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Quantity and Timing of Maternal Prenatal Smoking on Neonatal Body Composition: The Healthy Start Study

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Abstract

Objective—To examine the dose-dependent and time-specific relationships of prenatal smoking with neonatal body mass, fat mass (FM), fat-free mass (FFM) and fat to fat-free mass ratio (F:FFM), as measured by air displacement plethysmography (PEA POD).

Study design—We analyzed 916 mother-neonate pairs participating in the longitudinal pre-birth cohort study, Healthy Start. Maternal prenatal smoking information was collected in early-, mid- and late-pregnancy by self-report. Neonatal body composition was measured by PEA POD following delivery. Multiple general linear regression models were adjusted for maternal and neonatal characteristics.

Results—For each additional pack smoked during pregnancy, neonatal body mass was significantly reduced (adjusted mean difference: −2.8 grams; 95% confidence interval [CI]: −3.9 to −1.8; $P<0.001$), FM (−0.7 g [−1.1 to −0.3]; $P<0.001$) and FFM (−2.1 g [−2.9 to −1.3]; $P<0.001$). Neonates exposed to prenatal smoking throughout pregnancy had significantly less body mass ($P<0.001$), FM ($P<0.001$) and FFM ($P<0.001$) compared with those unexposed. However, neonates of mothers who only smoked before late-pregnancy had no significant differences in body mass ($P = 0.47$), FM ($P = 0.43$) or FFM ($P = 0.59$) compared with unexposed offspring.

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Conclusions—Exposure to prenatal smoking leads to systematic growth restriction. Smoking cessation before late-pregnancy may reduce the body composition consequences of exposure to prenatal smoking. Follow-up of this cohort is needed to determine the influence of catch-up growth on early-life body composition and the risk of childhood obesity.

Keywords

Adiposity; ADP; developmental origins; fat mass; fat-free mass; fetal programming; obesity; PEA POD; pregnancy; tobacco

From 2000 to 2010, the prevalence of prenatal smoking has only decreased from 13.3% to 12.3%.[1] Exposure to prenatal smoking is associated with numerous adverse outcomes, such as growth restriction[2–4], medically indicated and spontaneous pre-term birth[5, 6] and abortion.[7] There also are associations between intrauterine tobacco exposure and later-life morbidities, including asthma[8] and childhood overweight and obesity.[9–12] Fetal growth restriction leads to compensatory acceleration in the rate of growth early in life, also known as catch-up growth.[13] Offspring that demonstrate postnatal catch-up growth have an increased risk for later chronic diseases.[14, 15] It has been theorized that catch-up growth, as a result of exposure to prenatal smoking, may be responsible for these long-term adverse effects.

The current knowledge base is limited regarding the relationships between the quantity and timing of prenatal smoking and measures of neonatal body composition: fat mass (FM) and fat-free mass (FFM) and their ratio, fat to fat-free mass (F:FFM). In general, previous studies of prenatal smoking[16–21] analyzed growth restriction using birth weight and indirect measures (e.g. skinfolds) for neonatal body composition. Only one study[2] directly measured neonatal body composition, albeit using a less accurate measure relative to more novel body composition systems.[22] Using birth weight or indirect measures of body composition may be a biased representation of body composition. Understanding how neonatal body composition is affected by prenatal smoking may lead to a better understanding of the fetal programming effects. Our aims were to assess the dose-dependent and time-specific associations of intrauterine tobacco exposure and neonatal body composition. We hypothesized that exposure to prenatal smoking would be associated with an overall reduction in neonatal body mass, primarily accounted for by a reduction in FFM, and a comparable proportionate reduction in FM resulting in similar F:FFM. Further, we hypothesized that these relationships would be dose-dependent and time-specific with growth restriction primarily being attributable to late-pregnancy smoking.

Methods

Healthy Start is an ongoing prospective pre-birth cohort study in Colorado that enrolls ethnically-diverse pregnant women and follows them until delivery. The study was approved by the Colorado Multiple Institutional Review Board. Participants are primarily recruited at the prenatal obstetrics clinics located at the University of Colorado Hospital (UCH) Outpatient Pavilion within the Anschutz Medical Campus of the University of Colorado - Denver. Women were not eligible if multiple births were expected or if they had a previous stillbirth, were less than 16-years of age at consent or had a gestational age at the time of

baseline research visit greater than 24-weeks. Participants were excluded from analyses if they withdrew consent before delivery or if their index pregnancy resulted in fetal death or a very preterm birth (i.e. less than 32-weeks). A total of 1,092 mother-neonate pairs who were enrolled in the study and delivered between March 19, 2010 and November 1, 2013 were eligible to participate in this study. The women were invited to participate in three research visits. The first visit occurred during early-pregnancy (median = 17-weeks), followed by a second visit during mid-pregnancy (median = 27-weeks) and a third visit following delivery (median = 1-day).

Exposure - Prenatal Smoking

Information about prenatal smoking was ascertained through interview-administered questionnaires at each of the three prenatal research visits. Data were collected on the quantity and duration of early-, mid- and late-pregnancy smoking. The duration of exposure per week to secondhand smoke during these periods was also assessed. Subjects reported the average number of cigarettes per day that they generally smoked. An interviewer recorded the value within a pre-specified range (eg, < 1 cigarette/day; 1–4 cigarettes/day; 5–14 cigarettes/day; 15–24 cigarettes/day or 25 cigarettes/day or more). For analytic purposes, the center of each range was taken and used to estimate total packs smoked during pregnancy. Duration of prenatal smoking was calculated based on the sum of the differences between dates of a) conception and the first prenatal research visit (i.e. early-pregnancy); b) the first and second prenatal research visits (i.e. mid-pregnancy); and c) the second prenatal research visit until date of delivery (i.e. late-pregnancy). The quantity of prenatal smoking reported at a specific research visit was used in conjunction with the duration between visits. Among smokers who missed their mid-pregnancy visit (n = 21), we took the mean number of cigarettes smoked per day during their two completed visits to estimate the quantity of prenatal smoking, and the duration by using the observed median time (65-days) from our cohort between early- and mid-pregnancy visits.

We separately tested the associations of total packs smoked during pregnancy and time-specific relationships on neonatal body mass, FM, FFM and F:FFM. Time-specific analyses compared: (1) neonates of mothers who smoked throughout pregnancy relative to non-smokers; (2) neonates of mothers who smoked before late-pregnancy to non-smokers; and (3) an exploratory analysis of neonates of mothers who smoked throughout pregnancy to before late-pregnancy.

Outcomes – Neonatal Body Mass and Composition

PEA POD (COSMED, Rome, Italy) is a 2-compartment model that measures neonatal body mass, FM (i.e. adipose tissue) and FFM (ie, water, bone, and non-bone mineral and protein) in both absolute and proportionate terms. We took the ratio of absolute measures for FM and FFM to calculate F:FFM. To measure these variables, the PEA POD system uses a densitometric technique based on air displacement plethysmography (ADP).[22] This technique is reliable and valid for measuring neonatal body composition.[22–25] Trained clinical personnel measured each neonate by PEA POD twice, and if %FM differed by >2%, then a third exam was conducted. Neonatal body composition was generally measured

within 24 hours following delivery (median = 1-day). To reduce measurement error for each outcome, we took the mean of the two closest measures.

Covariates

Covariate information was collected on mother-neonate pairs during research visits and through medical record abstraction. Maternal age at delivery was calculated based on offspring delivery date and maternal date of birth. Data on education, gravidity, household income and race/ethnicity were collected through research questionnaires. Maternal pre-pregnancy weight from research visits and medical records and maternal height measured at the baseline research visit were used to calculate pre-pregnancy body mass index (BMI). Weight during pregnancy was measured at research visits and also abstracted from medical records (median = 12 measurements per participant). Total gestational weight gain was estimated using mixed models predicting gestational weight gain at 39-weeks of gestation (mean gestational age of the cohort). Maternal physical activity levels were ascertained through a validated[26, 27] pregnancy physical activity questionnaire (PPAQ) during each research visit. Gestational age at delivery was estimated using ultrasound data, self-reported last menstrual period or both. Neonatal birth weight and length were obtained during the delivery visit and from medical records. Using United States national reference data,[28] small-for-gestational age (SGA) was indicated as a birth weight below the 10th percentile for gestational age, given sex of the offspring.

Data Analyses

All statistical analyses were conducted in SAS 9.3 (SAS Institute, Cary, NC). Relationships between prenatal smoking and continuous and categorical maternal and neonatal characteristics were analyzed by t-tests and χ^2 tests, respectively. Simple linear models were first tested. Multiple linear regression models (PROC GLM) were then constructed. Standard confounders of the relationship between prenatal smoking and offspring growth restriction including maternal age, education, household income and race/ethnicity, and gestational age at delivery and chronological age at PEA POD were initially entered into models. Next, independent variables were individually entered into the models. A variable remained in the model if a Partial F-test showed that the covariate meaningfully contributed to predicting the outcome of interest (p-value <0.10) or if the adjusted estimate of prenatal smoking was meaningfully altered (i.e. ≥10% change). Pre-pregnancy BMI and race/ethnicity were tested as potential effect modifiers of the relationship between prenatal smoking and neonatal body composition.

The dose-dependent associations of prenatal smoking were shown by plotting predicted neonatal FM and FFM as a function of packs smoked during pregnancy with 95% confidence limits. For the plots, categorical predictors were set at the reference group, and continuous covariates were set to their mean values.

Results

Of the 1,092 mothers who were eligible, 916 mother-neonate pairs had complete data on exposures and outcomes of interest and were analyzed. Prenatal smoking status (smokers vs.

non-smokers) was not significantly different between those with complete compared with missing data ($\chi^2 = 0.10$; $P = 0.75$). Further, there were no clinically relevant differences in main variables of interest, including maternal age (27.7 vs. 27.7 years), gravidity (1.4 vs. 1.4), pre-pregnant BMI (25.8 vs. 25.8 kg/m^2), gestational weight gain (14.4 vs. 14.4 kg), gestational age (275 vs. 276 days), birth length (49.2 vs. 49.2 cm), birth weight (3,227 vs. 3,255 g), offspring sex, racial/ethnic distribution, physical activity, educational attainment and household income between the eligible cohort and those used in final analyses.

In our cohort, 9.2% (n = 100) of mothers reported prenatal smoking. Of the 100 prenatal smokers, 46 smoked throughout pregnancy and 30 smoked only during early- and/or mid-pregnancy. The other 24 prenatal smokers reported smoking during early- and late-pregnancy (n = 3); mid- and late-pregnancy (n = 12); and only late-pregnancy (n = 9). Among prenatal smokers, the median estimated number of packs smoked during pregnancy was 29 (range: 3 to 257).

On average, mothers who smoked during pregnancy relative to non-smokers were significantly younger and had more previous pregnancies (Table I). Compared with non-smokers, prenatal smoking mothers were significantly more likely to have educational attainment of high school or less ($P<0.001$) and lower household income ($P<0.001$), and were less likely to be Hispanic ($P<0.001$). No significant differences were found between the two groups for pre-pregnancy BMI, gestational weight gain or chronological age at PEA POD exam (Table I).

Dose-dependent associations

Following adjustment for gestational age and chronological age at PEA POD, offspring sex, gravidity, maternal age, race/ethnicity, educational status, household income, gestational weight gain, pre-pregnancy BMI and physical activity, for each additional pack smoked during pregnancy, there was a 2.8 grams (95% confidence interval [CI]: −3.9 to −1.8; $P<0.001$) decrease in neonatal body mass. This decrease was accounted for by a 0.7 g ([−1.1 to −0.3]; $P = 0.001$) decrease in FM and a 2.1 g ([−3.0 to −1.3]; $P<0.001$) reduction in FFM (Figure). There was a statistically significant relationship, per pack smoked, with the F:FFM ratio (adjusted mean difference: −0.0002 [−0.0003 to −0.00002]; $P = 0.02$), suggesting a proportionally greater dose-dependent reduction in FM relative to FFM. Pre-pregnancy BMI and race/ethnicity were not statistically significant effect modifiers of these associations.

Time-specific associations

Smoking throughout pregnancy compared with non-smokers—Following statistical adjustment for the previously mentioned maternal and offspring characteristics, neonates of mothers who smoked throughout pregnancy had significantly less body mass ($P<0.001$), FM ($P<0.001$) and FFM ($P<0.001$) compared with neonates of mothers who were non-smokers. Similar direction and significance of the association as the dose-dependent model was observed in F:FFM ($P = 0.008$; Table II).

Smoking before late-pregnancy compared with non-smokers—After adjustment, neonates of mothers who smoked before late-pregnancy had no significant differences in

neonatal body mass (P = 0.47), FM (P = 0.43), FFM (P = 0.59) or F:FFM (P = 0.43), compared with neonates of mothers who did not smoke during pregnancy (Table II).

Smoking throughout pregnancy compared with before late-pregnancy—In exploratory analyses, we compared neonates of mothers who smoked throughout pregnancy with neonates of mothers who smoked during early- and/or mid-pregnancy. Following adjustment, neonates who were exposed to smoking throughout pregnancy had significantly less body mass, FM and FFM. F:FFM was also significantly reduced (Table II).

Exclusion of mothers exposed to secondhand smoke during late-pregnancy—In both dose-dependent and time-specific models where sensitivity analyses removed non-smoking mothers who were exposed to secondhand smoke more than 1 hour per week during late-pregnancy (n = 61), greater reductions in neonatal body mass, FM, FFM and F:FFM among neonates exposed to prenatal smoking were observed.

Discussion

We found that associations between prenatal smoking and neonatal body mass and composition were dose-dependent and time-specific. The dose-dependent models showed significant reductions in neonatal FM and FFM. Time-specific analyses showed that mothers who smoked throughout pregnancy compared to those who stopped before late-pregnancy had neonates with significantly reduced FM and FFM. Our data provide novel evidence that prenatal smoking results in overall neonatal growth restriction. However, if smoking cessation occurs before late-pregnancy, neonates will be phenotypically similar to those who were not exposed during pregnancy, possibly reducing the likelihood of postnatal catch-up growth.

Using indirect measures of body composition, studies have suggested that prenatal smoking significantly reduces neonatal body mass through reductions in FFM.[16–21] Harrison et al[16] analyzed 285 term Caucasian neonates and found that prenatal smoking significantly reduces birth weight. Using skinfold measurements, they found no relationship between prenatal smoking and subcutaneous fat between exposed and unexposed neonates. In a subsequent study by Samper et al[21], 1216 Caucasian mothers and their term singleton births were analyzed. Using sum of skinfolds as an indirect measure of adiposity, neonates of mothers who smoked had lower values than unexposed neonates, but subcutaneous fat distribution was again not significantly different between groups. Analyzing 129 term neonates, Lindsay et al[2] directly measured neonatal body composition using total body electrical conductivity and found significant differences in FFM among exposed relative to unexposed neonates (2,799 g ± 292 g vs. 2,965 g ± 359 g; P = 0.02), but did not find significant differences in FM (343 g ± 164 g vs. 387 g ± 216 g; P = 0.32). This study may have been limited by comparing mothers who smoked at any point during pregnancy to those who were non-smokers, and only having 30 prenatal smokers. Our findings in a larger cohort, using more precise measures of neonatal body composition, suggest a greater proportionate reduction in FM relative to FFM. This finding was consistent between dose-dependent and time-specific analyses. Moreover, sensitivity analyses removing mothers who were non-smokers, but exposed to secondhand smoke during late-pregnancy, indicate that

our findings from our main analyses, across outcomes, may be conservative. In unadjusted analyses, there were no statistically significant differences between neonates exposed and unexposed to prenatal smoking in %FM or %FFM in unadjusted analyses (Table I). However, following adjustment, F:FFM was statistically significantly different in dose-dependent and time-specific models.

Our time-specific findings have strong biological support, because both FM and FFM primarily develop during late-pregnancy, and are consistent with previous studies focused on birth weight. MacArthur et al studied 4,341 pregnant women, 1,235 of which were prenatal smokers, and found that smoking cessation before 16-weeks of gestation resulted in neonates with comparable anthropometric measures to those who were never exposed to prenatal smoking.[29] In a large study of 11,177 women with term singleton births, Lieberman et al demonstrated that the risk of SGA was similar between mothers who began smoking during late second or third trimester relative to those who smoked throughout pregnancy.[30] The researchers also found that the risk of SGA was attenuated among mothers who quit smoking before the third trimester.[30] In a prospective study with 160 prenatal smokers, Bernstein et al showed that third trimester cigarette consumption was the strongest predictor of birth weight percentile.[20]

Our study has some limitations. Prenatal smoking was assessed by self-report. However, several studies that compared self-reported prenatal smoking with exhaled carbon monoxide[31] and plasma[32, 33] and urine[34] cotinine levels found that self-reported smoking is a valid marker of tobacco exposure. Nevertheless, if mothers who smoked during pregnancy reported as non-smokers, this bias would likely underestimate the true association. Given total body mass changes after birth, by design, we tried to measure all newborns with 24-hours of delivery, to avoid confounding by weight loss in the first days of life. The difference in postnatal age at PEA POD exam between neonates exposed to prenatal smoking compared with those unexposed was not significantly different (Table I). As a result, any bias due to age when measured by PEA POD would likely result in attenuated associations.

In summary, our findings suggest that both the dose and timing of exposure to prenatal smoking is associated with systematic growth restriction, which has significant public health implications. Given the fairly static prevalence of prenatal smoking[1], the public health benefits of smoking cessation before or during early stages of pregnancy may be vast, including decreasing the offspring's future risk for several chronic diseases. Based on our findings, smoking cessation efforts should not be lessened as pregnancy progresses. Follow-up data on anthropometric and body composition changes during postnatal life will lead to a better understanding of the relationship between exposure to prenatal smoking and catch-up growth and development of childhood obesity.

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Abbreviations

BMI	body mass index
CI	confidence interval
FM	fat mass
FFM	fat-free mass
F:FFM	fat to fat free mass ratio
PPAQ	pregnancy physical activity questionnaire
SGA	small-for-gestational age

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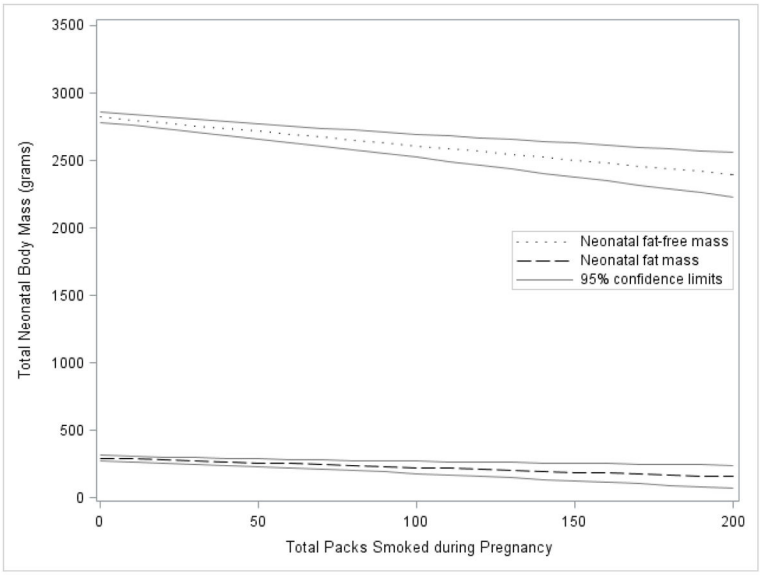

Figure.

Adjusted mean neonatal fat-free mass and fat mass by total packs smoked during pregnancy with 95% confidence limits

Table 1

Characteristics of Healthy Start mother-neonate pairs used in complete case analyses by prenatal smoking status (N = 916)

	Prenatal Smoking[†]		
	Yes	No	
Characteristics	**n = 85 (9.3%) Mean (95% CI)**	**n = 831 (90.7%) Mean (95% CI)**	***P***
Maternal age (years)	24.8 (23.7, 25.9)	28.0 (27.6, 28.4)	<0.001
Gravidity	2.1 (1.6, 2.5)	1.3 (1.2, 1.4)	<0.001
Pre-pregnancy BMI (kg/m^2)	26.6 (25.3, 28.0)	25.7 (25.2, 26.1)	0.17
Gestational weight gain (kg)[a]	14.5 (14.0, 15.0)	14.4 (14.3, 14.5)	0.76
Gestational age (days)	274 (272, 276)	276 (276, 277)	0.04
Age at PEA POD exam (days)	1.8 (1.3, 2.3)	1.5 (1.3, 1.6)	0.16
Birth length (cm)	48.3 (47.8, 48.7)	49.3 (49.2, 49.4)	<0.001
Birth weight (g)	3,037 (2,947, 3,128)	3,277 (3,246, 3,308)	<0.001
Birth weight z-score	−0.8 (−1.0, −0.7)	−0.4 (−0.4, −0.3)	<0.001
Total body mass (g)	2,924 (2,835, 3,014)	3,141 (3,111, 3,171)	<0.001
Neonatal fat mass (g)	261 (233, 290)	295 (285, 306)	0.05
Neonatal fat-free mass (g)	2,663 (2,590, 2,735)	2,845 (2,822, 2,869)	<0.001
Neonatal fat mass (%)	8.7 (7.9, 9.5)	9.1 (8.8, 9.4)	0.34
Neonatal fat-free mass (%)	91.3 (90.5, 92.1)	90.9 (90.6, 91.2)	0.34
Fat to fat-free mass (F:FFM) (g)	0.10 (0.09, 0.11)	0.10 (0.10, 0.11)	0.32

Characteristics	**n (%)**	**n (%)**	***P***
Small-for-gestational age[b]			0.08
Yes	17 (20.0)	109 (13.1)	
No	68 (80.0)	722 (86.9)	
Sex			0.66
Male	46 (54.1)	429 (51.6)	
Female	39 (45.9)	402 (48.4)	
Race/ethnicity			<0.001
Non-Hispanic black	29 (34.1)	126 (15.2)	
Hispanic	13 (15.3)	202 (24.3)	
Non-Hispanic white	38 (44.7)	451 (54.3)	
Other	5 (5.9)	52 (6.3)	
Vigorous activity (> 6.0 METs)[c]			0.13
Yes	3 (3.5)	68 (8.2)	
No	82 (96.5)	763 (91.8)	
Education			<0.001
High school degree/GED or less	49 (57.6)	252 (30.3)	
More than high school	36 (42.4)	579 (69.7)	
Household income			<0.001

Characteristics	n (%)	n (%)	*P*
≤$20,000	33 (38.8)	109 (13.1)	
$20,001 to $40,000	11 (12.9)	121 (14.6)	
>$40,001 to $70,000	18 (21.2)	444 (53.4)	
Don't Know	23 (27.1)	157 (18.9)	

† Self-reported smoking at any study specific research visit

[a] Predicted gestational weight gain at 39-weeks of gestation

[b] Birth weight less than 10th percentile given gestational age and sex

[c] Self-reported vigorous physical activity (>6.0 METs) at two or more study specific research visits

Table 2

Summary effects of time specific exposure to prenatal smoking on neonatal body mass and composition

Models and Outcomes	Effect Size [β] (95% CI)†	p-value
Model 1: Smoked throughout pregnancy vs. non-smokers		
Body mass (g)	−296 (−411, −180)	<0.001
Fat mass (g)	−81.2 (−127, −35.3)	<0.001
Fat-free mass (g)	−215 (−303, −126)	<0.001
F:FFM (g)	−0.02 (−0.04, −0.005)	0.008
Model 2: Smoked before late-pregnancy vs. non-smokers		
Body mass (g)	59.9 (−102, 222)	0.47
Fat mass (g)	25.9 (−38.8, 90.6)	0.43
Fat-free mass (g)	34.0 (−89.6, 158)	0.59
F:FFM (g)	0.008 (−0.01, 0.03)	0.43
Model 3: Smoked throughout vs. before late-pregnancy		
Body mass (g)	−371 (−559, −183)	<0.001
Fat mass (g)	−103 (−170, −36.1)	0.003
Fat-free mass (g)	−268 (−423, −113)	0.001
F:FFM (g)	−0.03 (−0.05, −0.002)	0.03

†Adjusted by gestational and chronological age, offspring sex, gravidity, maternal age, race/ethnicity, educational status, household income, gestational weight gain, pre-pregnancy BMI and physical activity.