Exposure to Prenatal Smoking and Early-Life Body Composition: The Healthy Start Study

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Objectives: To examine associations between exposure to prenatal smoking and early-life changes in fat mass (FM), fat-free mass (FFM), and anthropometrics.

Methods: About 670 mother–offspring pairs were analyzed in the longitudinal Healthy Start study. Maternal smoking data were collected during prenatal research visits. Offspring body composition and size were measured by air displacement plethysmography at delivery and postnatal follow-up (5 months) visits.

Results: Comparing exposed and unexposed offspring, exposure to prenatal smoking was significantly associated with reduced neonatal FM ($P = 0.007$) and FFM ($P = 0.02$). In contrast, at 5 months, exposed offspring had comparable FM ($P = 0.61$) and FFM ($P = 0.41$). After subsequent adjustment for birth weight, offspring exposed to prenatal smoking had significantly greater FFM (154.7 g, 0.5, 309.0; $P = 0.049$) and sum of skinfolds (2.7 mm, 0.06, 5.3; $P = 0.04$). From delivery to follow-up, exposed offspring had significantly greater increases in FFM (156.4 g, 2.8, 310.1; $P = 0.046$) and sum of skinfolds (2.7 mm, 0.06, 5.3; $P = 0.04$), even after adjustment for respective delivery measures.

Conclusions: Exposure to prenatal smoking was significantly associated with rapid postnatal growth, which may increase the offspring’s risk of metabolic diseases.

Introduction

Prenatal smoking increases the risk of intrauterine growth restriction and during postnatal life exposed offspring may exhibit a phenomenon known as “catch-up growth.” Catch-up growth is a compensatory acceleration in the rate of growth, which may happen during fetal or early postnatal life (1). The onset of rapid compensatory growth is thought to be related to the cessation of the adverse environment (2). Compensatory growth has been shown in animal (1-3) and human (4-6) studies. Offspring that demonstrate postnatal compensatory growth have an increased risk for later chronic diseases (7,8). It has been theorized that rapid postnatal growth, as a result of exposure to prenatal smoking, may in part, program these long-term adverse effects, particularly obesity. Studies have demonstrated that exposure to prenatal smoking is associated with several later-life morbidities including asthma (9), increased insulin resistance (10) and childhood overweight and obesity (11-15).

Studies (4-6,16,17) have examined the association between prenatal smoking and postnatal growth, but gaps in knowledge still remain, specifically, studies have typically examined postnatal growth through total body mass, as opposed to directly measuring body composition. Total body mass lacks specificity as it includes fat and lean tissues, which may be particularly important to measure given fat mass (FM) has been shown to be related with adverse health effects (18). We aimed to examine postnatal growth through anthropometric and direct measures of body composition [i.e. FM and fat-free mass (FFM)] during early life, measured by air displacement plethysmography [PEA POD; COSMED, Rome, Italy].

We hypothesized that at postnatal follow-up, offspring exposed to prenatal smoking would have compensatory growth with higher or at least comparable FM, FFM and anthropometrics compared to unexposed offspring. Further, changes in FM, FFM and anthropometrics between delivery and postnatal follow-up would be significantly greater among exposed relative to unexposed offspring, independent of measures at birth.

Methods

We explored our hypotheses using the Healthy Start study, an ongoing longitudinal, pre-birth cohort in Colorado that follows...
Enrolled mother-offspring pairs with a delivery date between July 17, 2010 and November 1, 2013 (n = 831)

Excluded (n = 38)
- Terminated consent: 6
- Fetal deaths: 13
- Very pre-term births: 19

Eligible cohort (n = 793)

Incomplete data (n = 123)

Analytic cohort (n = 670)

Figure 1 Study flow diagram for Healthy Start among enrolled participants with a delivery date between July 17, 2010, and November 1, 2013.

Outcomes—Offspring body composition and anthropometric measures

The body composition system PEA POD, uses densitometric techniques based on air displacement plethysmography to measure total body mass and two compartments in the offspring: FM (i.e., adipose tissue) and FFM (i.e., water, bone, and non-bone mineral and protein) in both absolute and proportionate terms (19). This technique has been shown to be reliable and valid for measuring early-life body composition in multiple studies (19-22) with the mean percentage error in volume measurements as low as <0.05% (20). Trained clinical personnel measured each offspring by PEA POD at delivery (median = 1 day) and postnatal research visits. At each visit, PEA POD was conducted twice, and if %FM differed by >2%, then a third exam was conducted. To reduce measurement error for each outcome, we took the mean of the two closest measures for each visit.

Offspring weight and length were obtained at delivery and postnatal research visits and through medical records. Z scores at delivery and follow-up were calculated using the Centers for Disease Control and Prevention (CDC) growth charts (23). Offspring skinfolds (i.e., mid-thigh, subscapular and triceps) and head circumference were measured twice at delivery and postnatal research visits by trained clinical personnel. If skinfolds or head circumference differed by >1.0 mm or >1.0 cm, respectively, a third measure was done. The mean of the two closest measures for each visit was used in analyses. The three measures of skinfolds taken at the delivery and postnatal visit were each summed and used as an indirect measure of total adiposity. Change in FM, FFM, and anthropometric measures were calculated by subtracting the postnatal follow-up measure from the delivery measure.

Covariates

Covariate information was collected on mother-offspring pairs during delivery and postnatal 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, obtained from research visits and medical records, and maternal height, measured at the first prenatal visit, were used to calculate pre-pregnancy body mass index (BMI). Weight during pregnancy was measured at the three research visits and also abstracted from medical records (median = 12 measurements per participant). Total gestational weight gain (GWG) was estimated using mixed models predicting GWG at 39 weeks of gestation (mean gestational age of the cohort). Physical activity levels were ascertained through a validated (24) Pregnancy Physical Activity Questionnaire (PPAQ) during each prenatal research visit. Reported duration of activity was multiplied by the respective MET value, according to the compendium of physical activities (25) and where possible, pregnancy-specific MET values (26), to estimate mean total energy expenditure (MET-hours/week) during pregnancy. Gestational age at delivery was abstracted through medical records or calculated by delivery and due date. Offspring chronological age when measured by air displacement plethysmography at the delivery and postnatal research visits was calculated by taking the difference between the date of birth and respective research visit. The difference in chronological age at delivery and postnatal visits was calculated and adjusted for

Ethically diverse pregnant women. The Healthy Start study recruited pregnant women from prenatal obstetrics clinics located at the University of Colorado Hospital Outpatient Pavilion within the Anschutz Medical Campus of the University of Colorado—Denver. Women were not eligible if multiple births were expected or they had a previous stillbirth, were <16 years of age at consent or had a gestational age at the time of baseline research visit >24 weeks. Of 831 mother-offspring pairs with delivery date between July 17, 2010 and November 1, 2013, participants were excluded from analyses if they withdrew consent before delivery (n = 6) or if their index pregnancy resulted in fetal death (n = 13) or a very preterm birth (i.e., <32 weeks) (n = 19). After exclusion, 793 mother-offspring pairs were eligible for this analysis and 670 met criteria for the analytic cohort (i.e., complete outcome and exposure data) (Figure 1). During recruitment, all mothers provided written informed consent. The Healthy Start study protocol and procedures were approved by the Colorado Multiple Institutional Review Board.

Enrolled pregnant women were invited to participate in three prenatal research visits and one postnatal follow-up. The first prenatal 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 during hospitalization stay (median = 1 day). Postnatal follow-up visits occurred between 3 and 9 months after birth (25th percentile = 4 months; median = 5 months; 75th percentile = 6 months).

Exposure—Prenatal smoking

Information about prenatal smoking was ascertained through interview-administered questionnaires during prenatal research visits. Data were collected on the quantity and duration of early-, mid-, and late-pregnancy smoking. For this study, we dichotomized prenatal smoking by mothers who reported smoking at any of the three prenatal research visits and mothers who did not report smoking at any visit.
in models assessing change in outcomes between visits. Using United States national reference data (27), small-for-gestational age was indicated as a birth weight below the 10th percentile for gestational age, given sex of the offspring. Data on exclusivity of breastfeeding, including duration and use of formula, were collected at the postnatal research visit.

Data analysis
All statistical analyses were conducted in SAS 9.3 (SAS Institute, Cary, NC). Relationships between exposure to prenatal smoking and continuous and categorical maternal and offspring characteristics were analyzed by t tests and χ² tests, respectively. Models were generated using dependent variables from delivery and postnatal follow-up research visits and the change in offspring outcomes between the two time points. Simple linear models were first tested. Multiple linear regression models (PROC GLM) were then constructed. Potential confounders were individually entered into 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 effect size of prenatal smoking was meaningfully altered (i.e., ≥10% change). Models were further adjusted for measures taken at delivery visits.

Results
Of the 793 mother–offspring pairs who were eligible to participate in this analysis, 670 (exposed = 47) had complete data with weight-for-length at delivery and postnatal follow-up; 590 (exposed = 41) had complete data with sum of skinfolds and head circumference at both visits; 536 (exposed = 36) participants had complete data with body composition measured by air displacement plethysmography at postnatal follow-up; and 473 (exposed = 33) participants had complete data with body composition measured by air displacement plethysmography at both visits. Mothers who reported prenatal smoking were somewhat less likely to have completed a postnatal visit and therefore be used in analysis as compared to nonsmoking mothers, but the difference was not statistically significant (78.3% vs. 85.0%; χ² = 1.9; P = 0.17). Further, on average, there were no clinically relevant differences in variables of interest including maternal age (28.28 vs. 28.33 years), offspring sex, racial/ethnic distribution and follow-up difference (2.7 mm [0.06, 5.3]; P = 0.049), but the significance of the association between prenatal smoking and offspring FM was not altered (P = 0.33) (Table 2).

Exposure to prenatal smoking and offspring outcomes at delivery visit
Following adjustment for gestational age at delivery, chronological age when measured by air displacement plethysmography, offspring sex, maternal race/ethnicity, educational status, household income, gravidity, bwg, pre-pregnancy BMI and mean total energy expenditure during pregnancy, neonates of mothers who smoked during pregnancy had significantly reduced FM (adjusted mean difference: −68.2 g. 95% confidence interval [CI]: −117.9 to −18.6; P = 0.007), FFM (−113.8 g [−209.5 to −18.0]; P = 0.02) and birth weight z score (adjusted mean difference: −0.29, 95% [CI]: −0.50 to −0.08; P = 0.007) compared to neonates of mothers who were non-smokers.

Birth length z score and birth weight-for-length z score were not statistically significantly different in exposed relative to unexposed neonates (P = 0.15 and P = 0.15, respectively), nor was head circumference (P = 0.73) or sum of skinfolds (P = 0.38) (Table 2).

Exposure to prenatal smoking and offspring outcomes at postnatal follow-up
After adjustment for the previously mentioned covariates and exclusive breastfeeding status, offspring at postnatal follow-up exams who were exposed to prenatal smoking did not have significantly different FM (P = 0.61) or FFM (P = 0.41) compared to unexposed offspring. Following additional adjustment for birth weight, FFM was significantly greater among exposed relative to unexposed offspring (154.7 g [0.5 to 309.0]; P = 0.049), but the significance of the association between prenatal smoking and offspring FM was not altered (P = 0.33) (Table 2).

Sum of skinfolds was marginally significantly greater among exposed relative to unexposed offspring (P = 0.05) (Table 2). Following additional adjustment for respective delivery visit measures, differences in weight-for-length z score (P = 0.40) and head circumference (P = 0.71) remained non-significant, but sum of skinfolds at follow-up became statistically significantly greater among exposed relative to unexposed offspring (2.7 mm [0.06, 5.3]; P = 0.04).

Changes in offspring outcomes between delivery and follow-up
Following adjustment for gestational age at delivery, change in chronological age between body composition exams, offspring sex, maternal race/ethnicity, educational status, household income, gravidity, bwg, pre-pregnancy BMI, exclusive breastfeeding status and mean total energy expenditure during pregnancy, change in offspring FFM was statistically significantly greater among offspring exposed to prenatal smoking compared to unexposed (168.5 g [15.4 to 321.6]; P = 0.03). On average, change in FM was greater among exposed offspring, but the difference was not significant (P = 0.48). Although the association between prenatal smoking and offspring FFM was slightly attenuated by additional adjustment for neonatal FFM, the change in postnatal FFM remained statistically significant (156.4 g [2.8 to 310.1]; P = 0.04).
Mean change in weight-for-length \( z \) score in exposed relative to unexposed offspring was again not statistically significant \((P = 0.21)\), nor was head circumference \((P = 0.93)\). Change in sum of skinfolds was statistically significantly greater among exposed relative to unexposed offspring \((3.1 \text{ mm} [0.3, 5.9]; P = 0.03)\). Following additional adjustment for respective delivery visit measures, differences in weight-for-length \( z \) score \((P = 0.40)\) and head circumference \((P = 0.72)\) remained non-significant, and although slightly attenuated, sum of skinfolds was still statistically significantly greater among offspring exposed to prenatal smoking relative to unexposed \((2.7 \text{ mm} [0.06, 5.3]; P = 0.04)\).

**Discussion**

In this large, longitudinal study, we provide evidence of associations between exposure to prenatal smoking and early-life body composition and size. Exposure to prenatal smoking was associated with systematic growth restriction during intrauterine life, indicated by significantly lower FM and FFM at delivery. In contrast, at follow-up, offspring exposed to prenatal smoking did not appear to differ in FM and FFM. However, after adjustment for birth measures, postpartum FFM and sum of skinfolds were significantly greater among those exposed to prenatal smoking relative to unexposed. Moreover, the change in FFM and sum of skinfolds between delivery and postnatal follow-up was significantly greater in exposed compared to unexposed offspring, even after further adjustment for respective birth measures. Taken together, our results suggest that there is rapid postnatal growth in exposed offspring, primarily as a result of exposure to prenatal smoking, despite and only partly influenced by reduced size at birth.

We found that mean offspring FM at postpartum follow-up and the postnatal change between visits were greater in exposed relative to those unexposed, but the differences were not statistically significant (Table 2). However, sum of skinfolds measured at follow-up and the change between the two research visits were significantly greater in exposed offspring relative to unexposed (Table 1).

| Characteristic | Prenatal smoking\( ^{a} \) | \( n = 47 \) (7.0\%) | \( n = 623 \) (93.0\%) | \( P \) |
|---------------|-----------------------------|------------------|------------------|-------|
| Maternal age (years) | Yes | 24.7 (5.4) | 28.6 (5.9) | <0.001 |
| Gravida\( ^{b} \) | No | 2.0 (2.0) | 1.3 (1.5) | 0.01 |
| Pre-pregnancy BMI (kg m\(^{-2}\)) | Yes | 25.9 (6.2) | 25.8 (6.3) | 0.89 |
| Gestational weight gain (kg)\( ^{c} \) | No | 14.8 (2.1) | 14.3 (2.1) | 0.15 |
| Gestational age at birth (days) | Yes | 274.9 (7.4) | 276.7 (9.2) | 0.20 |
| Mean total energy expenditure (MET-hours/week)\( ^{d} \) | No | 226.8 (139.2) | 188.6 (81.8) | 0.004 |
| Delivery visit\( ^{e} \) | Yes | 1.5 (1.5) | 1.6 (2.3) | 0.75 |
| Abdominal circumference (cm) | No | 29.1 (1.7) | 29.5 (2.3) | 0.32 |
| Head circumference (cm) | Yes | 33.9 (1.2) | 34.2 (2.0) | 0.46 |
| Mid-thigh circumference (cm) | No | 13.5 (1.1) | 13.8 (1.4) | 0.29 |
| Sum of skinfolds (mm) | Yes | 14.7 (2.7) | 15.3 (3.5) | 0.27 |
| Birth length \( z \) score | No | −0.4 (0.7) | −0.1 (0.7) | 0.002 |
| Birth weight \( z \) score | Yes | −0.8 (0.6) | −0.3 (0.8) | <0.001 |
| Birth weight-for-length \( z \) score | No | −0.03 (0.7) | 0.06 (0.8) | 0.46 |
| Neonatal fat mass (g) | Yes | 238.0 (103.9) | 297.0 (147.0) | 0.01 |
| Neonatal fat-free mass (g) | No | 2,691 (268.5) | 2,867 (316.9) | <0.001 |
| Postnatal follow-up visit\( ^{f} \) | Yes | 174.6 (41.7) | 167.4 (43.4) | 0.27 |
| Abdominal circumference (cm) | No | 41.3 (3.6) | 41.5 (3.9) | 0.78 |
| Head circumference (cm) | Yes | 42.5 (2.1) | 42.3 (1.9) | 0.62 |
| Mid-thigh circumference (cm) | No | 22.5 (2.6) | 22.1 (2.9) | 0.30 |
| Sum of skinfolds (mm) | Yes | 38.7 (8.6) | 36.9 (7.9) | 0.16 |
| Length-for-age \( z \) score | No | 0.2 (1.1) | 0.2 (1.1) | 0.77 |
| Weight-for-age \( z \) score | Yes | −0.05 (0.9) | 0.07 (1.1) | 0.44 |
| Weight-for-length \( z \) score | No | −0.2 (1.1) | −0.1 (1.3) | 0.83 |
| Offspring fat mass (g) | Yes | 1,590 (528.8) | 1,666 (501.1) | 0.40 |
| Offspring fat-free mass (g) | No | 5,331 (656.3) | 5,185 (619.4) | 0.19 |
exposed offspring. A potential explanation for why direct measures of FM were not significantly different at follow-up, but indirect measures were, could be that larger offspring were not able to be measured by air displacement plethysmography.

Previous studies have been mixed with regard to when offspring exposed to prenatal smoking are similar in size compared to those unexposed. Conter et al. (6) followed 12,987 mother-offspring pairs from birth to 6 months of age. They found that weight at birth and 3 months were significantly lower in offspring exposed to prenatal smoking relative to unexposed offspring; however, at 6 months significant differences were no longer observed (6). In a subsequent study, the Avon Longitudinal Study of Parents and Childhood (ALSPAC) (4) analyzed 1,299 mother–offspring pairs from birth to 5 years of age. The authors found that within the first year of life, offspring exposed to prenatal smoking were no longer significantly different in weight ($P < 0.90$) or length ($P < 0.20$) (4). In another study, Kanellopoulos et al. (16) followed 200 mother–offspring pairs from birth to 6 years of age. The authors found that offspring exposed to ≥15 cigarettes per day compared to those who were unexposed, had significantly lower body mass until 3 years of age. Further, offspring length/height remained significantly different between the two groups until 6 years of age (16). In our study, the observed significant differences in offspring FM and FFM at birth by exposure to prenatal smoking were diminished or completely reversed by 5 months of age.

The deleterious effects of rapid postnatal growth are not entirely known, but it has been postulated that rapid postnatal growth associated with being exposed to prenatal smoking may be related to early-life developmental changes predisposing offspring to an increased likelihood of obesity later in life. This phenomenon is paramount to understand and potentially mitigate in early life as childhood BMI and adiposity measures, even among 2- to 5-year old children, appear to track into adulthood (28).

Several biologic mechanisms have been suggested explaining the relationship between exposure to prenatal smoking and later-life

### TABLE 1. (Continued).

| Characteristic                  | Yes $n = 47$ (7.0%) | No $n = 623$ (93.0%) | $P$  |
|--------------------------------|---------------------|---------------------|------|
| Exclusive breastfeeding$^f$     |                     |                     |      |
| Yes                            | 3 (6.4)             | 239 (38.4)          | <0.001|
| No                             | 44 (93.6)           | 384 (61.6)          |      |
| Small-for-gestational age$^g$   |                     |                     |      |
| Yes                            | 10 (21.3)           | 79 (12.7)           | 0.09 |
| No                             | 37 (78.7)           | 544 (87.3)          |      |
| Sex                            |                     |                     |      |
| Male                           | 26 (55.3)           | 327 (52.5)          | 0.71 |
| Female                         | 21 (44.7)           | 296 (47.5)          |      |
| Race/ethnicity                 |                     |                     |      |
| Non-Hispanic black             | 18 (38.3)           | 81 (13.0)           | <0.001|
| Hispanic                       | 6 (12.8)            | 137 (22.0)          |      |
| Non-Hispanic white             | 20 (42.5)           | 368 (59.1)          |      |
| Other                          | 3 (6.4)             | 37 (5.9)            |      |
| Education                      |                     |                     |      |
| High school degree/GED or less | 26 (55.3)           | 164 (26.3)          | <0.001|
| More than high school          | 21 (44.7)           | 459 (73.7)          |      |
| Household income$^h$           |                     |                     | <0.001|
| ≤$20,000                       | 19 (40.4)           | 74 (11.9)           |      |
| $20,001 to $40,000             | 8 (17.0)            | 94 (15.1)           |      |
| >$40,000                       | 8 (17.0)            | 358 (57.5)          |      |
| Don’t know                     | 12 (25.5)           | 97 (15.6)           |      |

$^a$Self-reported smoking at any prenatal research visit.  
$^b$Total number of previous pregnancies.  
$^c$Predicted gestational weight gain at 39 weeks of gestation.  
$^d$Mean total energy expenditure during pregnancy.  
$^e$Outcome measures may not equal 670 due to missing data.  
$^f$Offspring exclusively breastfed from birth to follow-up visit.  
$^g$Birth weight < 10th percentile, given gestational age and sex.  
$^h$Total household income before taxes during the past year.
| Outcome                                | Model 1<sup>a</sup> |                                       | Model 2<sup>b</sup> |                                       |
|----------------------------------------|----------------------|---------------------------------------|----------------------|---------------------------------------|
|                                        | Exposed Adjusted     | Unexposed Adjusted                   | Exposed Adjusted     | Unexposed Adjusted                   |
|                                        | mean (SE) Beta (95% CI) P | mean (SE) Beta (95% CI) P | mean (SE) Beta (95% CI) P | mean (SE) Beta (95% CI) P |
| Delivery visit                         |                      |                                      |                      |                                      |
| Head circumference (cm)                | 34.0 (0.3) 0.1 (-0.6, 0.8) 0.73 | 33.9 (0.1) 0.1 (-0.6, 0.8) 0.73 | 42.3 (0.2) 0.1 (-0.4, 0.6) 0.64 | 42.2 (0.1) 0.1 (-0.4, 0.6) 0.71 |
| Sum of skinfolds (mm)                  | 14.7 (0.5) -0.5 (-1.6, 0.6) 0.38 | 15.2 (0.2) -0.2 (-0.4, 0.1) 0.15 | 39.9 (1.3) 0.1 (-0.3, 0.5) 0.61 | 37.2 (0.5) 0.2 (-0.2, 0.6) 0.40 |
| Birth length z score                   | -0.33 (0.1) -0.17 (0.04) 0.15 | -0.39 (0.04) -0.3 (-0.5, -0.1) 0.007 | -0.08 (0.1) -0.11 (0.1) 0.15 | -0.08 (0.1) -0.11 (0.1) 0.15 |
| Birth weight z score                   | -0.68 (0.1) -0.39 (0.04) 0.15 | -0.3 (-0.5, -0.1) 0.007 | -0.08 (0.1) -0.11 (0.1) 0.15 | -0.08 (0.1) -0.11 (0.1) 0.15 |
| Birth weight-for-length z score        | -0.08 (0.1) 0.1 (-0.4, 0.1) 0.15 | -0.2 (-0.4, 0.1) 0.15 | -0.08 (0.1) 0.1 (-0.4, 0.1) 0.15 | -0.08 (0.1) 0.1 (-0.4, 0.1) 0.15 |
| Fat mass (g)                           | 219.5 (24.2) -68.3 (-117.9, -18.6) 0.007 | 287.7 (9.0) -68.3 (-117.9, -18.6) 0.007 | 1,735 (85.1) 84.4 (-85.5, 254.3) 0.33 |
| Fat-free mass (g)                      | 2,677 (46.5) -113.8 (-209.5, -18.0) 0.02 | 2,791 (17.4) -113.8 (-209.5, -18.0) 0.02 | 5,348 (77.3) 154.7 (5.0, 309.0) 0.049 |
| Postnatal follow-up visit             |                      |                                      |                      |                                      |
| Head circumference (cm)                | 42.3 (0.3) 0.1 (-0.4, 0.6) 0.64 | 42.2 (0.1) 0.1 (-0.4, 0.6) 0.64 | 42.3 (0.2) 0.1 (-0.4, 0.6) 0.64 | 42.2 (0.1) 0.1 (-0.4, 0.6) 0.64 |
| Sum of skinfolds (mm)                  | 39.8 (1.3) 2.6 (-0.03, 3.3) 0.05 | 37.2 (0.5) 0.1 (-0.3, 0.5) 0.61 | 39.9 (1.3) 0.1 (-0.3, 0.5) 0.61 | 37.2 (0.5) 0.2 (-0.2, 0.6) 0.40 |
| Weight-for-length z score              | -0.03 (0.2) -0.1 (-0.3, 0.5) 0.61 | -0.1 (-0.3, 0.5) 0.61 | 1,735 (85.1) 84.4 (-85.5, 254.3) 0.33 |
| Fat mass (g)                           | 1,688 (86.1) 44.3 (-127.8, 216.5) 0.61 | 1,644 (82.7) 44.3 (-127.8, 216.5) 0.61 | 1,735 (85.1) 84.4 (-85.5, 254.3) 0.33 |
| Fat-free mass (g)                      | 5,251 (84.2) 70.9 (-97.7, 239.4) 0.41 | 5,180 (82.0) 70.9 (-97.7, 239.4) 0.41 | 5,348 (77.3) 154.7 (5.0, 309.0) 0.049 |
| Change from delivery to follow-up     |                      |                                      |                      |                                      |
| Head circumference (cm)                | 8.2 (0.4) -0.03 (-0.8, 0.7) 0.93 | 8.2 (0.1) 8.2 (0.1) 0.93 | 8.2 (0.2) 8.1 (0.1) 0.93 | 8.2 (0.2) 8.1 (0.1) 0.93 |
| Sum of skinfolds (mm)                  | 25.0 (1.4) 3.1 (0.3, 5.9) 0.03 | 21.9 (0.5) 3.0 (-0.2, 0.7) 0.21 | 24.7 (1.3) 22.0 (0.5) 0.04 | 22.0 (0.5) 2.7 (0.1, 5.3) 0.04 |
| Weight-for-length z score              | 0.01 (0.2) -0.3 (-0.7, 0.2) 0.01 | -0.3 (-0.7, 0.2) 0.01 | 0.01 (0.2) -0.3 (-0.7, 0.2) 0.01 | -0.3 (-0.7, 0.2) 0.01 |
| Fat mass (g)                           | 1,440 (88.4) 63.8 (-112.3, 234.0) 0.48 | 1,377 (84.2) 63.8 (-112.3, 234.0) 0.48 | 1,423 (88.7) 44.4 (-132.6, 221.3) 0.62 |
| Fat-free mass (g)                      | 2,573 (76.9) 168.5 (15.4, 321.6) 0.04 | 2,404 (29.7) 168.5 (15.4, 321.6) 0.04 | 2,560 (77.2) 156.5 (28.0, 310.1) 0.04 |

<sup>a</sup>Adjusted or standardized (z score) by gestational age at delivery, chronological age at respective exam, offspring sex, race/ethnicity, educational status, household income, gravidity, gestational weight gain, pre-pregnancy BMI, and mean total energy expenditure during pregnancy; postnatal measures were further adjusted by exclusivity of breastfeeding.

<sup>b</sup>As in footnote<sup>a</sup>, plus exclusivity of breastfeeding and respective outcome measure at delivery.
metabolic diseases, which in part, may occur during early development. In animal models, fetal nicotine exposure has been directly associated with offspring metabolic syndrome, adipose tissue dysregulation and pancreatic development (29). Further, glucose intolerance and insulin resistance were also observed during adulthood in exposed rats (29). Prenatal smoking may also affect neurodevelopment that increases the exposed offspring’s risk for obesity. A recent study (15) found that 13- to 19-year-olds exposed to prenatal smoking had an increased proclivity for fat in the diet along with reduced amygdala volume, which is known for regulation of aggression and fear, and stimulus-reward processing (30). As a result of intrauterine exposure to smoking, slight structural variations of the amygdala may mediate the relationship between exposure to prenatal smoking and rapid postnatal growth and later development of overweight/obesity (15). Our results suggest that compensatory growth starts very early postnatally, while most offspring are still breastfed, and is independent of potential differences in breastfeeding status. Nevertheless, even though we adjusted for exclusivity of breastfeeding status, more subtle differences in feeding patterns of the offspring including duration and quantity were not considered, and thus, rapid growth may still be partially mediated by dysregulation of satiety in exposed offspring or differences in feeding patterns (31). Further study is needed to explore the mechanisms by which exposure to prenatal smoking is associated with early postnatal compensatory growth and development of obesity later in life.

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 (32) and plasma (33,34) and urine (35) cotinine levels found that self-reported smoking is a valid marker of tobacco smoke exposure. Because of the relatively small sample of offspring exposed to prenatal smoking (n = 47), we were unable to explore time specific associations of exposure to prenatal smoking (e.g., late pregnancy) and infant postnatal growth outcomes. The body composition system, PEA POD, is indicated for measuring offspring <8 kg. Therefore, our findings may be truncated by offspring postnatal weight, which may explain why we did not see more substantial differences in postnatal FM by exposure status, despite observing significant differences in an indirect measure of body fat, sum of skinfolds. Moreover, offspring of mothers who reported prenatal smoking were less likely to complete a follow-up visit. Thus, our findings may underestimate the true postnatal differences in body size and composition measures between exposed and unexposed offspring. Lastly, due to the observational nature of this study, residual confounding of the findings, including unmeasured socioeconomic factors, may limit the results.

In summary, our study suggests that exposure to prenatal smoking is associated with systematic growth restriction at birth, but rapid compensatory growth postnatally. At 5 months of life, exposed and unexposed offspring were phenotypically similar in overall weight, length and body composition. Moreover, exposed offspring displayed faster growth in measures and indicators of lean mass and FM suggesting significant postnatal compensatory growth. This is supportive of a programmed mechanism in the offspring as a result of exposure to prenatal smoking during intrauterine life. Continued follow-up of this cohort may help identify additional sensitive periods for the development of childhood obesity and other associated morbidities in children exposed to prenatal smoking.

Acknowledgments

The authors gratefully acknowledge the Healthy Start Study Project Coordinator, Mrs. Mercedes Martinez, and the study investigators, participants, and personnel.

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