focused on maternal mood as a potential aversive environmental exposure to the fetus, capable of altering

brain–behavior development via mood-based changes in maternal biology.<sup>1</sup> Nevertheless, a vast body of DOHaD research has come under criticism because of maternal report functioning as the primary source of data, leading to ascertainment bias and shared method variance.<sup>48</sup>

We also found that prenatal depressive symptoms were associated with observed delays in motor skills (ie, strength), consistent with findings that prenatal stress and depressive symptoms are associated with impaired motor skills in infancy and childhood.<sup>17–19</sup> However, we did not find an association between prenatal stress or depressive symptoms with observed executive functions (except for depressive symptoms at a clinical level, discussed below). A meta-analysis of associations between prenatal stress and anxiety with deficits in child cognitive abilities suggests that these associations may be present but are not robust.<sup>49</sup> Our results can be interpreted within the context of average prenatal stress and subclinical prenatal depressive symptoms that characterized most of our participants in the FGS, that is, women with low-risk pregnancies.<sup>51</sup> There is a possibility that in the absence of clinical symptoms, average prenatal distress in low-risk pregnancies may not be associated with decrements in executive functions or motor skills. In other words, risk for long-term neurodevelopmental consequences due to prenatal distress might be less detrimental than frequently surmised.



**TABLE 3** Associations Between Maternal Prenatal Stress and Depressive Symptoms and Fetal Growth Velocity

	FGV			FGV 25 <sup>th</sup>	FGV 50 <sup>th</sup>	FGV 75 <sup>th</sup>
	$\beta$	SE	p	OR (95% CI)	OR (95% CI)	OR (95% CI)
Prenatal stress	0.053	0.099	.593	1.050 (0.939-1.166)	1.010 (0.979-1.045)	1.050 (0.951-1.160)
Prenatal depressive symptoms	-0.263	0.164	.109	0.940 (0.797-1.117)	0.980 (0.931-1.040)	1.010 (0.854-1.195)
Prenatal stress $\geq 85^{\text{th}}$	0.836	1.1412	.554	1.100 (0.264-4.615)	1.300 (0.809-2.078)	2.560 (0.734-8.934)
Prenatal depressive symptoms $\geq 10$	-0.237	1.932	.902	—	1.010 (0.535-1.908)	2.360 (0.522-10.679)

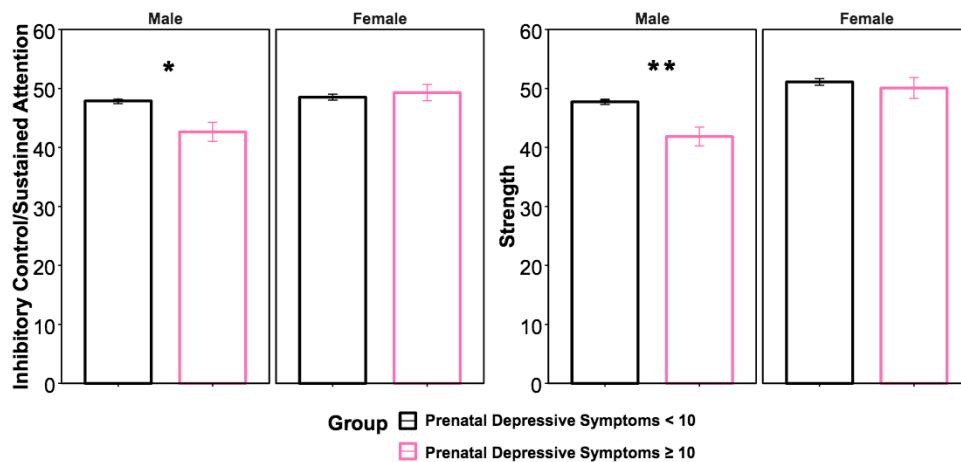
**Note:** Fetal growth velocity was treated as a repeat measure throughout gestation, and as a dichotomous measure at the 25<sup>th</sup>, 50<sup>th</sup>, and 75<sup>th</sup> percentiles. Maternal prenatal stress was measured on the Perceived Stress Scale (PSS), and depressive symptoms on the Edinburgh Postnatal Depression Scale (EPDS). Results reported are from the mixed effect models. When prenatal depressive symptoms were  $\geq 10$  cutoff, there were zero observations for FGV at the 25<sup>th</sup> percentile. FGV = fetal growth velocity; OR = odds ratio; SE = standard error.

To consider prenatal stress and depressive symptoms at a level more likely to be of clinical relevance, we created subgroups of women who reported high prenatal stress (ie,  $>85^{\text{th}}$  percentile) or prenatal depressive symptoms at a clinical level (ie, above a clinical cutoff of 10).<sup>46</sup> Similar to our main findings, high prenatal stress was associated only with maternal reports of child psychiatric problems. However, prenatal depressive symptoms at a clinical level were associated with deficits in observed executive functions (ie, cognitive flexibility) in addition to being associated with reported psychiatric problems. In previous studies, prenatal anxiety has been associated with decrements in child executive functions such as impairments in inhibitory control and working memory.<sup>4,14</sup> In both clinical and community-based samples, there is evidence that maternal prenatal stress, anxiety, or depression can be associated with deficits in neurodevelopment throughout childhood, across a

spectrum of stress and symptom severity.<sup>21</sup> Our findings add to this literature, as they are based on observed outcomes, and are more generalizable, as they are based on a racially and ethnically diverse population.

We examined outcomes according to biological sex. Consistent with the literature on male vulnerability to in utero exposures,<sup>31,50</sup> prenatal depressive symptoms at a clinical level were associated with impaired executive functions only in biological male children, specifically impairments in inhibitory control/sustained attention. We also found that prenatal depressive symptoms (ie, both average and at a clinical level) were more strongly associated with motor skill delays again in biological male children, specifically reduced strength. This is consistent with the literature that biological male children exposed to prenatal stress or depression show greater observed motor skill delays.<sup>17,18</sup> Our findings underscore a biological male vulnerability to

**FIGURE 1** Associations Between Maternal Prenatal Depressive Symptoms and Child Neurobehavior Moderated by Biological Sex



**Note:** Maternal prenatal depressive symptoms were measured on the Edinburgh Postnatal Depression Scale (EPDS). Please note color figures are available online. \*p < .05; \*\*p < .01.

maternal prenatal depressive symptoms, complicating low-risk pregnancies.

Our sample had a broad representation of racial and ethnic diversity. People who are Asian/Pacific Islander, Hispanic, and non-Hispanic Black account for nearly 40% of the US population, and remain consistently underrepresented in biomedical and clinical research,<sup>51</sup> including prenatal programming studies. Consistent with the literature on parental reports of child psychiatric problems,<sup>52</sup> we found that among women who were non-Hispanic White, there were stronger associations between prenatal stress/depressive symptoms and child internalizing problems such as anxiety and depression. In contrast, we did not find moderation by race and ethnicity for observed executive functions or motor skills, or for maternal reports of most child externalizing behaviors (ie, attention problems, conduct problems). Although the literature in this area is limited, a possible interpretation is that caretaker expectations for internalizing and externalizing child behaviors may differ according to racial and ethnic background, given that race and ethnicity are socially and culturally constructed.<sup>52,53</sup> One interpretation is that caregivers who are Asian/Pacific Islander, Hispanic, and non-Hispanic Black might be less tolerant of externalizing behaviors, and may consider internalizing behaviors as more normative.<sup>52</sup> In contrast, caregivers who are non-Hispanic White may be more concerned about internalizing problems and thus endorse seeing these symptoms in their children at higher rates. A more comprehensive discussion of symptom interpretation, problem definition, and parent report of children's behavior as they might differ by race and ethnic group can be found elsewhere.<sup>52</sup> Our post hoc findings add to the literature suggesting limits to the utility of parent report measures across different race and ethnic groups, possibly indicating that observer-rated standardized assessments may be more reliable and valid.<sup>27,52</sup> More research is warranted to clarify ways in which standardized measures of child neurodevelopment contribute to systemic racism in psychiatry, which may lead to more suitable treatments and improved care.<sup>54</sup>

Commensurate with persistent racial and ethnic inequalities in social and economic standing in the United States,<sup>55</sup> we found that women who self-reported as Hispanic and non-Hispanic Black were more likely to be in the lower levels of educational attainment and household income, as compared to women who self-reported as Asian/Pacific Islander and non-Hispanic White. We also found that for women with lower educational attainment, a signifier of socioeconomic status, there was a stronger association between prenatal stress and child depression problems, and for those with higher

educational attainment, there was a stronger association between prenatal depressive symptoms and child anxiety problems. We found no moderation by household income. Although race and ethnicity and educational attainment are interconnected, our findings for moderation by education background differ somewhat from those of moderation by race and ethnicity. We interpret these differences as indicating that educational attainment is also a factor in maternal perception of children's internalizing and externalizing behaviors. Further research is needed on the intersection of race and ethnicity with socioeconomic status to better understand their joint influences on child neurobehavior and psychiatric problems.

Prenatal programming proposes that maternal adversity operates through biological pathways to program fetal and child neurodevelopment. For example, fetal autonomic nervous system reactivity and newborn brain structure and function have been related to maternal mood.<sup>56-58</sup> Because there is evidence to support associations between a range of single time measurements of fetal growth (eg, birth weight, gestational age) with a range of child mental health outcomes,<sup>21,22,25</sup> we hypothesized mediation by FGV in our findings associating prenatal stress and depressive symptoms with child neurobehavior. However, we did not identify this association and mediation was not supported. These findings are consistent with previous findings whereby prenatal stress was not associated with neonatal anthropometric measurements.<sup>28</sup> A possible explanation is that FGV might not reflect more subtle variations in fetal development occurring as a result of prenatal stress, such as adverse changes in cellular growth, and differentiation and maturation of the brain and peripheral systems (eg, endocrine and immune-inflammatory systems). Changes in anatomy and connectivity, including corticolimbic regions associated with affective disorders, can occur because of increased concentrations of endocrine and immune stress mediators (eg, glucocorticoids, pro-inflammatory cytokines) active during stress-sensitive bidirectional cascades in maternal-placental-fetal compartments, and lead to offspring susceptibility for developing long-term neurodevelopmental problems and psychiatric disorders.<sup>21,59</sup> Such developmental changes may be independent of and not captured by FGV.

Strengths of our study include our integration of associations between maternal prenatal stress and depressive symptoms with multiple interrelated domains of child neurobehavior such as executive functions, motor skills, and psychiatric problems, within a cohort that has a broad representation of racial and ethnic diversity in the United States. Observational measures of executive

functions and motor skills are strongly associated with child psychopathology.<sup>6-8</sup> Furthermore, we included serial antenatal ultrasound measurements, a range of standardized observational measures, maternal self-reports, and maternal reports of child neurobehavior at 4 to 8 years of age. Despite leveraging the strengths of the ECHO-FGS, we were faced with certain limitations. As indicated, our measures of child psychiatric outcomes relied on maternal reports, which raises the possibility of shared method variance with maternal self-report measures of prenatal stress and depressive symptoms.<sup>48</sup> Moreover, the NICHD Fetal Growth Studies did not include assessment of maternal prenatal anxiety, limiting the range in specificity of our prenatal adversity exposures. Compared to prenatal depression, prenatal anxiety is more consistently associated with decrements in child neurodevelopment, implying that prenatal influences operate through different pathways. Future studies that specify prenatal influences will contribute to a more comprehensive understanding of underlying mechanisms, as opposed to clustering them and implying common effects.<sup>21</sup> Although we were able to specify differences between prenatal stress and depressive symptoms, we lacked specificity in terms of other common prenatal adversities including, but not limited to, stressful life events, prenatal anxiety, and pregnancy-related anxiety. Finally, the average levels of prenatal stress and low levels of prenatal depressive symptoms reported in our community-based sample, although characteristic of low-risk pregnancies,<sup>31</sup> may have limited our ability to detect prenatal influences on poor fetal growth or adverse changes in child neurobehavior.

Our study is one of the largest cohorts with observational assessments of child cognitive abilities in addition to maternal reports of child psychiatric problems, and is, to our knowledge, the only cohort with a broad representation of the racial and ethnic diversity in the United States. In addition to finding associations between prenatal stress and depressive symptoms with multiple interrelated domains of child neurobehavior, we also corroborate prior evidence of biological male vulnerability to prenatal adversity.<sup>31,50</sup> Prenatal depressive symptoms, but not prenatal stress, were associated with observed decrements in executive functions and motor skills, especially in children who were biologically male. Prenatal stress during otherwise low-risk pregnancies might not pose as much of a risk to child neurodevelopment as initially theorized. Maternal reports of child psychiatric problems were the only instance in which we found differences moderated by race and ethnicity, indicating that results based on this style of reporting might

not generalize to all racial and ethnic groups. Maternal depressive symptoms during pregnancy, especially when clinically relevant, may contribute to child cognitive deficits and psychopathology. Even small differences in prenatal distress may warrant attention, as these may have long-lasting implications not only for women's mental health and well-being, but also for that of their developing children.

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