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Effect of Prenatal Smoke Exposure on Birth Weight: The Moderating Role of Maternal Depressive Symptoms

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Abstract

Introduction: Both prenatal smoke exposure and depression have been linked to lower birth weight, a risk factor for morbidity and mortality. Few studies have looked at the interaction between these risk factors and none have used a biomarker to objectively measure prenatal smoke exposure. The current study sought to examine independent and interactive effects of cotinine and depression on birth weight. The effect of race was also explored.

Method: Data were drawn from a prospective study of pregnant women ($N = 568$) in the southeastern United States. Maternal demographic, health information, depressive symptoms, and birth data were collected via self-report and medical record abstraction. Prenatal blood samples were assayed for cotinine.

Results: Controlling for covariates, multiple regression analyses indicated that both cotinine and depressive symptoms independently predicted lower birth weight and a significant interaction was also observed. Upon probing the interaction, a negative association between cotinine levels and birth weight was found in the context of higher depression but not lower depression scores. Similarly, logistic regression analyses revealed a significant interaction between cotinine and depression, such that cotinine predicted having a baby less than 2500 g among women who fell above the indicated cutoff score. African American women had the highest levels of cotinine and lowest weight babies; however, race was not a significant moderator.

Conclusions: Results suggest prenatal smoke exposure has a greater negative effect on birth weight for women endorsing co-occurring depressive symptoms. Findings can inform targeted interventions and assist medical providers with identifying women at increased risk for poor perinatal outcomes.

Implications: Despite the common occurrence of smoking during pregnancy and prenatal depression, the interaction between these risk factors on birth weight has rarely been examined. Further, the extant results have been mixed, likely due in part to difficulties in measurement. The current study was the first to use prenatal cotinine to assess bias-free, continuous levels of prenatal smoke exposure. Results indicate that prenatal cotinine was a significant predictor of birth weight only

in the context of maternal depressive symptoms. These findings have important implications for mitigating negative perinatal outcomes for pregnant women and their children.

Introduction

Despite medical advancements and wealth of resources, the United States ranks poorly among developed countries with respect to perinatal outcomes.¹ In particular, low birth weight rates have steadily increased over time, especially among minority women.^{2,3} Lower birth weight has been associated with difficulties throughout the life span, including poor cognitive functioning, behavioral problems, and chronic illness.⁴⁻⁶ Within the United States, 26 billion dollars are spent annually for complications related to preterm birth and low birth weight.^{7,8} Thus, identifying factors that mitigate risk for having a low birth weight baby is beneficial for children, families, and the public.

Maternal psychological symptoms^{9,10} and tobacco smoke¹¹⁻¹⁴ are common among pregnant women and are independent risk factors impacting birth weight. The prevalence of depression in pregnant populations ranges from 7% to 20%,^{15,16} with urban, minority women disproportionately affected.^{17,18} In addition, a large proportion (ie, between 8.4% and 20.6%) of women continue to smoke during pregnancy,^{19,20} and many nonsmokers are exposed to passive smoke.^{21,22} Further, these risk factors can co-occur: evidence suggests that depressed women are more likely to smoke^{16,23} or be exposed to smoke.^{24,25}

Although studies have examined the interactive effects of stress and substance use on birth outcomes,¹³ there is a paucity of literature examining prenatal depressive symptoms and smoke exposure in relation to birth weight. In a sample of postpartum women from the Pregnancy Risk Assessment Monitoring System in Minnesota, results showed that women who retrospectively indicated having a “hard time” during pregnancy and reported prenatal tobacco use were twice as likely to have a low birth weight baby, compared to self-reported nonsmokers who did not endorse mood difficulties.²⁶ Although strengths of this study include sample size ($N = 7457$), maternal mood was retrospectively reported using a single question. In a study of 896 pregnant women recruited during first trimester, Elsenbruch et al.²⁷ examined stress and depression using self-reported perceived social support and depressive symptoms on the Center for Epidemiological Studies Depression Scale (CES-D). Results indicated that birth weight was significantly reduced for infants of women with low perceived social support who also endorsed smoking during pregnancy. However, the interaction was not significant with depressive symptoms, and this study did not report the racial and ethnic composition of the sample. Additional research is warranted to better understand the synergy between these risk factors, particularly in samples where low birth weight is often more pronounced.

Notably, previous studies have relied on self-reported cigarette use and smoke exposure to measure prenatal smoking status. According to a recent comprehensive review of cumulative and interactive effects of chemical exposures (including tobacco) and psychosocial stress,¹³ no existing studies have used a biological marker to measure smoke exposure. Although comparisons between self-report and biological validation have shown congruency,^{14,28} misreporting of smoking status has been observed among pregnant women.^{29,30} Further, passive smoke exposure has also been linked to poor perinatal outcomes, including low birth weight.³¹ However, studies examining prenatal psychological functioning and smoking often focus on active, rather than passive smoke exposure,^{13,27} or

high versus low levels of smoking rather than a continuous measure.¹³ In addition, many pregnant women may be unaware of their level of passive smoke exposure.^{22,32} Using biochemical validation of smoke exposure, such as cotinine, can account for these limitations and provide a continuous, bias-free measurement of passive and active smoke exposure.

Another consideration is racial and/or ethnic differences in birth outcomes. Marked disparities in the rates of low birth weight among African American women, compared to other races, are well documented. Though the mechanisms are poorly understood, such patterns among African Americans have been attributed to younger gestational age, higher rates of premature births among African American women,³ and chronic worry about racial discrimination.³³ Furthermore, pregnant African American women are often at higher risk for smoke exposure during pregnancy, even among non-active smokers,^{22,34,35} as well as depression during pregnancy.^{17,18}

We used a subsample of women who participated in a prospective birth cohort to study the relationship among prenatal tobacco smoke exposure, self-reported depressive symptoms, and infant birth weight. Specifically, we (1) examined the relationship between maternal depressive symptoms, prenatal cotinine levels, and infants’ birth weight, and (2) studied the interaction between cotinine and maternal depressive symptoms in predicting birth weight. The impact of race on these associations was also examined.

Method

Participants and Procedures

This study is a secondary data analysis. Cases used in the current analyses were drawn from the Newborn Epigenetic Study (NEST), a prospective study of pregnant women in the southeastern United States aimed at examining the impact of prenatal exposures on the epigenome and child development. Pregnant women were recruited from prenatal clinics serving Duke University Hospital and Durham Regional Hospital obstetrics facilities from April 2005 to June 2011. Eligibility criteria included age at least 18 years, pregnant, English and/or Spanish speaking, and intention to use one of two obstetrics facilities for the index pregnancy to allow for access to labor and birth outcome data. The study was approved by the Duke University Institutional Review Board and conducted in accordance with the Declaration of Helsinki and guidelines established by the Federal Government for the protection of human subjects.

Participant identification and enrollment procedures are described in greater detail elsewhere.^{10,36} Briefly, all participants provided written informed consent at the time of enrollment during their prenatal visit. Women also provided a plasma blood sample and completed self-report or interview-administered questionnaires, which included questions regarding sociodemographic characteristics and maternal physical health, mental health, and lifestyle factors. Symptoms of depression were collected via the CES-D.³⁷ Questionnaires were offered in both English and Spanish.

Recruitment for the NEST study occurred in two waves. Pregnant smokers were oversampled during wave 1; there was no enrollment criterion regarding smoking status during wave 2. In addition, wave 2 participants completed measures of psychological functioning, including the CES-D. Thus, given the aims of the current

analyses, all participants included in this study were recruited during wave 2. Of the 2548 women approached to participate in wave 2 of the NEST study, 1700 (66.6%) were enrolled. The current analyses included a subsample of 568 women (mean age = 28.19 years, SD = 5.62 years). This subsample was chosen based on women who had completed the CES-D, child birth weight data, and plasma blood samples assayed for cotinine. Blood samples were selected for assay based on whether women had participated in later follow-up studies. Follow-up studies required proficiency in English; thus, compared to the larger NEST sample, fewer Hispanic participants were included in the current analyses. In addition, the current sample had a greater percentage of African Americans, a greater proportion of women who had completed college, fewer women who had completed less than high school or earned their General Education Diploma (GED), higher scores on the CES-D, lower cotinine levels, longer gestational length, and babies with larger birth weight compared to the larger NEST sample.

Cotinine Analysis

Blood plasma samples were collected from women during pregnancy (mean = 12.67 gestational weeks, SD = 5.5 weeks). Cotinine was measured using a high-performance liquid chromatography with tandem mass spectrometry (HPLC-MS-MS) method, with a limit of detection of 0.05 ng/mL and a reproducibility greater than 94%.^{38,39} To conduct the analyses, a 0.2-mL aliquot of plasma was well mixed with 20 μ L of 100 ng/ μ L of cotinine-D3 (internal standard) and 1 mL of methanol. After the mixture was centrifuged at 16 000g for 10 minutes, the supernatant was solvent evaporated, and the residue was reconstituted in 200 μ L of acetonitrile/water (15%:85%), vortexed, and then centrifuged at 16 000g for 10 minutes. A 20- μ L aliquot of this final solution was injected to the HPLC-MS-MS system equipped with a TSQ Quantum Access MAX triple stage quadrupole mass spectrometer (Thermo Fisher Scientific). We used a Phenomenex Luna (Torrance, CA) 3 μ C18 (50 \times 2 mm) column and an isocratic mobile phase elution (water/acetonitrile containing 0.1% formic acid: 85/15) at a flow rate of 200 μ L/min. The mass spectrometer was operated in a positive electrospray ionization mode. The capillary temperature and vaporizer temperature were at 350°C and 300°C, respectively. The ion spray voltage was set to 3000 V. Nitrogen sheath and auxiliary gases were set to 40 and 15 arbitrary units, respectively. The ion pairs of m/z 177/98, 180/80 were used to detect cotinine and cotinine-d3. Due to non-normality, cotinine values were natural log-transformed. As log transformations for values of zero are undefined, a constant of 0.001 was added to all cotinine values prior to the log transformation.

Maternal Depressive Symptoms

Depressive symptoms were measured using the CES-D, a commonly used self-report measure frequently utilized in studies with pregnant women.^{40,41} Respondents are asked to indicate how often they have experienced each symptom with response options ranging from 0 (rarely or none of the time) to 3 (most or all of the time) in the preceding week. Scores range from 0 to 60, with higher scores indicative of more depressive symptoms. A score of 16 is often recommended as the cutoff score for depression. The CES-D has been found to have good sensitivity and high internal consistency.^{37,42}

Birth Weight and Other Birth Information

Trained personnel abstracted birth information from medical records following delivery, including birth weight and other

potential covariates. Only data from singleton births were included in current analyses. Low birth weight was designated as less than 2500 g. Other information collected included child (eg, sex, gestational age at birth), maternal (eg, prepregnancy body mass index; age at delivery; presence or absence of preeclampsia, hypertension, gestational diabetes; self-reported use of depression medication during pregnancy), and demographic characteristics (maternal education, marital status, race or ethnicity). These variables were explored as potential covariates.

Data Analysis

Multiple linear and logistic regression analyses were conducted to examine the relationship between cotinine, depressive symptoms, and birth weight. Each independent variable (ie, cotinine and CES-D scores) was centered prior to computing interaction terms in moderation analyses. Covariates were entered into Block 1, centered independent variables were entered into Block 2, and the two-way interaction terms were entered into Block 3. Three-way interactions were also included in analyses examining the impact of race (ie, race \times cotinine \times depression score) and entered into Block 4. The Aiken and West^{43,44} method for probing moderators was used in cases of significant interactions. Using this procedure, simple slopes of the regression are plotted at different levels of the moderating variable. In addition, to probe dichotomous moderators, two new conditional moderator variables were computed, and regressions were rerun incorporating these new variables.^{43,44} All analyses were run in SPSS 24.

Results

Sample Demographics

Demographic characteristics are presented in Table 1. Given the small samples of women who reported their race as Hispanic or Other (3.4% and 4.4%, respectively), these groups were combined. CES-D scores ranged from 0 to 60 (mean = 13.21, median = 11, SD = 9.43) and 31.7% ($N = 180$) of the sample fell above the cutoff (ie, scores ≥ 16). Twenty-four women (4.2%) reported taking antidepressant medication at the time of study enrollment. The majority of women ($N = 448$, 78.8%) reported that they had not smoked at any time during their pregnancy; 19.9% ($N = 113$) endorsed smoking

Table 1. Sociodemographic Characteristics of Women in the Current Analyses

	N (%)
Race	
African American	296 (52.1)
Caucasian	228 (40.1)
Hispanic or Other	44 (7.7)
Marital status	
Never married	174 (30.6)
Married	265 (46.7)
Living with partner	98 (17.3)
Divorced or separated	12 (2.1)
Other	13 (2.3)
Education	
<High school	80 (14.1)
High school or GED	114 (20.1)
Some college	124 (21.8)
College graduate	246 (43.3)

at some point during pregnancy. For the 558 women who answered questions regarding passive smoke exposure at home and/or work, 78.7% ($N = 447$) denied passive exposure whereas 19.5% ($N = 111$) reported experiencing passive smoke exposure. Mean plasma cotinine levels were 12.77 ng/mL (SD = 42.43, range = 0–371 ng/mL). Using cotinine cutoffs recommended by Benowitz et al.,⁴⁵ 70.8% ($N = 402$) of the sample had levels consistent with being unexposed, nonsmokers (<1 ng/mL), 10.6% ($N = 60$) had levels indicative of passive exposure (1–3 ng/mL), and 18.7% ($N = 106$) had levels indicative of active smoking (>3 ng/mL).

With regard to birth outcomes, mean birth weight was 3308.04 g (SD = 550.88, range 850–5422 g) and 6.5% ($N = 37$) of the sample fell in the low birth weight category. Average length of gestation was 39.13 weeks (SD = 1.74 weeks), and 8.3% ($N = 47$) of the sample was born prior to 37 weeks. Half of the babies born (50.7%) were males.

Potential Confounders and Statistical Controls

Covariates significantly associated with either independent variables or the dependent variable were included as covariates. This included race, level of education, maternal age at delivery, preeclampsia, gestational age, and use of depression medication during pregnancy (Table 2).

Prenatal Cotinine and Depressive Symptoms

Cotinine was significantly associated with depressive symptoms (CES-D continuous score: Pearson $r = .22$, $p < .001$; CES-D cutoff score: Spearman $\rho = .17$, $p < .001$), but at a level below the recommended cutoff for multicollinearity.⁴⁶

Prenatal Depressive Symptoms and Birth Weight

Results are presented in Table 3. Controlling for the aforementioned covariates, continuous scores on the CES-D significantly predicted birth weight, such that greater depressive symptoms were associated with reduced birth weight. In a separate multiple regression analysis, presence of depression, as indicated by CES-D scores at least 16, was not significantly associated with birth weight. Logistic regression analyses were used to assess whether depression scores increased the

odds of having a low birth weight baby. Controlling for aforementioned covariates, neither continuous nor dichotomous scores on the CES-D were associated with increased odds of having a low birth weight baby.

Prenatal Cotinine and Birth Weight

Controlling for covariates, cotinine significantly predicted birth weight, such that greater cotinine levels were associated with lower birth weight. Logistic regression analyses were used to assess whether cotinine levels predicted having a low birth weight baby; results were not significant (Table 3).

Interaction Between Cotinine and Maternal Prenatal Depressive Symptoms

Multiple regression analyses were used to test the moderating role of maternal depression on the relationship between cotinine levels and birth weight. Controlling for the aforementioned covariates, a significant interaction was observed between cotinine and continuous scores on the CES-D (Table 3). Probing the interaction revealed a significant, negative association between cotinine levels and birth weight in the context of higher levels of depression (ie, 1 SD above the mean on the CES-D). Cotinine did not predict birth weight in the context of low depression (ie, 1 SD below the mean on the CES-D). A significant interaction was also observed when using the CES-D cutoff score (Table 3). Results from probing the dichotomous moderator revealed that cotinine predicted birth weight for women with CES-D scores at least 16 and was not associated with birth weight for women whose CES-D scores were less than 16 (Figure 1).

Logistic regression analyses were also run to examine whether cotinine and depression interacted to predict having a low birth weight baby. Controlling for the covariates mentioned earlier, the interaction was not significant using the continuous CES-D score (Table 3). The interaction was significant when using the CES-D cutoff score. Probing the dichotomous moderator revealed that higher levels of cotinine increased the odds of having a low birth weight baby for women with CES-D score at least 16 but not for women with CES-D scores less than 16 (Table 3).

Table 2. Examination of Potential Covariates, Maternal Depression, and Birth Weight

Variables	Cotinine	Maternal depression (continuous)	Birth weight	Maternal depression (dichotomous)
		<i>Pearson correlations</i>		<i>t test</i>
Maternal age at delivery	-0.14**	-0.19***	0.05	4.26***
Gestational age at the time of delivery	-0.08	-0.04	0.61***	0.86
BMI at last menstrual period	0.07	0.07	-0.01	-1.40
		<i>t test</i>		<i>Chi-square</i>
Preeclampsia ^a	0.26	-1.30	3.49**	1.49
Hypertension ^a	1.41	0.86	-0.32	0.75
Gestational diabetes ^a	-0.93	-0.57	-0.22	0.001
Depression medication during pregnancy ^a	-3.31**	-2.98**	1.86	10.99**
Baby gender ^a	-1.12	-1.45	0.71	0.17
		<i>Analysis of variance (F)</i>		<i>Chi-square</i>
Race ^b	8.32***	9.06***	11.96***	9.02*
Maternal education ^b	27.08***	19.07***	4.59**	28.36***

Pearson correlations computed for all continuous variables; Spearman's ρ reported for all analyses with dichotomous variables. Due to non-normality, cotinine values were natural log transformed. Depression measured by self-report on CES-D. Dichotomous score cutoff at least 16. BMI = body mass index.

^aDichotomous variable.

^bVariable with more than two groups.

* $p < .05$, ** $p < .01$, *** $p < .001$.

Table 3. Results of Multiple Linear Regression and Logistic Regression Analyses Examining Depression and Cotinine Predicting to Birth Weight

<i>Multiple linear regressions predicting birth weight (continuous)</i>						
Independent variable(s)	<i>b</i>	β	<i>t</i>	<i>df</i>	Adj. <i>R</i> ²	<i>p</i>
CES-D continuous	-4.08	-.07	-2.02	559	0.40	.04*
CES-D cutoff	-60.42	-.05	-1.50	559	0.40	.13
Cotinine	-19.25	-.09	-2.64	559	0.41	.008**
CES-D continuous × cotinine	-1.58	-.07	-2.22	553	0.41	.03*
High CES-D	-30.91	-.15	-3.24	553	0.41	.001**
Low CES-D	-1.04	-.01	-0.10	553	0.41	.92
CES-D cutoff × cotinine	-35.46	-.24	-2.43	553	0.41	.02*
CES-D ≥ 16	-40.27	-.19	-3.44	553	0.41	.001**
CES-D < 16	-4.81	-.02	-0.51	553	0.41	.61

<i>Logistic regressions predicting low birth weight (<2500 g)</i>				
Independent variable(s)	OR	95% CI	Cohen's <i>d</i>	<i>p</i>
CES-D continuous scores	1.03	0.99 to 1.08	0.02	.20
CES-D cutoff score	1.59	0.61 to 4.10	0.26	.34
Cotinine	1.12	0.93 to 1.35	0.06	.22
CES-D continuous × cotinine	1.01	1.00 to 1.03	0.01	.11
CES-D cutoff × cotinine	1.71	1.16 to 2.53	0.30	.01*
CES-D ≥ 16	1.50	1.09 to 2.05	0.22	.01*
CES-D < 16	0.87	0.68 to 1.12	-0.08	.29

Covariates included race, level of education, maternal age at delivery, preeclampsia, gestational age, and use of depression medication during pregnancy. Due to non-normality, cotinine values were natural log transformed. CES-D = Center for Epidemiological Studies Depression Scale. Dichotomous score cutoff at least 16. *b* = unstandardized beta; β = standardized beta; *t* = *t*-score; *df* = degrees of freedom; Adj. *R*² = Adjusted R-Squared from the full model; OR = odds ratio; 95% CI = 95% confidence interval.

p* < .05, *p* < .01.

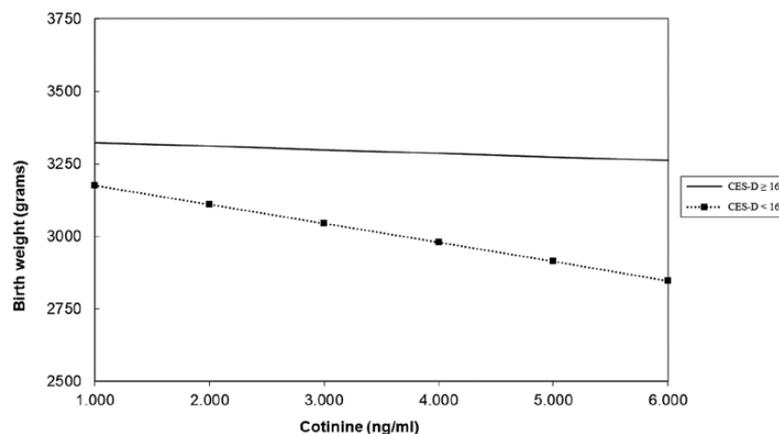


Figure 1. Plot of the simple slopes of interaction between cotinine and depressive symptoms predicting birth weight. Simple slopes of the regression were plotted above the Center for Epidemiological Studies Depression Scale (CES-D) cutoff and below the CES-D cutoff score. Results from probing the dichotomous moderator revealed that cotinine predicted birth weight for women above the CES-D cutoff, $\beta = -.19$, $b = -40.27$, $t(553) = -3.44$, Adj. *R*² = 0.41, *p* = .001, and was not associated with birth weight for women below the CES-D cutoff, $\beta = -.02$, $b = -4.81$, $t(553) = -.51$, Adj. *R*² = 0.41, *p* = .61.

Differences in Birth Weight, Depression, and Cotinine Based on Race

Birth weight differed significantly by race, $F(2, 565) = 11.96$, *p* less than .001. Post hoc comparisons using the Tukey Honest Significant Difference indicated that birth weight of babies born to African American women was significantly less (mean = 3203.76 g, SE = 31.42) than babies born to Caucasian women (mean = 3435.35 g, SE = 35.80). These results remained when controlling for gestational length. There

was not a significant difference in the number of babies falling within the low birth weight category by race, $X^2(2) = 0.42$, *p* = .81, and length of gestation did not differ by race, $F(2, 565) = 1.86$, *p* = .16. Rates of depressive symptoms also differed significantly by race, $F(2, 565) = 9.06$, *p* less than .001. Post hoc comparisons indicated that Caucasian women had significantly lower CES-D scores (mean = 11.39, SE = 0.62) compared to African American (mean = 14.07, SE = 1.40) and Hispanic or Other groups (mean = 16.89, SE = 1.40). Using the log-transformed value, cotinine levels also differed significantly by

race, $F(2, 565) = 8.32, p$ less than .001. Post hoc comparisons indicated that African American women had significantly higher levels (raw score mean = 16.34 ng/mL, SE = 2.46), compared to Caucasian (raw score mean = 9.16 ng/mL, SE = 2.80) and Hispanic or Other women (raw score mean = 7.50 ng/mL, SE = 6.38).

Examining Race as a Moderator

Separate multiple regression analyses were conducted to evaluate the impact of race on the relationship among cotinine, depressive symptoms, and birth weight. Controlling education, age at delivery, preeclampsia, gestational age, and prenatal depression medication use, and using the procedures described earlier, none of the interactions with race were significant in predicting to birth weight (CES-D scores \times race: $\beta = -.03, b = 0.78, t(559) = -.37, \text{Adj. } R^2 = 0.40, p = .71$; CES-D cutoff \times race: $\beta = -.03, b = -11.13, t(559) = -.26, \text{Adj. } R^2 = 0.40, p = .79$; cotinine \times race: $\beta = .05, b = 5.19, t(553) = .69, \text{Adj. } R^2 = 0.41, p = .49$). Additional three-way interactions were also computed. Results were not significant when looking at the continuous CES-D scores, $\beta = .02, b = 0.22, t(553) = .29, \text{Adj. } R^2 = 0.41, p = .78$, or the CES-D cutoff scores, $\beta = -.03, b = -2.30, t(553) = -.15, \text{Adj. } R^2 = 0.41, p = .88$.

Logistic regression analyses were used to examine the impact of race on the relationship among cotinine, depression, and the likelihood of having a low birth weight baby. Neither the two-way interactions (CES-D scores \times race: odds ratio [OR] = 1.05, $d = 0.03, 95\%$ confidence interval [CI] = 1.00 to 1.11, $p = 0.05$; CES-D cutoff \times race: OR = 1.28, $d = 0.13, 95\%$ CI = 0.46 to 3.50, $p = 0.64$; cotinine \times race: OR = 0.92, $d = -0.04, 95\%$ CI = 0.78 to 1.10, $p = 0.37$) nor three-way interactions (continuous CES-D scores \times race \times cotinine: OR = 1.00, $d = -0.00, 95\%$ CI = 0.98 to 1.01, $p = 0.68$; CES-D cutoff \times race \times cotinine: OR = 0.89, $d = -0.07, 95\%$ CI = 0.60 to 1.31, $p = 0.55$) were significant.

Discussion

This study examined independent and interactive effects of maternal depressive symptoms and cotinine exposure during pregnancy on infant birth weight. Consistent with previous studies,^{9-11,13,14} results indicated that a greater number of maternal depressive symptoms and higher cotinine levels independently predicted lower birth weight. In addition, an interaction was observed between these risk factors, such that cotinine was only predictive of birth weight in the context of higher maternal depressive symptoms—even after controlling for gestational weeks. This suggests a specific relationship between this combination of prenatal exposures and low birth weight, over and above the length of pregnancy. These findings are important given the increasing prevalence of low birth weight births within the United States,^{1,2} and the broad, negative long-term outcomes associated low birth weight.⁴⁻⁶

Much of the existing research examining interactive effects of smoking and maternal psychopathology has focused on prenatal stress exposures, demonstrating that self-reported smoking in pregnancy is significantly associated with low birth weight in the context of higher stress and anxiety.^{13,27} Fewer studies have examined maternal depression in conjunction with prenatal smoke exposure on birth weight, and results have been mixed,^{26,27} likely due in part to retrospective reporting and methods by which depression (ie, single question about mood vs. questionnaire) and smoking (ie, self-reported cigarette use) were measured. The current study expands upon this research by evaluating depressive symptoms using a brief, reliable,

and commonly used measure of depressive symptoms (ie, CES-D), allowing for greater utility across clinical settings, and through its prospective study design, which helps to reduce bias associated with retrospective reporting.

Further, the current study is the first to utilize a biological marker in the examination of the relationship between prenatal smoke exposure and psychological symptoms on birth weight. Use of cotinine allows for an objective measure of prenatal smoke exposure. This is particularly relevant, given the aforementioned difficulties associated with accurately measuring active and passive smoke exposure in pregnancy using dichotomized (eg, “low” vs. “high,” “smoker” vs. “non-smoker”), self-reported measures.^{13,26,27} Within this study, the interaction between depressive symptoms and self-reported smoking during pregnancy was not significant (results not shown). Further, smoker type identified by cotinine levels⁴⁵ (ie, active smoker vs. non-active smoker, active smoker vs. passively exposed vs. not exposed) did not significantly moderate the relationship between depression and birth weight (results not shown). The cotinine cutpoints chosen for the current analyses were based upon those recommended by Benowitz et al.⁴⁵ and used in other studies examining prenatal smoke exposure³⁸; however, different cutpoints have been proposed to indicate prenatal smoke exposure due to alterations in metabolism during pregnancy.³⁹ For example, Florescu et al.³⁹ suggested the reference value of 10 ng/mL to distinguish between active and passive exposure. However, using these alternative cutpoints, the interaction was again not significant (results not shown). Thus, using a continuous measure of smoke exposure based on a biomarker increased our power to detect significant effects of smoke exposure on birth weight that might not have been identified using self-report or cutpoints.

A secondary goal of the current study was to examine the impact of race on associations among prenatal cotinine, depressive symptoms, and birth weight. Consistent with previous results,^{3,22,33-35} African American women had lower birth weight babies and higher cotinine levels, suggestive of greater prenatal smoke exposure. In terms of depression, women within the Hispanic or Other group reported the highest scores on the CES-D, followed by African Americans; Caucasian women reported the lowest levels of depressive symptoms. However, race was not a significant moderator in any of the analyses. The lack of significant moderation was surprising given the relationships observed among race, cotinine, depressive symptoms, and birth weight. Taken together, the results underscore previous findings indicating that racial minorities, particularly African American women, may be at higher risk for experiencing negative pre- and perinatal outcomes, but ongoing research is needed to better clarify the confluence of risk factors that may be driving these outcomes.

Results should be interpreted within the context of certain limitations. First, there were few low birth weight babies in the study sample, potentially limiting our ability to determine the relationship between cotinine, depressive symptoms, and risk for having a low birth weight infant. Second, the half-life of cotinine is between 48 and 72 hours and only a single sample was collected toward the end of the first trimester; multiple samples collected over the duration of pregnancy would have allowed for a calculation of the average level of smoke exposure throughout gestation and exploration of the potential impact of timing of smoke exposure on birth weight. For example, previous studies have identified a 27-g reduction in birth weight for every cigarette smoked during the third trimester of pregnancy.¹⁴ In addition, due to funding limitations, only plasma samples from women who participated in later follow-up studies were

analyzed for cotinine. In addition, the current sample differed from the larger NEST sample in several ways and may not be as generalizable to ethnically diverse, densely urban areas.

Despite these limitations, findings from this study are meaningful, as both smoking and maternal depressive symptoms are modifiable risk factors. These results have several important clinical implications, particularly for obstetricians and health providers working with pregnant women. Specifically, the current study indicates that women who experience smoke exposure in combination with depressive symptoms may constitute a highly vulnerable population for negative perinatal outcomes. Although providers should continue to strongly recommend smoking cessation before and during pregnancy, results also indicate that assessing for any smoke exposure and depressive symptoms concurrently may be warranted. Encouragingly, smoking cessation treatment during pregnancy has been found to have a positive impact on depressive symptoms,⁴⁷ and treatment for smoking⁴⁸ and depression⁴⁹ during pregnancy have been shown to increase birth weight.

Although the study adds to the literature by investigating risk factors that may influence birth weight, identifying mechanisms underlying this pathway was outside the scope of the current analyses. It may be that prenatal depression increases pregnant women's vulnerability to smoke exposure through both direct and indirect pathways. For example, evidence suggests that depressed women are less likely to engage in optimal prenatal care (eg, attend birth preparation classes, take recommended doses of folic acid)⁵⁰ and are more likely to be exposed to tobacco smoke actively^{16,23} and passively.^{24,25} With regard to biological processes, the hypothalamic-pituitary-adrenal axis is hypothesized to be an important mechanism by which prenatal distress is transferred to the fetus.⁵¹ Further, animal⁵² and human studies¹⁰ have shown that psychological distress during pregnancy can impact the offspring's epigenome. Future studies should examine potential mechanisms underlying the prenatal depression and smoke exposure interaction in predicting birth outcomes.

In conclusion, the current study provides novel data regarding the interaction between prenatal depressive symptoms and smoke exposure. Using a biological marker of smoke exposure, results suggest that self-reported depressive symptoms in combination with prenatal smoke exposure results in a significant reduction in infant birth weight. Further investigation of mechanisms underlying the relationship between prenatal depression, smoking, and birth weight is needed.

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Declaration of Interests

None declared.

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