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Low-Level Prenatal Exposure to Nicotine and Infant Neurobehavior

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Abstract

Objective—To examine the association between prenatal exposure to nicotine from tobacco smoke and infant neurobehavior using tobacco biomarkers and a sensitive and comprehensive measure of infant neurobehavior.

Study design—Participants were 318 infants (206 White, 95 Black, 17 Other) and their mothers. Prenatal tobacco smoke exposure was measured twice during pregnancy and once at delivery using maternal serum cotinine. Infant neurobehavior was assessed with the NICU Network Neurobehavioral Scale at approximately five weeks after birth.

Results—Prenatal tobacco smoke exposure was significantly associated with infant neurobehavior after controlling for important covariates, but the specific behaviors associated with exposure varied by race. In White infants, higher cotinine was associated with increased arousal ($p=.030$) and excitability ($p=.034$), and decreased self-regulation ($p=.010$). In contrast, among Black infants, higher cotinine was associated with decreased arousal ($p=.001$), excitability ($p=.021$), and special handling required to complete the assessment ($p=.003$), and increased self-regulation ($p=.021$) and hypotonicity ($p=.016$). In secondary analyses, we found racial differences in the effects of postnatal exposure to second hand smoke and low-level prenatal exposure.

Conclusions—Low-level prenatal tobacco smoke exposure is associated with infant neurobehavior at five weeks of age, but the specific effects differ by race. These effects may reflect racial differences in nicotine metabolism that are similar to differences reported in adult and child studies of tobacco.

Indexing Terms

tobacco smoke; prenatal exposure; infant neurobehavior

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CONFLICT OF INTEREST STATEMENT

No competing interests to declare.

1. INTRODUCTION

By report, approximately 30% of US women of childbearing age smoke, and only a fraction quit smoking during pregnancy [1,2] resulting in inevitable exposure of the fetus to tobacco smoke. In 2002, 11% of US women reported smoking during pregnancy [3]. This does not account for second hand tobacco smoke (SHS) exposure of pregnant women by smoking spouses or partners, and it may therefore underestimate the magnitude of prenatal exposure. Nicotine levels in amniotic fluid and in fetal circulation can be detected at levels 88% and 15% higher than maternal levels, respectively [4,5], indicating an amplification of exposure for the fetus.

Prenatal exposure to tobacco smoke has been linked with negative developmental [6] and behavioral outcomes in childhood [7–13]. During neurological examination, infants of women who smoked during pregnancy exhibited abnormal reflexes [14,15], both hypertonicity [12, 16] and hypotonicity [15], increased nervous system excitation, [14] irritability [12], and need for special handling to complete an exam [13], and decreased alertness [15]. They also had elevated scores for neonatal withdrawal [15].

Infant neurobehavioral assessments are more comprehensive examinations that can yield insight into the organization and function of the nervous system, as well as behavioral composition and adaptability to the extrauterine environment. Neurobehavioral assessment of infants has been successfully employed in research describing characteristics of normal infants [17] and examining a variety of prenatal insults ranging from prematurity [18,19] to maternal depression [20–22] to drug exposure [23–32].

Studies of the impact of prenatal exposure to tobacco smoke on later developmental and behavioral outcomes are fraught with limitations due to a reliance on relatively crude measures of exposure as well as a lack of prospective measurement of maternal smoking behavior that may fluctuate widely throughout pregnancy [33]. Published studies specifically examining the impact of prenatal tobacco smoke exposure on infant neurobehavior are limited with small sample sizes and use of surveys and/or biomarkers of exposure collected only at delivery. In addition, while there is increasing evidence that SHS exposure is detrimental to children, published studies have only compared infants of smokers versus nonsmokers [13,34,35]. Law [34] reported increased stress/abstinence signs, excitability, increased tone, and abnormal reflexes among infants of smokers. Mansi [35] found increased irritability and decreased attention among infants of women who smoked during pregnancy. Stroud [13] reported infants of women who smoked required more special handling during the assessment with trends toward increased excitability and arousal.

To our knowledge, no study has examined the impact of low-level tobacco smoke exposure on infant neurobehavior. Our objective was to examine the association between prenatal exposure to tobacco smoke and infant neurobehavior using an objective biomarker of tobacco smoke exposure and a sensitive measure of neurobehavior that provides a comprehensive assessment in early infancy.

2. METHODS

2.1 Subjects

The cohort on which this study is based consists of 468 healthy women, at least 18 years of age, who were enrolled in the Health Outcomes and Measures of the Environment Study at 16 $\pm$ 3 weeks of pregnancy. Women resided within pre-selected enrollment areas, received prenatal care from one of the eight participating obstetrical clinics, and planned to deliver at one of the three participating hospitals. Details regarding recruitment and enrollment

procedures are described elsewhere [36]. This is a socioeconomically diverse sample including urban, suburban, and rural participants. Institutional review boards of all involved research institutions, hospitals, and laboratories approved the study protocol.

Of the 468 enrolled women, 398 remained in the study to delivery and delivered live infants. For the current study, we excluded 9 sets of twins and 57 infants who did not receive the 5-week neurobehavioral assessment. We also excluded five infants of mothers with severe depression, based on Beck Depression Index II [37] scores greater than 34, to reduce the potential confounding effect of these outliers. The final sample for this analysis includes 318 infants.

2.2 Survey Data

Mothers were surveyed during pregnancy and at the 5 week home visit for collection of demographic and socioeconomic status variables, reported use of and exposure to tobacco smoke, and use of illicit drugs and alcohol during pregnancy. Mothers also completed the Beck Depression Inventory [37] both prenatally and at 5 weeks to measure depression symptoms. Mothers scoring >19 on the BDI-II were coded as experiencing moderate to severe depression in accordance with the BDI-II manual.

2.3 Serum Cotinine

Reported use of and exposure to tobacco products can be inaccurate due to recall bias and lack of detailed information regarding smoking patterns and exposure factors such as proximity to smoker and air flow. Biological markers of exposure can be used to measure actual body burden and help reduce the uncertainties of self-report data [38]. We used serum cotinine, a metabolite of nicotine, to objectively measure prenatal exposure to tobacco smoke. Maternal serum was collected twice during pregnancy, at about 16 and 28 weeks gestation, and at delivery. Cotinine assays were performed at CDC's Environmental Health Laboratories using published methods [39–41]. For samples below the limit of detection (0.015 ng/mL), we randomly imputed values from the left tail of the log normal distribution after excluding smokers and women with cotinine levels >20 ng/mL. Correlations between serum cotinine values collected at the three time points and estimated mean and maximum values were very high ($r = .88 - .94$). We used the maximum level over the three samples in all analyses because it required fewer imputations. A log base 2 transformation was employed for analyses of cotinine. Use of the log base 2 transformation means that for each doubling of the cotinine level, there is an increase in the neurobehavioral outcome scale equal to the beta coefficient for log cotinine.

2.4 Neurobehavioral Examinations

The Neonatal Intensive Care Unit Network Neurobehavioral Scale (NNNS) [42] was administered at approximately 5 weeks of age during a home visit. The NNNS is a neurobehavioral assessment instrument that integrates several infant assessment tools with heaviest influence from the Neonatal Behavioral Assessment Scale (NBAS) [43]. The measure is appropriate for infants 30 to 46 weeks gestational age and is especially sensitive to the capabilities and vulnerabilities of high-risk infants such as those born prematurely or prenatally exposed to potentially neurotoxic substances. It involves evaluation of neurologic and behavioral qualities of the newborn as well as observation of both overt and subtle signs of stress during the exam. The typical exam requires about 30 minutes. It begins with an observation of baseline respiration and tone. If the infant is asleep, a sequence of habituation items is presented to measure the infant's ability to process visual, auditory, and tactile stimuli, and to protect sleep. The habituation package is often omitted due to the sleep requirement. Examination of primitive reflexes, as well as passive and active tone ensues, followed by social interaction components of the assessment and an assessment of attention. A few additional neurological items are completed, followed by another observation of respiration and tone to

complete the assessment. Analysis of NNNS raw data results in summary scores on 13 dimensions including: habituation, attention, arousal, self-regulation, special handling needed from the examiner to assist the infant through the exam, quality of movement, excitability, lethargy, non-optimal reflexes, asymmetrical reflexes, hypertonicity, hypotonicity, and stress/abstinence. Exams were completed in a quiet room by certified examiners who were masked to serum cotinine levels of the mothers, their reported smoking status, and reported SHS exposure.

2.5 Statistical Analysis

Bivariate associations between serum cotinine and neurobehavioral outcomes guided our construction of multivariable regression models using linear and logistic regression analyses. Birth weight, age in days at the time of the assessment, and infant sex were retained as covariates in all final regression models irrespective of the statistical significance as they are known contributors to neurobehavior. Other covariates included maternal and newborn characteristics that may affect neurobehavioral performance: maternal age, income, maternal employment, maternal education, marital status, parity, marijuana and alcohol use, maternal blood lead during pregnancy, weight change from birth to five weeks, and maternal depression either during pregnancy or at 5 weeks. Covariates/confounders were retained in the final model for the individual NNNS subscale if they significantly affected neurobehavior or removal changed the cotinine estimate by greater than ten percent. We also conducted an examination of associations between cotinine and outcome by race that resulted in additional regression analyses stratified by race. For all but the hypotonia subscale, analyses consisted of linear regression. For the hypotonia subscale, the distribution of the data required categorization of the data and use of logistic regression for analysis.

We conducted secondary analyses to help clarify the relationships between tobacco smoke exposure and neurobehavioral outcomes. First, we examined possible influences of postnatal SHS exposure on neurobehavior using detailed maternal reports of SHS exposure at the time of the five-week assessment. Next, we estimated the impact of low-level prenatal tobacco smoke by restricting the analysis to infants whose mothers had a cotinine level of ≤ 10 ng/mL as levels >10 ng/mL are indicative of active smoking or SHS exposure at a level high enough to potentially have the same impact as active smoking [44]. Due to small numbers of women who either reported that they were active smokers or had a cotinine level of >10 ng/mL, we were unable to examine the neurobehavioral outcomes among these more heavily exposed infants as a separate group.

3. RESULTS

3.1. Descriptive Variables

The characteristics of the 318 singleton infants and their mothers are shown in Table 1. The mean maternal age at delivery was 30 years, and the majority of women were married, had a greater than high school education or the equivalent, and were employed. By medical chart review, the mean gestational age of infants was 39 weeks, and the mean birth weight was 3449g. Racial makeup of the infants was 65% White (n=206), 30% Black (n=95), and 5% Other (4 American Indian, 8 Asian/Pacific Islander, 4 Hispanic, 1 unknown). In race-stratified analyses, we compared only White and Black infants to aid clearer interpretation of the findings.

3.2. Exposure Variables

Fifteen percent of the mothers in the sample reported they were smokers prior to pregnancy recognition. Ten percent of women reported active smoking during pregnancy (n=33 - 11 White, 20 Black, 2 Other), smoking an average of 0.6 cigarettes per day. Fifteen percent of the nonsmoking women reported that they were exposed to SHS in their home on a regular basis.

While 25% of the women either smoked or were exposed to SHS by self-report, cotinine was detectable in serum samples for 79% of the women. Eight percent of women (n=27; 5 White, 20 Black, 2 Other) had maximum serum cotinine levels > 10 ng/mL, a level that has been used to classify active smokers [44]. Of the 33 women who reported actively smoking during pregnancy, 23 (69.7%) had serum cotinine levels >10 ng/mL. Similarly, of the 27 women who had serum cotinine levels >10 ng/mL, 23 (85.2%) reported actively smoking during pregnancy (4 White, 17 Black, 2 Other). Of the 239 women who reported no exposure to tobacco smoke, either by smoking actively or receiving SHS exposure, only 3 (1.3%) had serum cotinine levels >10 ng/mL. While these comparisons offer some support for the relationship between maternal report and biomarkers of exposure, they also demonstrate that survey data may result in an under representation of exposure.

In bivariate analyses, higher serum cotinine was associated with less than high school education ($p<.001$), single marital status ($p<.001$), lower income ($p<.001$), unemployment ($p=.01$), younger age ($p<.001$), marijuana use ($p<.001$), and depression ($p<.001$) among women. Serum cotinine was also associated with decreased birth weight ($p=.001$), male sex ($p=.02$), and Black race ($p<.001$) in the offspring.

3.2 Newborn Neurobehavior

The number of infants receiving scores on habituation and hypertonicity subscales of the NNNS were too small for meaningful interpretation (n = 29 and n = 13, respectively), so we excluded these subscales from analyses in accordance with other researchers who have used the NNNS as an outcome [13,34]. Neurobehavioral scores for the remaining NNNS subscales were comparable with those reported for other healthy infants [13,45]. In bivariate analyses, serum cotinine was significantly associated with: lower attention scores ($\beta = -0.062$, $p = 0.045$), poorer quality of movement ($\beta = -0.025$, $p = 0.045$), and increased stress signs ($\beta = 0.007$, $p = 0.003$). There were also trends related to decreased self-regulation ($\beta = -0.031$, $p = 0.066$) and increased lethargy ($\beta = 0.068$, $p = 0.066$). Significant race by cotinine interactions were found for the arousal ($\beta = 0.071$, $p=.01$), regulation ($\beta = 0.070$, $p=.01$), and excitability ($\beta = -0.178$, $p=.02$) subscales.

3.3 Stratified analyses

We conducted regression analyses stratified by race because we found significant differences among nearly all covariates by race, both cotinine and reported exposure differed significantly by race (Table 1), and significant race by cotinine interactions were discovered for several NNNS subscales. Table 2 shows regression results for full models with all covariates included as well as for the most parsimonious final models that only include the retained covariates. Birth weight, age in days at the time of the assessment, and sex were standard covariates retained in all regression models. Table 3 provides information on covariates retained in final models for Black and White infants.

In final models for White infants, serum cotinine was associated with increased arousal and excitability, as well as decreased self-regulation and a trend toward decreased attention. In contrast, among Black infants, serum cotinine was associated with decreased arousal, excitability, and required special handling, as well as increased self-regulation and hypotonicity.

In secondary analyses, we found that both current exposure to SHS at the time of the assessment and variations in cotinine even at low levels during pregnancy were associated with infant neurobehavior that again differed by race (Table 4). Among White infants, each of the previously identified relationships between prenatal tobacco smoke exposure and neurobehavior at five weeks remained when controlling for current SHS exposure, and a

significant association between serum cotinine and decreased attention arose. Next, we examined whether the relationship of prenatal tobacco exposure persisted for infants with low-level exposure. When women with cotinine levels indicative of either active smoking or higher levels of SHS exposure during pregnancy were removed, the relationships between prenatal serum cotinine and decreased attention and regulation and increased excitability remained significant, but the relationship with increased arousal was no longer statistically significant for White infants. Among Black infants, controlling for SHS exposure at the time of the neurobehavioral assessment resulted in statistically significant relationships with decreased arousal and increased regulation, but associations with decreased handling and excitability and increased hypotonicity were attenuated. Exclusion of infants whose mothers had cotinine levels > 10 ng/mL resulted only in a statistically significant relationship between prenatal tobacco smoke and increased regulation at 5 weeks for Black infants. Table 5 provides information on covariates retained in secondary analysis models for Black and White infants accounting for passive SHS exposure at 5 weeks and limiting the sample to those with low exposure.

4. DISCUSSION

We examined the relationship between prenatal tobacco smoke exposure and infant neurobehavior. The relatively normative sample of infants was derived from women who smoked at levels reflective of nationally reported levels [3,46]. We found significant differences in infant neurobehavior at age five weeks in relation to exposure to tobacco smoke during pregnancy; however, the relationships between exposure and neurobehavioral outcome differed dramatically by race.

Among White infants, as prenatal tobacco smoke exposure increased, infants were more disturbed and agitated during the assessment. In addition, they were less able to self-regulate and calm themselves, requiring more intervention from the examiner. These infants also showed a trend toward a reduced ability to focus on the examiner and to participate in portions of the neurobehavioral assessment that require active engagement and socialization that became significant when we accounted for SHS exposure concurrent with the 5-week assessment. These results are consistent with previous studies reporting increased excitability [34], decreased attention [35], and a need for additional examiner assistance [13] during the NNNS in association with maternal smoking during pregnancy. They are also consistent with studies that have used other infant assessments reporting increased nervous system excitation [14] and decreased alertness [15] in relation to maternal smoking during pregnancy.

When controlling for reported postnatal SHS exposure, this behavioral profile of agitation and inattention was strengthened in relation to prenatal exposure suggesting that in general, prenatal exposure remained as influential to neurobehavior as postnatal SHS for as long as five weeks after birth in these White infants. When limiting our analyses to infants with low-level exposure during pregnancy, determined by serum cotinine levels ≤ 10 ng/mL, we found that infants still exhibited decreased attention and self-regulation and increased excitability, but the association with increased arousal was no longer statistically significant. This suggests that among White infants, higher levels of tobacco smoke exposure are necessary to impact infant arousal, but that even very low levels of prenatal exposure that may result from minimal maternal SHS exposure can negatively impact the infant's ability to handle stimulation, self-regulate, and participate in focused interaction when stressed.

In contrast, among Black infants, as prenatal tobacco smoke exposure increased, infants were more relaxed and self-controlled during the assessment, requiring less assistance from the examiner to complete the exam. These results in aggregate could suggest that the neurobehavior among Black infants was less affected by exposure to tobacco during pregnancy and that they were much better equipped neurologically and behaviorally to participate in the assessment

than White infants. However, there was no indication that they participated at an elevated level as would be revealed by higher scores in alertness. It appears that as exposure increased among Black infants, they actually became less responsive during the exam, were less able to interact socially, and were less affected of the manipulation of the examiner.

When controlling for SHS exposure at the time of the exam, these Black infants remained less aroused and better self-regulated, but all other relationships were attenuated. This suggests that among Black infants, prenatal exposure remains critical in influencing a low arousal level and better self-regulation, but that SHS exposure at the time of the assessment overrides other neurobehavioral effects of prenatal exposure. When limiting the analyses to infants with very low-level exposure during pregnancy, only the relationship with increased self-regulation remained. This suggests that self-regulation among Black infants continues to be affected by prenatal exposure, but that in other areas of neurobehavior, Black infants are more likely to be affected by higher levels of tobacco during pregnancy and may be less sensitive to lower levels of exposure, and that the impact of postnatal SHS exposure overpowers the effect of prenatal exposure in Blacks. However, we suggest that these findings should be interpreted with caution due to the small sample size and potentially reduced analytic power.

It is not surprising that we found racial differences in the effects of prenatal tobacco exposure on infant neurobehavior. There is substantial evidence from research on adults indicating that Blacks often have higher cotinine levels than whites and Hispanics despite similar smoking prevalence rates [46] and fewer reported cigarettes per day [47]. Similarly, racial differences in cotinine levels have been reported among adolescent smokers [48,49], pregnant smokers [50], and children exposed to SHS [51]. Further study has found slower metabolism of nicotine among Blacks when compared with Whites [52,53]. Given these reports, it is possible that racial differences in fetal and infant metabolism of nicotine also exist, and that subsequent neurobehavioral outcomes may also vary by race. Perera [54] found higher umbilical cord serum cotinine in Black versus Hispanic newborns, but neurobehavioral outcomes are not reported. We know of no other studies of cotinine levels in early infancy. Previously published studies have included small samples and have included race solely as a covariate rather than a major contributor to outcome. An advantage of the present study is that we had a larger sample of both White and Black infants to explore potential racial differences. However, as with most subgroup analyses, the study was underpowered to fully examine differences in gradients of exposure. For example, among Black infants, the coefficient for self regulation ($\beta=0.077$, $se=0.027$, $p=.006$) falls only slightly when considering SHS exposure at 5 weeks ($\beta=0.062$, $se=0.032$, $p=.077$). Because of the change in sample size, we see an associated change in standard error and thus effect size and significance. For this reason, we report both betas and standard errors in our tables so that the relative effect sizes for our population may be useful for planning future studies. Despite these power limitations, our study provides convincing evidence that future studies of relationships between tobacco smoke exposure and infant neurobehavior should include sufficient samples of diverse racial backgrounds and exposure levels.

The study has several limitations. First, although we had serial measures of prenatal tobacco smoke exposure, we lacked a biomarker of SHS exposure concordant with the neurobehavioral assessment at five weeks of age. Second, although this is the first known study to examine racial differences in infant neurobehavior using serial cotinine levels, the stratified analysis of the data based on race resulted in smaller sample sizes, was associated with reduced effect sizes as discussed above, and diminished our ability to fully detect neurobehavioral differences. Third, the sample included very few women who actively smoked during pregnancy. Nevertheless, the exposure patterns resemble those in nationally reported female smoking rates [55] and rates of smoking during pregnancy [3]. Lastly, although there are clear racial differences in the metabolism of nicotine, it is important to acknowledge that race may be

acting as a proxy for other sociodemographic differences that could impact infant neurobehavior. Factors such as maternal depression [56,57] and socioeconomic strain [58] have been linked with diminished attention, alertness, and interaction patterns in infants, as well as increased arousal and stress responses. It is imperative that future investigations examining the link between prenatal tobacco smoke and infant neurobehavior include samples that are more sociodemographically balanced to allow clarity in illuminating potential racial differences in outcome distinct from those that may be confounded by sociodemographic characteristics.

In a sample of infants whose exposure to tobacco smoke during pregnancy resembled nationally-reported rates, we found significant differences in neurobehavioral outcomes associated with higher tobacco smoke exposure. These outcomes varied by race. With higher levels of tobacco smoke exposure, White infants were more excitable, aroused, and less able to calm themselves, whereas Black infants were less responsive during the assessment. These racial differences in neurobehavior could be related to metabolic differences in nicotine metabolism as disparities in the consequences of nicotine exposure. The findings of this study suggest that even low levels of exposure to tobacco smoke may impact infant neurobehavior. Additional study is required to further investigate these relationships and differentiate the influences that prenatal tobacco smoke and postnatal SHS exposure may have on neurobehavioral profiles of infants of different races.

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Table 1
 Characteristics of Full Sample and by Infant Race

Maternal Characteristics	Full Sample (N=318)	White (N=206)	Black (N=95)	p-value for Black vs White
Maternal age at delivery (years) ^a	30 (5.6)	31.9 (4.5)	26.0 (5.8)	< 0.0001
Married	222 (70%)	190 (92%)	19 (21%)	< 0.0001
Not married, living with someone	41 (13%)	11 (5%)	28 (29%)	
Not married, living alone	55 (17%)	5 (2%)	48 (50%)	
Household income ^b	55K (28K, 85K)	75K (45K, 95K)	17.5 (7.5K, 28K)	< 0.0001
Employed	268 (84%)	180 (87%)	72 (76%)	0.0067
> HS or GED	257 (81%)	195 (95%)	49 (52%)	< 0.0001
Moderate to severe depression (during pregnancy or postpartum)	71 (22%)	26 (13%)	39 (41%)	<0.0001
Alcohol use during pregnancy				0.39
Never drank alcohol during pregnancy	197 (62%)	121 (59%)	62 (65%)	
Drank <1 alcoholic drink per month	76 (24%)	57 (28%)	17 (18%)	
Drank >1 alcoholic drink per month	45 (14%)	28 (14%)	16 (17%)	
Marijuana use during pregnancy	21 (7%)	3 (1%)	18 (19%)	< 0.0001
Tobacco smoke exposure				
Mother smoked before pregnancy	49 (15%)	21 (10%)	25 (26%)	0.0004
Active smoker during pregnancy	33 (10%)	11 (5%)	20 (21%)	<0.0001
Passive exposure during pregnancy	67 (21%)	30 (15%)	33 (35%)	<0.0001
Any exposure during pregnancy	79 (25%)	34 (16%)	41 (43%)	< 0.0001
Number cigarettes smoked/day ^a	0.6 (3.2)	0.01 (0.54)	1.9 (5.5)	0.003
Number cigarettes exposed/day ^a	4.2 (11.3)	2.8 (9.1)	7.1 (14.6)	0.01
Maternal serum cotinine >LOD	252 (79%)	161 (72%)	91 (96%)	< 0.0001
Maternal max serum cotinine (geomean) ^c	0.087 (0.0005, 13.9)	0.033 (0.0011, 0.996)	0.82 (0.003, 229)	< 0.0001
Infant Characteristics				
Male	149 (47%)	105 (51%)	36 (38%)	0.04
Birth weight (grams) ^a	3449 (562.5)	3569 (560)	3200 (472)	< 0.0001
Birth length (cms) ^a	51.3 (2.5)	51.8 (2.4)	50.0 (2.2)	<0.0001
Head circumference (cms) ^a	34.4 (1.7)	34.7 (1.6)	33.6 (1.6)	<0.0001
Gestational age (weeks) ^a	39.2 (1.4)	39.4 (1.6)	38.9 (1.6)	0.008
Age at 5-week exam (days) ^a	34.4 (4.9)	34.6 (5.0)	33.7 (4.8)	0.13
Birth order				0.0006
First child	140 (44%)	113 (51%)	27 (28%)	
Second child	104 (33%)	68 (30%)	36 (38%)	
> Second child	74 (23%)	42 (19%)	32 (34%)	

Data presented as N (%),

^a Mean (SD),

^b Median (25th, 75th percentile) or

^c Geometric Mean (95% confidence interval)

Table 2
Associations Between Prenatal Tobacco Smoke Exposure and Infant Neurobehavioral Outcomes by Race

NNNS Subscale	White (n=206)				Black (n=95)			
	Full Model	Final Model	Full Model	Final Model	Full Model	Final Model	Full Model	Final Model
	Estimate	SE ^a	p	Estimate	SE ^a	p	Estimate	SE ^a
Attention	-0.068	0.052	0.192	-0.092	0.047	0.051	0.071	0.039
Arousal	0.049	0.022	0.026	0.044	0.020	0.030	-0.080	0.023
Regulation	-0.051	0.025	0.042	-0.058	0.022	0.010	0.076	0.032
Handling	-0.0002	0.012	0.998	-0.0008	0.011	0.938	-0.031	0.010
Excitability	0.128	0.061	0.037	0.125	0.058	0.034	-0.172	0.073
Hypotonia^b	-0.075	0.091	0.406	-0.026	0.076	0.737	0.222	0.092

^a standard error

^b estimate from the logit model

Covariates included in the full model: birth weight, age in days at the time of assessment, sex, maternal age, income, maternal employment, maternal education, marital status, parity, marijuana and alcohol use, maternal blood lead during pregnancy, weight change from birth to five weeks, maternal depression either during pregnancy or at five weeks. Birth weight, age in days at the time of assessment, and sex were retained in all models.

Table 3

Covariates in Final Models to Accompany Table 2

NNNS Subscale	Covariates	Black (n=75)		White (n=206)	
		β (se) [p-value]	Covariates	β (se) [p-value]	Covariates
ATTENTION	Age at exam (days)	-0.046 (0.028) [p=0.105]			Age at exam (days)
	Male gender	0.376 (0.291) [p=0.201]			Male gender
	Birth weight (kgm)	0.157 (0.294) [p=0.595]			Birth weight (kgm)
	Maternal employment	0.308 (0.321) [p=0.341]			Maternal age (years)
	Drink > 1/month	0.553 (0.364) [p=0.133]			Maternal employment
	Marijuana	-0.939 (0.411) [p=0.025]			
AROUSAL	Age at exam (days)	0.008 (0.015) [p=0.578]			Age at exam (days)
	Male gender	-0.119 (0.149) [p=0.425]			Male gender
	Birth weight (kgm)	-0.161 (0.151) [p=0.290]			Birth weight (kgm)
	Drink > 1/month	-0.652 (0.200) [p=0.002]			Maternal age (years)
	Marital status1 *	0.278 (0.219) [p=0.209]			Weight change (kgm)
	Marital status2 *	0.160 (0.216) [p=0.461]			
	Parity=1	0.362 (0.176) [p=0.043]			
	Parity>=2	0.083 (0.093) [p=0.374]			
	Marijuana	0.629 (0.223) [p=0.006]			
	Maternal lead (log base e)	0.353 (0.167) [p=0.038]			
REGULATION	Age at exam (days)	-0.010 (0.018) [p=0.588]			Age at exam (days)
	Male gender	-0.270 (0.175) [p=0.126]			Male gender
	Birth weight (kgm)	0.408 (0.177) [p=0.024]			Birth weight (kgm)
	Marijuana	-0.500 (0.257) [p=0.056]			Weight change (kgm)
	Income (\$)	0.007 (0.004) [p=0.092]			
	Maternal lead (log base e)	-0.475 (0.194) [p=0.017]			
HANDLING	Age at exam (days)	0.005 (0.006) [p=0.451]			Age at exam (days)
	Male gender	-0.058 (0.064) [p=0.366]			Male gender
	Birth weight (kgm)	0.065 (0.065) [p=0.324]			Birth weight (kgm)
	Maternal age (years)	-0.014 (0.007) [p=0.042]			Maternal employment

NNNS Subscale	Covariates	Black (n=75)		White (n=206)	
		β (se) [p-value]	β (se) [p-value]	Covariates	β (se) [p-value]
	Maternal less than high school education	-0.172 (0.071) [p=0.017]		Maternal less than high school education	0.067 (0.098) [p=0.497]
	Parity=1	0.161 (0.077) [p=0.039]		Weight change (kgm)	-0.067 (0.082) [p=0.416]
	Parity>=2	0.053 (0.046) [p=0.246]		Parity=1	-0.006 (0.053) [p=0.915]
	Marijuana	0.204 (0.096) [p=0.035]		Parity>=2	0.036 (0.032) [p=0.258]
	Maternal lead (log base e)	0.127 (0.075) [p=0.095]		Maternal lead (log base e)	-0.032 (0.052) [p=0.536]
	Drink > 1/month	-0.199 (0.087) [p=0.026]			
EXCITABILITY	Age at exam (days)	0.006 (0.049) [p=0.905]		Age at exam (days)	0.058 (0.026) [p=0.029]
	Male gender	0.449 (0.482) [p=0.354]		Male gender	0.351 (0.278) [p=0.208]
	Birth weight (kgm)	-0.827 (0.491) [p=0.096]		Birth weight (kgm)	0.056 (0.241) [p=0.816]
	Marijuana	1.122 (0.682) [p=0.104]		Weight change (kgm)	-0.920 (0.467) [p=0.050]
	Income (\$)	-0.010 (0.012) [p=0.424]		Income (\$)	0.004 (0.004) [p=0.221]
HYPOTONICITY	Age at exam (days)	-0.140 (0.071) [p=0.049]		Age at exam (days)	0.006 (0.036) [p=0.877]
	Male gender	-0.889 (0.679) [p=0.190]		Male gender	-0.177 (0.386) [p=0.647]
	Birth weight (kgm)	0.422 (0.701) [p=0.547]		Birth weight (kgm)	0.611 (0.325) [p=0.060]
	Maternal age (years)	0.116 (0.064) [p=0.068]		Maternal age (years)	0.065 (0.040) [p=0.103]
	Parity=1	-1.631 (0.832) [p=0.050]		Weight change (kgm)	0.191 (0.661) [p=0.773]
	Parity>=2	-0.284 (0.432) [p=0.512]		Income (\$)	-0.012 (0.006) [p=0.025]
	Marijuana	-1.847 (1.053) [p=0.079]		Parity=1	-0.737 (0.440) [p=0.094]
	Drink > 1/month	1.498 (0.812) [p=0.065]		Parity>=2	-0.131 (0.229) [p=0.568]

* Marital status 1 is "not married, but living together", Marital status 2 is "not married, living alone."

Table 4

Associations Between Prenatal Tobacco Smoke Exposure and Infant Neurobehavioral Outcomes by Race; Accounting for Passive Exposure to SHS Concurrent with 5-Week Assessment and Excluding Heavy Prenatal Exposure by Cotinine >10ng/mL

NNNS Subscale	White – Accounting for Passive Exposure				Black - Accounting for Passive Exposure			
	Estimate	SE ^a	p	Low Cotinine Only (n=201)	Estimate	SE ^a	p	Low Cotinine Only (n=75)
Attention	-0.134	0.051	0.009	-0.135	0.067	0.045	0.051	0.067
Arousal	0.055	0.022	0.013	0.048	0.031	0.120	-0.057	-0.061
Regulation	-0.085	0.024	0.0005	-0.094	0.034	0.006	0.076	0.109
Handling	0.004	0.012	0.697	-0.0006	0.016	0.971	-0.017	-0.024
Excitability	0.151	0.062	0.017	0.194	0.086	0.026	-0.122	-0.135
Hypotonia ^b	-0.016	0.082	0.846	0.051	0.116	0.659	0.204	0.094

^a standard error

^b estimate from the logit model

Covariates included in the full model: birth weight, age in days at the time of assessment, sex, maternal age, income, maternal employment, maternal education, marital status, parity, marijuana and alcohol use, maternal blood lead during pregnancy, weight change from birth to five weeks, maternal depression either during pregnancy or at five weeks. Birth weight, age in days at the time of assessment, and sex were retained in all models.

Table 5
Covariates to Accompany Table 4, Accounting for Passive Smoke Exposure at 5 Weeks

NNNS Subscale	Covariates	Black (n=75)		White (n=201)	
		β (se)	[p-value]	β (se)	[p-value]
ATTENTION	Age at exam (days)	-0.025	(0.033) [p=0.456]		
	Male gender	0.433	(0.341) [p=0.209]		
	Birth weight (kgm)	-0.205	(0.377) [p=0.588]		
	Maternal employment	0.094	(0.406) [p=0.819]		
	Drink > 1/month	0.652	(0.437) [p=0.141]		
	Marijuana	-1.196	(0.592) [p=0.048]		
	Passive smoking	0.160	(0.385) [p=0.679]		
AROUSAL	Age at exam (days)	0.004	(0.016) [p=0.770]		
	Male gender	-0.281	(0.160) [p=0.085]		
	Birth weight (kgm)	-0.117	(0.174) [p=0.505]		
	Drink > 1/month	-0.798	(0.220) [p=0.001]		
	Marital status 1 *	0.158	(0.220) [p=0.477]		
	Marital status 2 *	0.113	(0.212) [p=0.596]		
	Parity=1	0.315	(0.177) [p=0.080]		
	Parity>=2	0.159	(0.101) [p=0.120]		
	Marijuana	0.917	(0.325) [p=0.006]		
	Maternal lead (log base e)	0.481	(0.173) [p=0.007]		
	Passive smoking	-0.322	(0.184) [p=0.085]		
				0.019	(0.009) [p=0.046]
				0.076	(0.101) [p=0.456]
REGULATION	Age at exam (days)	0.002	(0.020) [p=0.908]		
	Male gender	-0.270	(0.193) [p=0.168]		
	Birth weight (kgm)	0.356	(0.206) [p=0.089]		
	Marijuana	-0.758	(0.379) [p=0.050]		
	Income (\$)	0.009	(0.005) [p=0.064]		
	Maternal lead (log base e)	-0.598	(0.208) [p=0.006]		
	Passive smoking	0.312	(0.241) [p=0.199]		
HANDLING	Age at exam (days)	0.002	(0.007) [p=0.771]		
				0.014	(0.010) [p=0.165]
				-0.121	(0.111) [p=0.279]
				-0.090	(0.097) [p=0.353]
				0.454	(0.189) [p=0.017]
				0.422	(0.181) [p=0.021]
				0.008	(0.004) [p=0.075]

NNNS Subscale	Covariates	Black (n=75)		White (n=201)	
		β (se) [p-value]		β (se) [p-value]	
EXCITABILITY	Male gender	-0.072 (0.076) [p=0.348]		Male gender	-0.020 (0.048) [p=0.672]
	Birth weight (kgm)	0.123 (0.082) [p=0.139]		Birth weight (kgm)	-0.025 (0.042) [p=0.548]
	Maternal age (years)	-0.014 (0.008) [p=0.103]		Maternal employment	0.120 (0.074) [p=0.107]
	Maternal less than high school education	-0.151 (0.089) [p=0.093]		Maternal less than high school education	0.078 (0.101) [p=0.444]
	Parity=1	0.152 (0.086) [p=0.082]		Weight change (kgms)	-0.083 (0.084) [p=0.324]
	Parity>=2	0.075 (0.057) [p=0.196]		Parity=1	0.002 (0.054) [p=0.970]
	Marijuana	0.164 (0.173) [p=0.346]		Parity>=2	0.042 (0.032) [p=0.199]
	Maternal lead (log base e)	0.145 (0.083) [p=0.087]		Maternal lead (log base e)	-0.024 (0.053) [p=0.656]
	Drink > 1/month	-0.219 (0.106) [p=0.042]		Passive smoking	-0.081 (0.079) [p=0.305]
	Passive smoking	-0.222 (0.086) [p=0.012]			
	Age at exam (days)	-0.004 (0.056) [p=0.940]		Age at exam (days)	0.053 (0.027) [p=0.051]
	Male gender	0.266 (0.542) [p=0.625]		Male gender	0.309 (0.281) [p=0.273]
HYPOTONICITY	Birth weight (kgm)	-0.684 (0.587) [p=0.248]		Birth weight (kgm)	0.066 (0.246) [p=0.788]
	Marijuana	1.895 (0.974) [p=0.056]		Weight change (kgms)	-1.050 (0.473) [p=0.028]
	Income (\$)	-0.008 (0.014) [p=0.540]		Income (\$)	0.004 (0.004) [p=0.282]
	Passive smoking	-0.956 (0.662) [p=0.153]		Passive smoking	-0.394 (0.456) [p=0.389]
	Age at exam (days)	-0.182 (0.093) [p=0.051]		Age at exam (days)	0.007 (0.037) [p=0.853]
	Male gender	-2.351 (1.023) [p=0.022]		Male gender	-0.194 (0.395) [p=0.622]
	Birth weight (kgm)	2.760 (1.300) [p=0.034]		Birth weight (kgm)	0.665 (0.335) [p=0.048]
	Maternal age (years)	0.153 (0.101) [p=0.128]		Maternal age (years)	0.072 (0.041) [p=0.079]
	Parity=1	-2.390 (1.139) [p=0.036]		Weight change (kgms)	0.417 (0.677) [p=0.538]
	Parity>=2	0.103 (0.514) [p=0.842]		Income (\$)	-0.013 (0.006) [p=0.021]
	Marijuana	-0.719 (2.407) [p=0.765]		Parity=1	-0.913 (0.462) [p=0.048]
	Drink > 1/month	-0.060 (1.123) [p=0.958]		Parity>=2	-0.138 (0.231) [p=0.550]
	Passive smoking	1.206 (0.920) [p=0.190]		Passive smoking	-0.534 (0.634) [p=0.399]

* Marital status 1 is "not married, but living together", Marital status 2 is "not married, living alone."