Neonatal Adipocytokines and Longitudinal Patterns of Childhood Growth

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Objective: Adipocytokines are markers of fetal metabolism, but their association with childhood growth is unclear. This study examined associations of neonatal adipocytokines with longitudinal childhood adiposity measures in a prospective cohort of pregnant women and their children.

Methods: Leptin and adiponectin concentrations at delivery and children’s BMI z scores between age 4 weeks and 8 years were measured. Differences in BMI z scores and rates of BMI z score change by leptin (n=257) and adiponectin (n=271) terciles were estimated.

Results: Children in the middle (mean difference: 0.2; 95% CI: −0.1 to 0.4) and highest (0.4; 95% CI: 0.1 to 0.6) leptin terciles had greater BMI z scores than children in the lowest tercile. Associations were null after adjustment for birth weight z score. Children in the lowest adiponectin tercile had greater gains in BMI z score (change per year: 0.10; 95% CI: 0.08 to 0.13) than children in the middle (0.07; 95% CI: 0.04 to 0.09) and highest terciles (0.04; 95% CI: −0.01 to 0.05) (adiponectin × age interaction P<0.001).

Conclusions: Lower adiponectin levels were associated with increased rates of BMI gains in the first 8 years of life. Though leptin was positively associated with BMI, this association may be confounded by birth weight.

Introduction

Childhood obesity increases the risk of cardiovascular disease, metabolic diseases, and obesity in adulthood (1). Recent estimates from the National Health and Nutrition Examination Survey show that 17% of US children and adolescents have obesity, and nearly 6% have extreme obesity (2). While nutrition and physical activity play an important role in the risk of childhood obesity, there is compelling evidence that environmental influences during fetal development can alter the risk of obesity and cardiometabolic diseases (3). For example, increased gestational weight gain is associated with increased risk of childhood obesity (4), while inadequate gestational weight gain during pregnancy is associated with cardiometabolic risk in offspring (5).

Adipocytokines, including leptin and adiponectin, are hormones released primarily by adipose and placental tissue (6,7). Leptin, which mediates satiety and hunger through hypothalamic signaling, is positively associated with obesity and cardiometabolic risk in adults (7-11). Adiponectin has anti-inflammatory properties and influences glucose utilization and insulin sensitivity in peripheral tissues (6,8,12). In adults, adiponectin concentrations are decreased in individuals with obesity and metabolic syndrome (6,8,12). In newborns, both leptin and adiponectin are positively associated with birth weight and, thus, possibly act as biomarkers of adiposity and metabolism (13,14).

The impact of fetal adipocytokines on growth and obesity risk during childhood is unclear. Evidence from animal studies has suggested that fetal leptin and adiponectin exposure induces changes in hypothalamic circuits and adipose tissue deposition, respectively, which may in turn increase offspring adiposity (15,16). Fewer studies have quantified the association between fetal adipocytokines and growth (i.e., change in anthropometry over time), and the results have been inconclusive (17-26). In one cohort, cord blood leptin was associated with slower weight gain between birth and age 2 years but positively associated with both BMI and adiposity measures (fat mass and waist circumference) at age 9 years (20,21). In that same cohort, cord blood adiponectin was also positively associated with fat mass and waist circumference during adolescence (20). In a second cohort, cord blood leptin was inversely associated with fat mass during adolescence (18).
To fill this gap in the literature, we examined the association between neonatal adipocytokines and longitudinal measures of adiposity during childhood using data from an ongoing prospective cohort of pregnant women and their children. We hypothesized that cord blood leptin and adiponectin concentrations would be predictive of adiposity and rates of adiposity change during childhood. Further understanding the relationship of fetal adipocytokines and growth and adiposity gain during childhood may help to define these markers of adiposity risk and aid in the development of risk stratification and intervention strategies among high-risk populations.

Methods

Study population

We used data from the Health Outcomes and Measures of the Environment (HOME) Study, a prospective pregnancy and birth cohort in the Cincinnati, Ohio, region (27). Between March 2003 and January 2006, we recruited pregnant women from seven prenatal care clinics affiliated with three delivery hospitals who were 16–3 weeks gestation, ≥18 years old, English speaking, living in a home built prior to 1978, without a known diagnosis of cancer, diabetes, thyroid, seizure, or bipolar disorder, and without HIV infection. Women provided written informed consent for both themselves and their child. The Institutional Review Boards (IRB) of Cincinnati Children’s Hospital Medical Center and the delivery hospitals approved the study. The Brown University IRB relied on the determinations made by the Cincinnati Children’s Hospital Medical Center IRB.

Among 401 women who enrolled in the study and did not drop out prior to delivery, we excluded those who had multiples, stillbirths, or infants with chromosomal or genetic abnormalities (n = 14, 3.5%), newborns with insufficient umbilical cord serum for measurement of adipocytokines (n = 94, 23.4%), and mother-child pairs with missing covariate information or without at least one subsequent follow-up visit (n = 22, 5.5%). An additional 14 children (3.5%) missing neonatal leptin measurements were excluded from the leptin analyses but were included in the adiponectin analyses. A total of 271 children returned for 1,338 follow-up visits at an average of 35 days (SD 5, n = 262) and 1.1 (SD 0.1, n = 240), 2.1 (SD 0.1, n = 207), 3.2 (SD 0.1, n = 184), 4.2 (SD 0.1, n = 137), 5.3 (SD 0.2, n = 147), and 8.2 (SD 0.6, n = 161) years of age.

Neonatal adipocytokine measurement

We measured neonatal leptin and adiponectin concentrations in previously frozen venous umbilical cord serum obtained at delivery using an enzyme-linked immunosorbent assay (ELISA) sandwich assay and a BioTek microtiter FLx808 plate reader (BioTek Instruments, Inc., Winooski, Vermont). Quality control samples and reagent blanks were included in each analytic batch, with coefficients of variation for repeated, blinded, quality control samples of 11% (leptin) and 17% (adiponectin). Levels of detection were 0.8 ng/mL (leptin) and <2 µg/mL (adiponectin).

Child anthropometry

We abstracted gestational age, weight, and length at birth from medical records and calculated gestational age- and sex-standardized birth weight z scores (28). We conducted home visits at age 4 weeks, and children and their parents returned to the study clinic at ages 1, 2, 3, 4, 5, and 8 years. Using a digital scale, we measured weight with the child wearing only a dry diaper or undergarments. At the 4-week and 1-year visits, we measured recumbent length with a length board and measured standing height with a wall-mounted stadiometer without the child’s shoes or head coverings for all other visits. We calculated age- and sex-specific BMI z scores according to World Health Organization standards (i.e., standard deviation scores [SDS]) (29). At age 8 years, we measured waist circumference using a measuring tape placed around a horizontal plane defined by the right and left iliac crests with the child wearing only undergarments. We also measured body fat percentage at age 8 years using a Tanita (Arlington Heights, Illinois) children’s body fat monitor.

Covariates

Trained research staff collected data on potential confounders of neonatal adipocytokines and childhood growth using computer-assisted questionnaires and medical chart abstraction. Maternal sociodemographic factors included age, race, education, and income. Perinatal factors included parity, maternal BMI at 16 weeks gestation, gestational diabetes mellitus, and maternal serum cotinine concentration at approximately 16 weeks gestation (a biomarker of tobacco exposure).

Statistical analysis

We began by calculating univariate statistics of neonatal adipocytokine concentrations according to covariate categories. We then examined the relationship of leptin and adiponectin concentrations with BMI z scores during childhood. We categorized leptin and adiponectin concentrations into terciles, using the lowest terciles as the reference category for the analyses.

To examine the association between neonatal adipocytokines and longitudinal BMI z scores during childhood, we used multivariable linear regression with generalized estimating equations and an exchangeable covariance matrix. This allowed us to estimate differences in BMI z scores as a function of child age while also accounting for the within-child correlation of the repeated BMI z scores. We estimated the average annual linear BMI z score slope (i.e., rate of BMI z score change) between age 4 weeks and 8 years for children in each of the adipocytokine terciles. To do this, we included child age, the adipocytokine terciles, and an age × adipocytokine interaction term in the model. We kept the adipocytokine × age interaction term in the final linear model if the P value for the interaction term was < 0.05, and then we estimated yearly changes in BMI z score for each adipocytokine tercile using the linear combination estimates from the model. If the P value for the interaction term was not statistically significant, we did not include the adipocytokine × age interaction term in the final model and subsequently estimated differences in BMI z scores across all ages between the adipocytokine terciles, using the lowest tercile as the reference.

We selected potential confounders to include in the final model based on the prior literature (6,30). Our primary analysis was adjusted for maternal age, race, income, parity, maternal BMI, cotinine concentrations, child age, and child sex. Inclusion of other covariates, such as gestational age, maternal gestational diabetes mellitus, maternal glucose concentrations after oral glucose tolerance testing, and delivery mode, did not change the regression estimates and were therefore not included in the final model.
Secondary analyses
We evaluated if sex modified the association between neonatal adipocytokines and BMI z score changes during childhood using both a stratified analysis and all second- and third-order product interaction terms between child age, child sex, and adipocytokine terciles.

To evaluate for confounding by birth weight, gestational weight gain, and maternal hyperglycemia, we additionally adjusted for birth weight 

TABLE 1 Neonatal cord serum adipocytokine concentrations according to participant covariates (The HOME Study, 2003-2006)

| Characteristic                        | n (%) | Leptin (ng/mL), median (25th, 75th) | Adiponectin (µg/mL), median (25th, 75th) |
|---------------------------------------|-------|------------------------------------|------------------------------------------|
| Overall                               | 271   | 9.8 (5.5, 16)                      | 42 (30, 53)                              |
| Maternal age (y)                      |       |                                    |                                          |
| 18-25                                 | 53 (20)| 7.6 (4.6, 11)                      | 36 (26, 45)                              |
| >25-35                                | 176 (65)| 11 (6.1, 17)                      | 44 (32, 54)                              |
| >35                                   | 42 (15)| 11 (7.2, 15)                      | 44 (34, 56)                              |
| Maternal race                         |       |                                    |                                          |
| Non-Hispanic white                    | 183 (67)| 10 (5.4, 17)                      | 45 (34, 56)                              |
| Non-Hispanic black                    | 70 (26)| 9.9 (6.7, 15)                      | 35 (27, 48)                              |
| Other                                 | 18 (7 )| 7.3 (5.1, 8.1)                     | 38 (27, 49)                              |
| Maternal education                    |       |                                    |                                          |
| High school or less                   | 55 (20)| 9.4 (6.7, 17)                      | 37 (26, 55)                              |
| Tech school or some college           | 67 (25)| 8.8 (5.4, 17)                      | 38 (30, 47)                              |
| Bachelor’s or more                    | 149 (55)| 11 (5.3, 15)                      | 45 (34, 56)                              |
| Household income ($/y)                |       |                                    |                                          |
| <20,000                               | 79 (29)| 11 (5.4, 15)                      | 47 (37, 58)                              |
| 20,000-40,000                         | 99 (37)| 11 (7.1, 17)                      | 45 (34, 55)                              |
| >40,000-80,000                        | 44 (16)| 8.5 (5.2, 16)                      | 36 (27, 45)                              |
| >80,000                               | 49 (18)| 9.5 (5.2, 16)                      | 33 (25, 45)                              |
| Parity                                |       |                                    |                                          |
| 0                                     | 120 (44)| 9.8 (5.4, 16)                      | 43 (33, 54)                              |
| 1                                     | 89 (33)| 8.5 (5.3, 15)                      | 43 (32, 53)                              |
| 2+                                    | 62 (23)| 11 (6.6, 18)                      | 36 (26, 52)                              |
| Maternal BMI (kg/m²)                  |       |                                    |                                          |
| <25 (normal)                          | 119 (44)| 8.3 (4.3, 13)                      | 42 (33, 53)                              |
| 25-30 (overweight)                    | 91 (34)| 9.6 (5.5, 17)                      | 45 (32, 56)                              |
| >30 (obesity)                         | 61 (22)| 14 (8.0, 21)                      | 40 (26, 50)                              |
| Maternal serum cotinine (ng/mL)       |       |                                    |                                          |
| <0.015 (unexposed)                    | 107 (40)| 8.7 (4.2, 16)                      | 43 (34, 56)                              |
| 0.015-3 (secondhand)                  | 137 (50)| 10 (7.3, 16)                      | 42 (30, 52)                              |
| >3 (active)                           | 27 (10.0)| 8.2 (5.5, 16)                     | 33 (21, 59)                              |
| Delivery type                         |       |                                    |                                          |
| Vaginal                               | 198 (73)| 9.0 (5.5, 15)                      | 43 (31, 55)                              |
| Cesarean section                      | 73 (27)| 12 (5.7, 19)                      | 40 (27, 48)                              |
| Infant sex                            |       |                                    |                                          |
| Female                                | 148 (55)| 12 (7.3, 18)                      | 43 (31, 55)                              |
| Male                                  | 123 (45)| 8.1 (3.9, 14)                      | 42 (30, 53)                              |
| Gestational age (wk)                  |       |                                    |                                          |
| <37 (preterm)                         | 15 (5 )| 2.8 (1.5, 6.2)                     | 24 (16, 42)                              |
| ≥37 (term)                            | 256 (95)| 10 (6.4, 16)                      | 43 (32, 54)                              |
| Birth weight z score (percentile)     |       |                                    |                                          |
| <10th (small for gestational age)     | 20 (7 )| 4.9 (2.6, 8.1)                     | 40 (28, 47)                              |
| 10th to 90th (appropriate for gestational age) | 210 (78)| 9.0 (5.5, 15)                     | 43 (30, 53)                              |
| >90th (large for gestational age)     | 41 (15)| 16 (13, 28)                       | 42 (32, 53)                              |

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several sensitivity analyses of our primary results. We excluded participants with the following conditions that may affect fetal growth: maternal obesity (defined as BMI >30 kg/m², n=61), gestational diabetes mellitus (n=12), preterm birth (defined as gestational age <37 weeks, n=15), and births that were small for gestational age (defined as gestational age- and sex-standardized birth weight z score <10th percentile, n=20). We also conducted a sensitivity analysis excluding the 4-week anthropometry measures, as our initial exploratory analysis suggested that this may be an influential time point in the association between adipocytokine concentrations and growth in these data.

Finally, we examined associations between neonatal adipocytokine concentrations and adiposity measures at age 8 years. We classified children as having overweight or obesity at age 8 years if their age- and sex-specific BMI z score was ≥1 SDS according to World Health Organization standards (29). We calculated risk for overweight and obesity at age 8 years according to neonatal leptin (n=154) and adiponectin (n=161) terciles using modified Poisson regression with robust standard errors. Using linear regression, we estimated differences in BMI z score, waist circumference, and body fat percentage across terciles of neonatal leptin and adiponectin. All 8-year adiposity measure models were adjusted for maternal age, race, income, parity, maternal BMI, cotinine concentrations, and child sex. The waist circumference and body fat percentage models were additionally adjusted for child age at the time of the 8-year study visit.

Results

Women in the study sample were predominantly white (67%), college educated (55%), and multiparous (54%) (Table 1). Most children in the study were born at term (95%) and had a birth weight z score between the 10th and 90th percentile (78%). The distribution of covariates among women and children in the study sample did not differ significantly from the full HOME Study cohort (Supporting Information Table S1). Median neonatal serum leptin and adiponectin concentrations were 9.8 ng/mL and 42 µg/mL, respectively (Table 1). There was a weak positive correlation between cord serum leptin and adiponectin (Pearson correlation coefficient = 0.16, P=0.01).

After adjusting for maternal age, race, income, parity, maternal BMI, cotinine concentrations, child age, and child sex, there was a positive association between neonatal cord serum leptin concentrations and child BMI z scores (Figure 1, Supporting Information Table S2). The rate of change in BMI z scores did not vary by neonatal serum leptin concentrations (leptin × age interaction P=0.48). Children in the middle (mean BMI z score difference: 0.2 SDS units; 95% CI: −0.1 to 0.4) and highest (mean BMI z score difference: 0.4 SDS units; 95% CI: 0.1 to 0.6) leptin terciles had greater BMI z scores between age 4 weeks and 8 years than children in the lowest tercile (P=0.001 for trend).

Figure 1 Estimated child BMI z scores between age 4 weeks and 8 years by neonatal leptin terciles (n=257) (The HOME Study, 2003-2006). Cord serum leptin concentration ranges for each tercile: low (0.2-7.1 ng/mL, n=84), middle (7.2-13 ng/mL, n=85), and high (14-95 ng/mL, n=88). Model was adjusted for maternal race, age, maternal BMI, parity, cotinine concentrations, household income, child age, and child sex. Solid and dashed lines represent estimated mean child BMI z scores between age 4 weeks and 8 years. Shading represents the 95% CIs.
We found that the rate of change in BMI z score differed by neonatal adiponectin tercile (adiponectin × age interaction $P < 0.001$). Between age 4 weeks and 8 years, children in the lowest adiponectin tercile had greater gains in BMI z score (BMI z score change per year: 0.10 SDS units; 95% CI: 0.08 to 0.13) than children in the middle (BMI z score change per year: 0.07 SDS units; 95% CI: 0.04 to 0.09) and highest terciles (BMI z score change per year: 0.02 SDS units; 95% CI: −0.001 to 0.05) (Figure 2, Supporting Information Table S3).

In the secondary analysis, the association between neonatal leptin concentrations and childhood BMI z scores was similar in boys and girls (leptin × sex interaction term $P = 0.85$) (Supporting Information Table S2). In our sex-stratified analysis, differences in yearly gains in BMI z score by neonatal adiponectin tercile were stronger in girls (adiponectin × age interaction term for girls $P < 0.001$) but still present in boys (adiponectin × age interaction term for boys $P = 0.19$) (Figure 3, Supporting Information Table S3).

When we additionally adjusted for birth weight z score, the differences in BMI z scores across leptin terciles became null. Compared with children in the lowest leptin tercile, mean BMI z score difference for children in the middle leptin tercile was −0.10 SDS units (95% CI: −0.32 to 0.15) and −0.08 SDS units (95% CI: −0.34 to 0.19) for children in the highest leptin tercile (Supporting Information Table S4). In addition, the association between birth weight z score and BMI z score during childhood did not change with additional adjustment for leptin concentrations at birth. The adjusted absolute difference in BMI z score for each unit increase in birth weight z score was 0.40 SDS units (95% CI: 0.30 to 0.48) and 0.42 SDS units (95% CI: 0.31 to 0.53) without and with adjustment for neonatal leptin concentrations, respectively. In contrast, the association between neonatal serum adiponectin concentrations and gains in BMI z score did not change when we additionally adjusted for birth weight z score (Supporting Information Table S5).

Overall, our results were similar when we excluded women with obesity or gestational diabetes and infants born preterm or small for gestational age from the analysis (Supporting Information Table S4 and Table S5). Our results were also similar when the models were additionally adjusted for gestational weight gain z scores and maternal glucose concentrations (Supporting Information Table S4 and Table S5). The associations of neonatal leptin and adiponectin with BMI z scores and changes in BMI z score, respectively, were attenuated when we excluded the 4-week growth measures from the analysis (Supporting Information Table S4 and Table S5).

Most measures of adiposity and the risk of overweight or obesity at age 8 years did not differ by neonatal leptin tercile (Table 2). Consistent with our longitudinal analysis, children in the highest adiponectin tercile had a 38% (risk ratio: 0.62; 95% CI: 0.38 to 1.02) decreased risk of

![Figure 2](https://example.com/figure2.png)
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Obesity compared with those in the lowest adiponectin tercile. Children in the highest adiponectin tercile also had decreased waist circumference (difference: −2.6 cm; 95% CI: −6.0 to 0.7) and body fat percentage (difference: −1.9 percent; 95% CI: −4.3 to 0.4) compared children in the lowest adiponectin tercile (Table 2).

Discussion

In this prospective longitudinal cohort study, both leptin and adiponectin concentrations at birth were associated with childhood BMI z scores from infancy through school age. Specifically, higher leptin concentrations were associated with higher BMI z scores during the first 8 years of life, while lower adiponectin concentrations were associated with greater gains in BMI z score from age 4 weeks to age 8 years.

To our knowledge, this is the first study to report that higher cord serum adiponectin concentrations are associated with slower weight gain during childhood. Weight gain is an important outcome to consider given that we and others have observed that patterns of weight gain during early childhood are associated with risk for overweight and obesity later in childhood (32-34). Few studies have examined the association between adiponectin at birth and adiposity during childhood or adolescence. In a German cohort, Meyer et al. (26) found a positive association between cord plasma adiponectin concentrations and adiposity at ages 3 and 4 years but not at age 5 years. In a Boston, Massachusetts, cohort (19), cord plasma adiponectin concentrations were positively associated with skin fold thickness but not BMI at age 3 years; however, this association was null in early adolescence (18). Finally, cord plasma adiponectin concentrations were positively associated with fat mass and waist circumference at age 17 years in a UK cohort (20).

Previous studies have also reported both positive (20) and inverse (17,22,25) associations of neonatal leptin with childhood adiposity. Only two studies have followed children past age 7 years (18,20). Similar to the present study, Simpson et al. (20) found that cord plasma leptin concentrations were positively associated with BMI, waist circumference, and fat mass at age 9 years; however, these associations were null at age 17 years. Differences in the study results across the literature may arise from population-specific factors that influence growth and variations in the timing and methods of adiposity assessment.

The mechanism of action of fetal adipocytokines that gives rise to alterations in growth and obesity risk during childhood is largely unknown. Evidence from rodent models has shown that leptin influences the programming of hypothalamic circuits during gestation, which may influence ex utero energy metabolism through satiety and hunger signaling (15). Additionally, leptin may increase brown adipose tissue deposition and enhance the activity of thermoregulatory circuits, which may in
TABLE 2: Adjusted associations of neonatal cord serum leptin (n = 154) and adiponectin (n = 161) concentrations and childhood adiposity measures at age 8 years

| Leptin | Adiponectin |
|--------|-------------|
| BMI z score difference, $\beta$ (95% CI) | Waist circumference (cm), $\beta$ (95% CI) | Body fat percentage difference, $\beta$ (95% CI) | RR of overweight or obesity (95% CI) |
| Lowest tercile | Reference | Reference | Reference | Reference |
| Middle tercile | 0.25 (−0.25 to 0.75) | 0.0 (−0.5 to 0.5) | 0.15 (−0.1 to 0.4) | 0.82 (0.45 to 1.50) |
| Highest tercile | 0.06 (0.0 to 0.12) | 0.02 (−0.04 to 0.08) | 0.01 (−0.02 to 0.04) | 0.48 (0.23 to 0.95) |

Model adjusted for maternal race, age, income, parity, smoking status, and child sex. Waist circumference and body fat percentage model also adjusted for child age.

Regarding the mechanism by which adiponectin influences growth, fetal adiponectin has been shown to enhance fetal fat deposition at birth in mouse models (16). Moreover, adiponectin may play a role in both insulin sensitization and in the availability of nutrients such as fatty acids, which may in turn affect both fetal and childhood growth (6,39).

For instance, factors such as maternal nutrition, gestational weight gain, and placental function may influence fetal growth and adipocytokines levels. Moreover, physical activity and eating behaviors during childhood may influence childhood growth (30,40). In addition, our use of a linear model does not allow for inferences of growth patterns during specific periods of time. Future studies could consider focusing on the association of neonatal adipocytokines with specific periods of childhood growth using more advanced growth modeling techniques.

Additional limitations include modest sample size and inability to measure maternal adipocytokine concentrations, which have been associated with childhood adiposity in prior studies (18). Maternal adipocytokines cannot cross the placenta but may influence placental adipocytokine production during gestation (6,7). We speculate that inclusion of maternal adipocytokines in the analysis would produce similar results to those that we observed. Moreover, we estimated fetal adipocytokine concentrations at one point in time. Limited information is available regarding changes in adipocytokine concentrations after delivery (23,41). Some studies have suggested that trajectories of adipocytokine concentrations may be an important factor for growth and adiposity development in childhood, but this remains to be an avenue for future research (17,23).
Conclusion

In this longitudinal cohort study of pregnant women and their children, neonatal serum adipocytokine concentrations were predictive of adiposity and growth from infancy through school age. Higher leptin concentrations at birth were associated with increased BMI during the first 8 years of life, while lower adiponectin concentrations at birth were associated with greater BMI gains during infancy and childhood. Further examination of the role of adipocytokines in both developmental programming and as markers of obesity risk may aid in the development of intervention strategies to target high-risk populations.

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