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Associations of Maternal and Cord Blood Adipokines with Offspring Adiposity in Project Viva: Is There An Interaction with Child Age?

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Abstract

Objectives—Higher leptin and lower adiponectin correlate with adult and childhood adiposity, but it is unclear how exposure to these adipokines during gestation relates to offspring growth. We aimed to investigate the relationships of maternal and cord adipokines with offspring adiposity across childhood to early adolescence, as well as interactions with child age.

Methods—In mother-child pairs in the Project Viva cohort, we measured adipokines in mothers at 2nd trimester (n=1106) and in cord blood at birth (n=657). We measured offspring adiposity indices at early childhood (mean 3.3±SD 0.3 years), mid-childhood (7.9±0.8 years) and early adolescence (13.2±0.9 years). We analyzed associations of maternal and cord adipokines with offspring longitudinal adiposity using a linear mixed model adjusting for pre-pregnancy body mass index (BMI), gestational weight gain (GWG), and other confounders.

Results—Mothers with higher BMI and GWG had higher leptin. Offspring born to mothers with the highest vs. lowest quartile of leptin had lower BMI z-score (−0.49 units, 95% CI: −0.72, −0.26), waist circumference (−2.6 cm, 95% CI: −3.7, −1.5) and sum of subscapular and triceps skinfolds (−2.8 mm, 95% CI: −4.1, −1.4) in early life. An interaction term between maternal leptin and child age was positive, suggesting that the associations between maternal leptin and child

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Conflict of interest

We declare here that there is no potential conflict of interest and financial support for all authors to be disclosed.

adiposity were not constant over time. Offspring born to mothers with lowest vs. highest quartile of maternal adiponectin had lower early life adiposity (BMI z-score -0.27 units, 95% CI: -0.48 , -0.05). Results were similar for cord leptin but not cord adiponectin.

Conclusions—Our findings showed higher maternal and cord leptin, and lower maternal adiponectin are associated with lower offspring adiposity from childhood to early adolescence, independent of maternal BMI and GWG. However, the strength of these associations was not constant over time.

Keywords

Perinatal adipokines; leptin; adiponectin; cord blood; offspring adiposity; childhood; early adolescence

Introduction

Adipokines, protein messengers produced by adipose tissue, influence both the endocrine system and cell metabolism.¹ Recent studies have yielded new information on the endocrine role of these signals, among which leptin and adiponectin have been most widely investigated.²

Leptin production correlates with fat mass, and exerts a weight-reducing action by inducing hypophagia and increasing energy expenditure in animal models with leptin deficiency.^{3, 4} Given the growing interest in understanding the developmental origins of obesity, researchers have started to look at the role of maternal and cord blood leptin in programming later adiposity. A body of evidence has shown positive associations of cord blood leptin with infant weight and length at birth.^{5–8} However, in our previous work we found that maternal prenatal leptin and cord blood leptin at birth were both inversely associated with offspring adiposity in early and mid-childhood.^{9, 10} In contrast, results from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort showed that cord blood leptin was weakly associated with higher childhood and adolescent adiposity.¹¹

Adiponectin is exclusively produced by mature adipocytes in adults, including pregnant women.^{12, 13} Adiponectin is an important insulin sensitizer, and typically in adulthood, adiponectin levels are inversely related to measures of adiposity, leptin, and insulin resistance.¹³ However, during fetal development, adiponectin can also be expressed by a number of fetal tissues such as brown and white adipose tissue, and skeletal and smooth muscle. Therefore, adiponectin levels are directly related to leptin levels in the fetus.² Sivan *et al.* and Teague *et al.* reported that cord blood adiponectin was positively associated with weight at birth and adiposity during infancy,^{7, 8} and Simpson *et al.* reported that it was weakly associated with greater fat mass in late childhood and adolescence.¹¹

Prior human research relating maternal and cord blood adipokines to later offspring growth has been limited and inconsistent, especially with regards to longer-term follow-up into adolescence. Furthermore, given the different origins of adipokines in maternal and fetal circulations, their influence on offspring adiposity may differ. In this paper, we used data from a pre-birth cohort to assess associations of leptin and adiponectin, measured during

pregnancy and in cord blood at birth, with offspring adiposity across childhood to early adolescence. We hypothesized that higher maternal and cord blood leptin, and lower maternal and cord blood adiponectin, would be associated with lower early life adiposity, but the strength of such associations may change over time as the child gets older.

Methods

Study population

This is an observational longitudinal cohort study. Mothers and children were participants in Project Viva, an ongoing prospective cohort study of pre- and peri-natal influences on maternal, fetal and child health. Eligible pregnant women were recruited at in-person visits during the first trimester of pregnancy from 8 obstetric offices of Atrius Harvard Vanguard Medical Associations, a multi-site group practice in Eastern Massachusetts, as described elsewhere.¹⁴ Exclusion criteria included multiple gestation, inability to answer questions in English, gestational age ≥ 22 weeks at recruitment, and plans to move away from the study area before delivery.

We conducted follow-up in-person visits at mid-pregnancy (26–28 weeks gestation), delivery, early childhood (mean $3.3 \pm$ SD 0.3 years), mid-childhood (7.9 ± 0.8 years) and early adolescence (13.2 ± 0.9 years).

Of 2128 live births in the cohort, 1535 had blood available for assay of maternal adipokines from the 2nd trimester visit and 839 had cord blood adipokines measured. We included participants with any data at the 3 outcome time points. Of the 1255 participants in the analysis dataset, 270 had outcome data at only 1 time point, 272 had 2 time points, and 713 had 3 time points. Of the 270 with only 1 time point, 189 had early childhood, 23 had mid-childhood, and 58 had early adolescent outcome data. We included in the present analysis those with either of the two main exposures, and adiposity outcome measurements measured at any time point during childhood and early adolescence. We present the sample sizes for each analysis in Figure 1.

Mothers provided written informed consent at enrollment and each postnatal follow-up visit, and children provided verbal assent at the early adolescent visit. The institutional review board of Harvard Pilgrim Health Care approved the project in line with ethical standards established by Declaration of Helsinki.

Exposure Measures

We collected non-fasting maternal and cord blood via venipuncture. We immediately refrigerated whole blood and within 24 hours, blood samples were spun and blood components were separated into aliquots for storage in liquid nitrogen according to a standard protocol. Maternal and cord plasma leptin and adiponectin were measured using an immunoassay (Linco Research Inc, St Charles, MO), as described previously.^{9, 10}

Outcome Measures

Anthropometry—At early childhood, mid-childhood and early adolescent visits, trained research assistants measured standing height and weight according to standardized

protocols. Height was measured to the nearest 1.0 mm with a Shorr Stadiometer, and weight was measured to the nearest 0.1 kg with a calibrated scale (early childhood Seca model 881, Seca Corp, Hanover, Maryland; mid-childhood and early adolescence: Tanita model TBF-300A, Tanita Corporation of America, Inc., Arlington Heights, Illinois).¹⁴ We calculated body mass index (BMI) as weight divided by height squared (kg/m^2). We calculated age- and sex-specific height and BMI z-scores using the Centers for Disease Control and Prevention Growth Charts.¹⁵

Waist circumference was measured to the nearest 0.1 cm using a Hoechstmass measuring tape (Hoechstmass Balzer GmbH, Sulzbach, Germany). Subscapular (SS) and triceps (TR) skinfolds (mm) were measured to the nearest 0.2 mm in triplicates with Holtain Tanner Skinfold Caliper (Holtain Limited, London, UK). We calculated the sum (SS+TR) and ratio (SS/TR) of the two skinfold thicknesses.⁹

Fat and lean mass measures—At early adolescent visit, we performed whole body dual x-ray absorptiometry (DXA) scans with a Hologic Model Discovery A fan-beam scanner (Hologic, Bedford, Massachusetts). A single trained investigator checked all scans for positioning, movement, and artefacts, and defined body regions to assess whole body and regional fat mass. We used Hologic software QDR version 12.6 to determine total fat mass index, total lean mass index, trunk fat mass index, and total fat percentage.⁹ The calculation and units for the respective adiposity indices are as follows—total fat mass index (kg/m^2) = total fat mass (in kg) / height (in m)²; total lean mass index (kg/m^2) = total lean mass (in kg) / height (in m)²; trunk fat mass index (kg/m^2) = trunk fat mass (in kg) / height (in m)²; total fat percentage (%) = total fat mass (in kg) / weight (in kg) $\times$ 100%. These indices provide direct measures of fat (total fat mass index), lean (total lean mass), and trunk fat (trunk fat mass index) mass, each corrected for the height of the child at the time of measurement. Total fat percentage indicates the relative proportion of fat mass for the child's given weight. A total of 35 scans were evaluated by the same rater for a second time to check for consistency. Reliability represented by intra-class correlation (ICC) was more than 0.99 in our cohort.

Covariates—At recruitment, mothers reported their age, race/ethnicity, pre-pregnancy weight, smoking history (smoking during pregnancy, past smoker, and never-smoker), personal history of chronic systemic diseases (e.g. type 1 or type 2 diabetes mellitus, chronic hypertension) and highest educational attainment, as well as father's weight and height via questionnaire and interview. We calculated total and trimester-specific gestational weight gain (GWG) using self-reported pre-pregnancy weight and clinically measured weights recorded in the outpatient medical records.¹⁶ We identified gestational glucose abnormality (e.g. isolated hyperglycemia, gestational impaired glucose tolerance [GIGT] and gestational diabetes mellitus [GDM]) and gestational hypertensive disorders (e.g. gestational hypertension, pre-eclampsia [PE]) using data from clinical records¹⁷. We collected infant birth weight and delivery date from hospital medical records. We calculated birth weight for gestational age z-scores using national reference data from the United States Natality database and categorized infants as large (LGA), appropriate (AGA), or small for gestational

age (SGA).¹⁸ Mothers reported their child's race/ethnicity, which we categorized in this analysis as white, black, Hispanic, Asian or other.

Statistical Analysis

To assess our main hypothesis that maternal and cord blood adipokines were associated with offspring adiposity measures and such effects were age-dependent, we fit mixed linear models as a function of child age at outcome measurement. This method accounts for the correlation between repeated measures on the same individual at different ages. We estimated associations of perinatal adipokines with offspring adiposity indices modelled as continuous measures from early childhood to early adolescence, adjusted for covariates. Since the distributions of adipokines were skewed and maternal leptin and adiponectin were inversely correlated with other, we categorized adipokines into quartiles and used the lowest quartile of leptin (Q1) and the highest quartile of adiponectin (Q4) as the reference category. We included interaction terms between each quartile of exposure and child age to assess whether this association changed as age increased. We used maximum likelihood method of estimation and chose an unstructured working covariance matrix for the random effects variables (intercept and child age). The linear mixed model provided estimated model coefficients with 95% confidence intervals (CI). We also conducted likelihood ratio tests of the null hypothesis that all of the interaction terms (quartiles of adipokines*child age) were at zero ($p > 0.05$, two-sided).

We first fit unadjusted models including only exposure and child age (Model 1). As maternal pre-pregnancy BMI is known a major confounder,^{10, 19} we next fit models adjusted for maternal pre-pregnancy BMI (Model 2). To select additional covariates for adjustment, we identified potential confounders *a priori* via publications and applied a stepwise forward approach to select potential variables for adjustment. Based on changes on both estimate and square of coefficient correlation (r^2), we retained those that biologically and significantly contributed to our models, and ended up with the most parsimonious adjustment. Our final model for maternal exposures adjusted for maternal pre-pregnancy BMI, age at enrolment, smoking history, and college degree (yes or no), and GWG at exposure; paternal BMI; child sex and race/ethnicity; and the other adipokine at exposure (Model 3). Our final model for cord blood exposures adjusted for all confounders in Model 3 as well as birth weight for gestational age z-score (Model 4).

To assess the associations of maternal and cord blood adipokines with all adiposity measures collected at the early adolescent visit (BMI z-score, waist circumference, sum of skinfolds and DXA fat and lean mass), we performed linear regression analyses using the same four models as reported above. Because children attended the early adolescent visit at a range of ages, we included interaction terms between adipokine quartiles and child age. As none were significantly different from zero at the 0.05 level, we did not retain the interaction terms in the final model.

We also performed sensitivity analyses by including additional covariates, namely pre-pregnancy diabetes, pre-pregnancy hypertension, gestational glucose abnormality, gestational hypertensive disorders, household income, parity, preterm delivery, total energy intake during pregnancy and the same adipokines from the other time point (e.g. adjusting

for maternal 2nd trimester leptin in the cord blood leptin model), in the fully-adjusted model. We investigated potential effect modification by race/ethnicity, sex, maternal BMI, and birth weight-for-gestational age via adding multiplicative interaction terms with perinatal adipokines into the fully adjusted models. In linear mixed model, we further assessed robustness of results by including an additional interaction term of adipokines and square of child age as well as categorizing age into quartiles and quintiles. Statistical analyses were conducted by using SAS (version 9.3, SAS Institute, Cary NC, US) and STATA (version 11.1, STATA corp, Texas, US).

Results

Overall, maternal 2nd trimester leptin concentration was much higher than cord blood leptin, while cord blood adiponectin was higher than maternal 2nd trimester adiponectin (Table 1). Both leptin and adiponectin varied by maternal characteristics. For example, the median (IQR) 2nd trimester leptin concentration was 30.0 (19.7) ng/dL in mothers who were overweight or obese before pregnancy and 15.6 (14.4) ng/dL in women who were normal weight 22.0 (17.9) in mothers with high early pregnancy GWG and 17.2 (18.1) with early pregnancy GWG below the median; and 24.4 (18.3) ng/dL in mothers who smoked during pregnancy vs. 19.7 (18.2) among never smokers. The median (IQR) cord leptin concentration was 8.6 (10.2) ng/dL in offspring who were female vs. 6.0 (6.3) ng/dL in males; 7.6 (7.9) ng/dL in offspring born at term vs. 2.6 (2.9) ng/dL in those born preterm; and 11.9 (10.9) ng/dL in LGA, 6.7 (7.2) ng/dL in AGA, and 5.4 (5.4) in SGA offspring (Table 1).

Maternal leptin during pregnancy was inversely correlated with maternal adiponectin ($r = -0.12$, $p < 0.0001$) and positively correlated with cord blood leptin ($r = 0.12$, $p = 0.01$). Maternal adiponectin was inversely correlated with cord blood leptin ($r = -0.14$, $p = 0.002$). Cord blood adiponectin was positively correlated only with cord blood leptin ($r = 0.39$, $p < 0.0001$) but not associated with either of the maternal adipokines (Supplementary Table 1).

As expected, children were taller and heavier at each successive in-person visit (Table 2). At the early adolescent visit, mean $\pm$ SD fat percentage was $28.4 \pm 7.4\%$, total fat mass index 6.2 ± 2.9 kg/m², fat free mass index 14.7 ± 1.9 kg/m², and trunk fat mass index 2.3 ± 1.4 kg/m² (Table 2).

Table 3 reports the estimated associations of maternal leptin with early life adiposity measures (main effect), and estimated changes in these associations with each additional year of child age (Interaction). Table 4 shows results for maternal adiponectin. Children of mothers with highest quartile of leptin and lowest quartile of adiponectin during the 2nd trimester tended to have less adiposity. Specifically, in the fully adjusted model, we estimated that offspring born to mothers with the highest leptin quartile (Q4 vs. Q1) had BMI z-score that was 0.49 units lower (95% CI: -0.72 , -0.26). Similarly, we estimated that being in highest leptin quartile (vs. lowest) was associated with lower early life waist circumference (-2.6 cm, 95% CI: -3.7 , -1.5), waist-to-hip ratio (-0.03 units, 95% CI: -0.04 , -0.02) and SS+TR (-2.8 mm, 95% CI: -4.1 , -1.4) (Table 3). We further estimated that children of mothers in the lowest adiponectin quartile (Q1 vs. Q4) had lower early life

BMI z-score at age 0 (−0.27 units, 95% CI: −0.48, −0.05), waist circumference (−1.7 cm, 95% CI: −2.7, −0.6), hip circumference (−1.4 cm, 95% CI: −2.6, −0.2) and SS+TR (−1.8 mm, 95% CI: −3.1, −0.5) after adjusting for covariates (Table 4).

In the adjusted linear mixed models (Model 3), most of the interaction terms between adipokines and age were significant at the 0.05 level and positive for most of the associations reported (Tables 3 and 4). All likelihood ratio tests of the null hypothesis [i.e. that all of the interaction terms (quartiles of adipokines*child age) are zero] were also significant ($p < 0.05$). This implies that the association between maternal adipokines and offspring adiposity growth is not constant as the children age. For example, the estimates of association between highest maternal leptin and offspring BMI z-score were −0.49 units at birth, −0.40 units at year 3, −0.28 units at year 7 and −0.13 units at year 12, accordingly (Supplementary Figure 1). The estimate of association between lowest maternal adiponectin and offspring BMI z-score were −0.27 units at birth, −0.24 units at year 3 and −0.06 units at year 7 (Supplementary Figure 1). Thus, the effect size of associations between early adipokine exposure and later growth attenuated as child age increased. We also found that main effect of maternal adiponectin and offspring SS/TR was not significant, while their interaction term was significant (Tables 4). This is reflective of a significant rate of change in the outcome over time associated with each quartile of maternal adiponectin, even though the main effect of different quartiles of maternal adiponectin was not.

Similar trends of effect estimates and interactions were present for the associations between higher cord blood leptin and lower adiposity in childhood and adolescence (Supplementary Table 2). However, no associations were evident between cord blood adiponectin and offspring adiposity measures, except for the outcome of SS/TR (lowest vs. highest quartile= −0.08, 95% CI: −0.12, −0.03) (Supplementary Table 3).

Table 5 shows associations of perinatal adipokines with adiposity measures at early adolescence. Maternal leptin (Q4 vs. Q1) was inversely associated with offspring BMI z-score (−0.2 units, 95% CI: −0.4, 0.0) and total lean mass index (−0.9 kg/m², 95% CI: −1.4, −0.4), and cord blood leptin was inversely associated with offspring total lean mass index (−0.7 kg/m², 95% CI: −1.3, −0.03). Otherwise, maternal and cord leptin were not associated with offspring adiposity measures in adolescence.

Additional adjustment for maternal pre-gestational hypertension, type 1 or type 2 diabetes mellitus, or for gestational factors including gestational glucose abnormality and gestational hypertensive disorders, did not appreciably change the observed associations. Sensitivity analyses showed that our results did not substantively change when we alternatively modelled age as a quadratic function nor when we categorized age into quartiles or quintiles of the data. We did not observe evidence of effect modification by maternal pre-pregnancy obesity or parity, or offspring sex, size at birth or pre-term birth (all interactions $p > 0.05$).

Discussion

In this multi-ethnic pre-birth cohort, we observed associations of maternal and cord blood adipokines with offspring adiposity from childhood to early adolescence. The highest level

of maternal leptin during 2nd trimester, highest level of cord blood leptin, and lowest level of maternal adiponectin during 2nd trimester were consistently associated with lower offspring adiposity measures. However, the strength of such associations was not constant as children grew older. Contrary to our hypothesis, cord blood adiponectin was not associated with offspring adiposity measures across childhood and early adolescence.

Maternal and cord blood leptin

Substantial evidence has shown that cord blood leptin is directly associated with birth size,^{5–8} yet few studies have examined the relationship of cord blood leptin with subsequent offspring adiposity and growth into adolescence. This is important because leptin can influence the formation of hypothalamic circuits involved in homeostatic control of feeding beginning at birth.²⁰ Recent findings from the ALSPAC cohort reported that cord blood leptin was positively related with birth weight, yet associated with slower gains in weight, length and head circumference in early infancy (0–4 months);⁶ however, the association again became weakly positive during childhood at age 9.¹¹ The researchers suggested that leptin exposure could influence postnatal levels of satiety, peripheral metabolism and weight gain. Such findings were supported by Fonseca *et al.* in their study involving preterm newborns, which found cord blood leptin was negatively associated with the rate of changes in BMI and length among 96 preterm babies from birth to 64 postnatal weeks. These studies supported the idea that leptin appears to be exerting its effects in the brain, in regulating energy balance and inhibiting food intake during infancy.¹⁹

As maternal physiology influences energy supply to the fetus during pregnancy, which has no requirement for feelings of hunger and satiety,^{20, 21} high leptin in infants at delivery is more indicative of higher transfusion of placental leptin. The high level of leptin at birth might ensure proper development of food intake circuits with time, to meet the increased energy needs. Animal studies have shown that leptin receptors in the hypothalamus are only expressed after delivery.²⁰ In rodent models, leptin's ability to suppress food intake only emerges after weaning, when the effect of leptin on neuronal responses in arcuate nucleus of the hypothalamus switches from excitation to inhibition.²⁰ Taken together, these findings explain the strong associations between cord blood leptin with larger birth size, and the corresponding inverse associations during infancy.

Mothers with pre-pregnancy obesity, excessive weight gain and gestational hyperglycemia tend to have babies with higher birth weight and subsequent obesity. In addition, leptin levels tend to be higher among these mothers. However, our findings showed that maternal leptin in the highest within-cohort quartile seemed to be protective against increased offspring adiposity. In studies on rodents and obese humans, researchers suggested that even in the pregnant state, regardless maternal BMI status, leptin could still be functional (e.g. inhibiting food intake and increasing energy expenditure) at certain thresholds.²² Furthermore, in an experimental rodent model, inhibiting leptin receptor function in pregnant dams resulted in gestational diabetes, indicating that leptin during pregnancy is involved in the regulation of maternal glucose metabolism and insulin sensitivity.²³ Although these data were based on rodent experiments, it is possible that higher leptin level might gear fetal growth towards a healthier status by balancing maternal plasma glucose.

The association between maternal and cord blood leptin and offspring adiposity was independent of maternal BMI and weight gain during pregnancy.

Interestingly, we also found maternal and cord blood leptin was associated with lower lean mass index. It may be that the lower lean mass follows from the lower fat mass, since obese individuals need more muscle to move their greater total mass.²⁴ Although boys and girls have different proportions of body fat, especially after puberty, we did not see any differential associations of perinatal adipokines exposure with adiposity by sex.

Maternal and cord blood adiponectin

In adults, adiponectin is exclusively expressed in mature adipocytes, with increasing expression and secretion during the process of adipocyte differentiation, and higher adiponectin mRNA and protein expression in subcutaneous compared with visceral fat.^{12, 13} Epidemiological studies have shown adiponectin levels are lower in obese adults, and lower adiponectin level relates to a substantial increase in risk of hypertension, diabetes and cardiovascular disease regardless of body fat mass, suggesting that adiponectin may even contribute to the pathogenesis of these diseases.^{12, 13, 25, 26} Adiponectin is an important insulin sensitizer, and is inversely related to measures of insulin resistance.¹³ However, due to insufficient data, it is still not well-understood how maternal adiponectin may impact offspring growth.

Cord blood adiponectin can be expressed in several fetal tissues during mid and late gestation such as brown adipose tissue (BAT), white adipose tissue (WAT), skeletal muscle fibres of the diaphragm and iliopsoas, smooth muscle cells of the small intestine and arterial wall.² It is not derived from maternal circulation. The several sources of adiponectin expression in the fetus may account for the high adiponectin levels in cord blood. Previous studies showed that higher cord blood adiponectin was positively associated with larger offspring birth size and weight from delivery to infancy.^{7, 8} In our study, cord blood adiponectin was not related to offspring adiposity except for an inverse association with one central obesity index – the ratio of subscapular and triceps skinfolds.

Our study also showed that the lowest level of maternal adiponectin was associated with lower offspring adiposity in early life. A plausible explanation for this finding might be that the lowest level of adiponectin-related insulin resistance might lead to hyperinsulinemia in both mothers and their fetuses, and subsequently enhance fetal insulin-sensitivity via upregulation of the insulin receptor. Bacha *et al.* suggested that adiponectin levels explained a staggering 73% of the variance in insulin sensitivity in obese adolescents;²⁷ therefore, enhanced insulin sensitivity in newborns may lead to lipolysis and ketogenesis. In summary, we postulate that mothers with lower level of adiponectin might have enhanced insulin sensitivity with upregulated insulin receptors in newborns, which may explain the effect in reduced offspring adiposity in early life.

Strengths and Limitations

Our study has many strengths including its relatively large sample size, long follow-up until early adolescence, and prospective study design. In addition, prior human research relating maternal and cord blood adipokines to later offspring growth has had limited longer-term

follow-up. Our current findings have not only confirmed the inverse association between adipokines exposure during gestation and offspring adiposity until early adolescence; it also suggests that such associations were not constant over time, given the positive interaction with child age. Furthermore, we examined the separate contributions of maternal and cord blood leptin and adiponectin for offspring adiposity, systematically analysing adiposity from childhood to early adolescence, standardized protocols for repeated adiposity measurements and other covariates by trained staff.

However, there are also some limitations. First, even though the overall sample size was large, there are still missing data in some of the variables. When the final adjustment was applied, the missing values of co-variables reduced the final number for analysis. Second, adiposity includes subcutaneous fat and visceral fat. Even though we measured BMI and a series of subcutaneous and central fat indices, they still might not accurately indicate visceral fat. Therefore, our results may not be specific to visceral adiposity. Third, all outcome adiposity measures were not age- and sex-standardized except for BMI and height. Therefore, the reported estimates in our linear mixed model regarding association between maternal and cord adipokines and some of the adiposity measures such as waist circumference and sum of skin might be imprecise. However, we adjusted for age and gender in final model in order to minimize such bias. Lastly, there might be unmeasured confounders that we were unable to take into account.

In summary, in our observational, prospective pre-birth cohort study, maternal 2nd trimester adipokines (highest level of leptin and lowest level of adiponectin) and cord blood leptin at birth (but not adiponectin) were associated with lower early life adiposity. The interaction between adipokines exposure and child age however, suggests that these programming effects wane over time, perhaps because of developmental maturation in the adipokine-driven appetite regulation system, or perhaps because of intervening exposures such as shared maternal and child behaviors. Additional longitudinal follow-up will help further our understanding of long-term associations of gestational adipokine exposure with long-term health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Sample size for maternal-offspring pairs and cord blood-offspring pairs at each visit

Maternal and cord blood leptin and adiponectin concentrations according to participant characteristics; Data from mothers and children in Project Viva

Table 1

	N (%)	Leptin,		Adiponectin,	
		Median (IQR) ng/dL		Median (IQR), µg/dL	
		Maternal 2 nd -trimester	Cord blood	Maternal 2 nd -trimester	Cord blood
Total	N=1255	(n=1106)	(n=657)	(n=1106)	(n=657)
		20.1 (18)	7.3 (8.1)	13.7 (9.8)	29.4 (8.5)
Maternal characteristics					
<i>Age at enrollment</i>					
<35 years	880 (70.1)	20.8 (17.9)	7.1 (8.3)	13.7 (10)	29.6 (8.3)
≥35 years	375 (29.9)	17.8 (18.9)	8.0 (7.5)	13.7 (9.6)	29.3 (8.7)
<i>Race/ethnicity</i>					
Black	169 (13.5)	27.2 (18.3)	9.4 (11.6)	8.1 (7.2)	29.8 (10)
Hispanic	77 (6.2)	26.3 (18.2)	8.0 (6.9)	11.9 (11.2)	28.8 (7.9)
Asian	65 (5.2)	15.5 (15.4)	6.1 (8.8)	10.8 (11.8)	29.5 (8.4)
White	889 (71.0)	18.8 (17.7)	7.0 (7.6)	14.9 (9.4)	29.6 (8.3)
Other	52 (4.2)	21.2 (18.5)	9.1 (7.8)	12.1 (7)	27.8 (7.8)
<i>College graduate</i>					
No	378 (30.2)	22.7 (19.5)	7.3 (7.4)	11.8 (10.3)	29.7 (8.4)
Yes	874 (69.8)	18.7 (17.8)	7.2 (8.5)	14.3 (9.6)	29.4 (8.5)
<i>Chronic hypertension</i>					
No	1213 (98.5)	19.8 (17.9)	7.2 (8.1)	13.7 (9.8)	29.6 (8.3)
Yes	18 (1.5)	30.1 (16.4)	5.7 (9.4)	10 (9.9)	21.9 (5.3)
<i>Pre-pregnancy type 1 or 2 DM</i>					
No	1247 (99.6)	20.1 (18)	7.2 (8.1)	13.7 (9.8)	29.4 (8.4)
Yes	5 (0.4)	34.8 (20.4)	16.9 (14.9)	16.4 (10.2)	28.9 (11.1)
<i>Pregnancy smoking status</i>					
Never	866 (69.3)	19.7 (18.2)	7.6 (8.1)	13.6 (9.5)	29.5 (8.3)
Former	248 (19.9)	19.6 (18.3)	6.0 (7.1)	15 (11.1)	29.5 (8.1)
During pregnancy	135 (10.8)	24.4 (18.3)	7.5 (8.9)	11.6 (9.7)	28.4 (10.5)

	N (%)	Leptin,		Adiponectin,	
		Median (IQR) ng/dL		Median (IQR), µg/dL	
		Maternal 2 nd -trimester	Cord blood	Maternal 2 nd -trimester	Cord blood
		(n=1106)	(n=657)	(n=1106)	(n=657)
<i>Pre-pregnancy BMI</i>					
Under/normal weight <25 kg/m ²	798 (63.6)	15.6 (14.4)	6.5 (7.2)	15.1 (9.4)	29.3 (8.4)
Overweight/obese ≥25 kg/m ²	457 (36.4)	30.0 (19.7)	8.3 (9.8)	10.4 (8.7)	29.6 (8.7)
<i>Father's BMI</i>					
Under/normal weight <25 kg/m ²	429 (35.6)	18.5 (17.1)	7.2 (8.4)	13.9 (9.1)	28.9 (8.6)
Overweight/obese ≥25 kg/m ²	775 (64.4)	21 (18.8)	7.4 (7.8)	13.5 (10.5)	29.6 (8.1)
Gestational characteristics					
<i>Gestational weight gain to 2nd trimester</i>					
Lower 50th%tile <9.2 kg	623 (50.0)	17.2 (18.1)	7.1 (8.5)	13.5 (10.4)	29.4 (8)
Upper 50th%tile ≥9.2 kg	622 (50.0)	22.0 (17.9)	7.4 (7.7)	13.9 (9.3)	29.2 (9)
<i>Total GWG IOM categories</i>					
Inadequate	152 (12.2)	12.4 (13.4)	6.0 (7.2)	13.7 (10.2)	28.0 (8.2)
Adequate	362 (29.2)	15.0 (12.6)	6.9 (7.6)	14.4 (10.1)	30.2 (8.3)
Excessive	727 (58.6)	24.5 (18.4)	7.6 (8.1)	13.2 (9.6)	28.9 (8.6)
Nulliparous					
No	655 (52.2)	18.7 (18.9)	8.1 (7.9)	13.3 (9.7)	29.4 (8.1)
Yes	600 (47.8)	21.1 (17.2)	6.5 (8)	13.9 (10.2)	29.4 (8.9)
<i>Impaired glucose tolerance[†]</i>					
No	1040 (83.3)	19.6 (17.7)	7.1 (7.8)	14.1 (9.7)	29.3 (8.2)
Yes	208 (16.7)	23.1 (18.4)	8.3 (11.1)	10.8 (9.2)	29.8 (10.2)
<i>Gestational HTN/pF²</i>					
No	1090 (89.9)	19.4 (18)	7.3 (8.1)	13.8 (10)	29.7 (8.2)
Yes	123 (10.1)	25.9 (19.7)	6.7 (8.3)	12.3 (9.6)	27.6 (10.9)
Child characteristics					
Sex					
Male	639 (50.9)	20.3 (17.2)	6.0 (6.3)	13.8 (10.3)	29.0 (8.8)

	N (%)	Leptin,		Adiponectin,	
		Median (IQR) ng/dL		Median (IQR), µg/dL	
		Maternal 2 nd -trimester	Cord blood	Maternal 2 nd -trimester	Cord blood
		(n=1106)	(n=657)	(n=1106)	(n=657)
Female	616 (49.1)	19.5 (19)	8.6 (10.2)	13.5 (9.6)	29.7 (7.8)
<i>Gestational age at delivery</i>					
<37 weeks	79 (6.3)	20.7 (19.8)	2.6 (2.9)	11.9 (10.4)	23.1 (10.7)
≥37 weeks	1176 (93.7)	19.8 (18)	7.6 (7.9)	13.7 (9.7)	29.7 (8.2)
<i>Birth weight for gestational age categories</i>					
SGA <10th %tile	66 (5.3)	18.4 (15)	5.4 (5.4)	15.5 (8)	30.3 (6.1)
AGA 10-<90th %tile	1017 (81.1)	19.8 (18)	6.7 (7.2)	13.8 (9.7)	28.9 (8.6)
LGA ≥90th %tile	171 (13.6)	21.2 (18.8)	11.9 (10.9)	11.9 (10.2)	30.8 (7.4)
<i>Race/ethnicity</i>					
Black	173 (13.8)	26.2 (19.8)	9.2 (11.7)	8.7 (7.5)	29.2 (10.7)
Hispanic	54 (4.3)	26.9 (18.2)	7.3 (8.4)	9.1 (11.9)	27.8 (9.3)
Asian	43 (3.4)	16.1 (16.4)	6.7 (8.1)	11.3 (11.2)	30.2 (10.9)
White	844 (67.3)	18.8 (17.5)	7.1 (7.7)	15.0 (9.3)	29.6 (8.3)
Other	140 (11.2)	20.6 (17.5)	7.5 (7.3)	12.0 (9.7)	29.4 (8.3)

¹ Impaired glucose tolerance includes: gestational diabetes, gestational impaired glucose tolerance and isolated hyperglycemia

² Gestational hypertensive disorders: gestational hypertension or pre-eclampsia

Table 2

Adiposity measures in Project Viva across childhood to early adolescence; data among children with measured maternal 2nd trimester leptin (n=1106)

	Early childhood (n=985)	Mid childhood (n=835)	Early adolescence (n=793)
	Mean (SD)	Mean (SD)	Mean (SD)
Age, yrs	3.3, 0.3	7.9, 0.8	13.2, 0.9
<u>Anthropometry measures</u>			
Height, cm	97.4 (4.4)	128.5 (7.5)	159.8 (8.8)
Weight, kg	15.7 (2.1)	28.4 (6.9)	53.3 (13.8)
Height z-score, units *	0.25 (0.91)	0.24 (0.94)	0.34 (1.00)
BMI, kg/m ²	16.5 (1.4)	17.0 (2.7)	20.7 (4.2)
BMI z score, units *	0.45 (1.01)	0.34 (0.98)	0.33 (1.04)
Waist circumference, cm	51.3 (3.4)	59.6 (7.7)	72.7 (11.2)
Hip circumference, cm	56.6 (4.3)	67.8 (7.3)	88.2 (10.3)
Waist to hip ratio	0.91 (0.06)	0.88 (0.06)	0.82 (0.09)
SS + TR, mm	16.6 (4.0)	19.3 (9.1)	27.7 (13.2)
SS/TR	0.64 (0.16)	0.70 (0.18)	0.78 (0.23)
<u>DXA measures</u>			(n=561)
Fat percent, %	--	--	28.4 (7.4)
Total fat mass index, kg/m ²	--	--	6.2 (2.9)
Total lean mass index, kg/m ²	--	--	14.7 (1.9)
Trunk fat mass index, kg/m ²	--	--	2.3 (1.4)

* Height z-score and BMI z-score were both calculated based on national CDC 2000 reference data

Abbreviation: BMI, body mass index; SS + TR, sum of skinfolds, SS/TR, ratio of skinfolds.

Association of maternal 2nd-trimester leptin and adiposity indices across early childhood, mid childhood and early adolescence visits and interactions with child age; results from mixed models conducted among 1106 mother-child pairs in Project Viva

Table 3

2 nd Tri-Maternal Leptin in quartiles (Q2/Q3/Q4 vs. Q1)						
	Model 1		Model 2		Model 3	
	Main effect β (95% CI)	Interaction β (95% CI)	Main effect β (95% CI)	Interaction β (95% CI)	Main effect β (95% CI)	Interaction β (95% CI)
Anthropometry						
Height z-score						
Q1	Reference	Reference	Reference	Reference	Reference	Reference
Q2	0.05 (−0.13, 0.22)	−0.01 (−0.02, 0.01)	0.03 (−0.15, 0.20)	−0.01 (−0.02, 0.01)	−0.03 (−0.21, 0.16)	−0.01 (−0.02, 0.01)
Q3	0.11 (−0.06, 0.28)	−0.003 (−0.02, 0.01)	0.07 (−0.10, 0.25)	−0.003 (−0.02, 0.01)	0.00 (−0.18, 0.18)	−0.001 (−0.02, 0.01)
Q4	0.23 (0.06, 0.40)	−0.01 (−0.02, 0.01)	0.15 (−0.05, 0.35)	−0.01 (−0.02, 0.01)	0.04 (−0.17, 0.25)	−0.01 (−0.02, 0.01)
Weight, kg						
Q1	Reference	Reference	Reference	Reference	Reference	Reference
Q2	−0.2 (−0.9, 0.5)	0.1 (−0.06, 0.3)	−0.3 (−1.0, 0.4)	0.1 (−0.05, 0.3)	−0.4 (−1.2, 0.3)	0.1 (−0.1, 0.3)
Q3	−0.7 (−1.4, −0.03)	0.4 (0.2, 0.5)	−0.9 (−1.6, −0.1)	0.4 (0.2, 0.6)	−1.2 (−2.0, −0.4)	0.3 (0.1, 0.5)
Q4	−1.6 (−2.4, −0.7)	0.6 (0.4, 0.9)	−1.9 (−2.8, −1.0)	0.6 (0.4, 0.9)	−2.3 (−3.3, −1.4)	0.6 (0.4, 0.8)
BMI z-score, units						
Q1	Reference	Reference	Reference	Reference	Reference	Reference
Q2	0.11 (−0.09, 0.30)	0.01 (−0.01, 0.03)	−0.01 (−0.20, 0.19)	0.01 (−0.01, 0.03)	−0.12 (−0.32, 0.08)	0.01 (−0.01, 0.03)
Q3	0.19 (−0.01, 0.39)	0.02 (−0.004, 0.03)	−0.02 (−0.23, 0.18)	0.01 (−0.01, 0.03)	−0.22 (−0.43, 0.00)	0.02 (−0.003, 0.04)
Q4	0.25 (0.04, 0.45)	0.03 (0.01, 0.05)	−0.24 (−0.45, −0.02)	0.03 (0.01, 0.05)	−0.49 (−0.72, −0.26)	0.03 (0.01, 0.05)
Fat measures						
Waist Cir., cm						
Q1	Reference	Reference	Reference	Reference	Reference	Reference
Q2	−0.1 (−0.9, 0.7)	0.1 (−0.02, 0.3)	−0.3 (−1.1, 0.5)	0.1 (−0.02, 0.3)	−0.7 (−1.5, 0.2)	0.1 (−0.02, 0.3)
Q3	−0.6 (−1.6, −0.3)	0.3 (0.2, 0.5)	−1.0 (−1.9, −0.04)	0.3 (0.2, 0.5)	−1.4 (−2.5, −0.4)	0.3 (0.2, 0.5)
Q4	−1.1 (−2.0, −0.3)	0.6 (0.4, 0.8)	−1.9 (−2.9, −0.9)	0.6 (0.4, 0.8)	−2.6 (−3.7, −1.5)	0.6 (0.4, 0.8)
Hip Cir., cm						
Q1	Reference	Reference	Reference	Reference	Reference	Reference

2nd Tri-Maternal Leptin in quartiles (Q2/Q3/Q4 vs. Q1)

	Model 1			Model 2			Model 3		
	Main effect β (95% CI)	Interaction β (95% CI)	Main effect β (95% CI)	Interaction β (95% CI)	Main effect β (95% CI)	Interaction β (95% CI)	Main effect β (95% CI)	Interaction β (95% CI)	
Waist-to-Hip ratio	Q2	0.7 (-0.3, 1.7)	0.02 (-0.1, 0.2)	0.4 (-0.5, 1.4)	0.02 (-0.1, 0.2)	-0.1 (-1.1, 0.9)	0.02 (-0.1, 0.2)		
	Q3	0.6 (-0.4, 1.6)	0.2 (0.003, 0.3)	0.1 (-0.9, 1.2)	0.2 (0.002, 0.3)	-0.5 (-1.7, 0.6)	0.2 (-0.01, 0.3)		
	Q4	0.5 (-0.5, 1.5)	0.4 (0.2, 0.5)	-0.7 (-1.8, 0.5)	0.4 (0.2, 0.5)	-1.7 (-3.0, -0.5)	0.4 (0.2, 0.5)		
	Q1	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	
SS+TR, mm	Q2	-0.01 (-0.03, 0.00)	0.002 (0.00, 0.004)	-0.01 (-0.03, 0.00)	0.002 (0.00, 0.004)	-0.01 (-0.03, 0.00)	0.002 (0.00, 0.004)		
	Q3	-0.02 (-0.03, -0.01)	0.003 (0.001, 0.004)	-0.02 (-0.03, -0.01)	0.003 (0.001, 0.004)	-0.02 (-0.04, -0.01)	0.003 (0.001, 0.004)		
	Q4	-0.02 (-0.04, -0.01)	0.004 (0.002, 0.01)	-0.03 (-0.04, -0.02)	0.004 (0.002, 0.005)	-0.03 (-0.04, -0.02)	0.004 (0.002, 0.01)		
	Q1	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	
SS/TR	Q2	-0.8 (-1.8, 0.2)	0.3 (0.06, 0.5)	-1.0 (-2.0, 0.03)	0.3 (0.10, 0.5)	-1.3 (-2.3, -0.2)	0.3 (0.1, 0.5)		
	Q3	-1.2 (-2.4, -0.02)	0.5 (0.3, 0.7)	-1.5 (-2.7, -0.3)	0.5 (0.3, 0.7)	-1.7 (-3.0, -0.5)	0.5 (0.3, 0.7)		
	Q4	-1.6 (-2.6, -0.5)	0.7 (0.5, 1.0)	-2.3 (-3.5, -1.1)	0.7 (0.5, 1.0)	-2.8 (-4.1, -1.4)	0.7 (0.5, 1.0)		
	Q1	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	
SS+TR, mm	Q2	-0.02 (-0.05, 0.02)	0.001 (-0.004, 0.01)	-0.02 (-0.06, 0.01)	0.001 (-0.004, 0.01)	-0.03 (-0.06, 0.01)	0.001 (-0.003, 0.01)		
	Q3	-0.03 (-0.07, 0.01)	0.01 (0.003, 0.01)	-0.04 (-0.08, 0.00)	0.01 (0.003, 0.01)	-0.06 (-0.09, -0.02)	0.01 (0.004, 0.01)		
	Q4	-0.01 (-0.05, 0.03)	0.004 (0.000, 0.01)	-0.03 (-0.08, 0.01)	0.005 (0.000, 0.01)	-0.04 (-0.09, 0.00)	0.005 (0.000, 0.01)		
	Q1	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	

Abbreviation: BMI, body mass index; Waist Cir^r, waist circumference; Hip Cir^r, hip circumference; SS + TR, sum of skinfold, SS/TR, ratio of skinfold.Interaction: Maternal 2nd-trimester leptin in quartiles*Child age

Model 1. Child age;

Model 2. Model 1 + maternal pre-pregnancy BMI;

Model 3. Model 2 + maternal age at enrollment, college degree (yes or no), smoking during pregnancy (never, former, during pregnancy), gestational weight gain up to exposure, the other adipokine at exposure, paternal BMI, child sex and child race/ethnicity (Black, Hispanic, White, Asian, others).

Table 4

Association of maternal 2nd-trimester adiponectin and adiposity indices across early childhood, mid childhood and early adolescence visits; results from mixed models conducted among 1106 mother-child pairs in Project Viva

2 nd Tri-Maternal Adiponectin in quartiles (Q1/Q2/Q3 vs. Q4)						
	Model 1		Model 2		Model 3	
	Main effect β (95% CI)	Interaction β (95% CI)	Main effect β (95% CI)	Interaction β (95% CI)	Main effect β (95% CI)	Interaction β (95% CI)
Anthropometry						
Height z-score	Q1	0.12 (−0.04, 0.31)	0.000 (−0.02, 0.01)	0.08 (−0.10, 0.26)	0.000 (−0.02, 0.01)	0.06 (−0.13, 0.25)
	Q2	−0.01 (−0.19, 0.16)	−0.001 (−0.02, 0.01)	−0.03 (−0.20, 0.15)	−0.001 (−0.02, 0.01)	−0.05 (−0.23, 0.13)
	Q3	−0.13 (−0.30, 0.04)	0.001 (−0.01, 0.02)	−0.13 (−0.30, 0.04)	0.001 (−0.01, 0.02)	−0.14 (−0.31, 0.04)
	Q4	Reference	Reference	Reference	Reference	Reference
weight, kg	Q1	−1.4 (−2.3, −0.6)	0.4 (0.2, 0.7)	−1.7 (−2.6, −0.8)	0.4 (0.2, 0.7)	−2.0 (−2.9, −1.1)
	Q2	−0.2 (−1.0, 0.6)	−0.1 (−0.2, 0.2)	−0.3 (−1.1, 0.5)	−0.001 (−0.2, 0.2)	−0.4 (−1.2, 0.5)
	Q3	−0.1 (−0.9, 0.7)	−0.01 (−0.2, 0.2)	−0.1 (−0.9, 0.7)	−0.01 (−0.2, 0.2)	−0.2 (−1.0, 0.6)
	Q4	Reference	Reference	Reference	Reference	Reference
BMI z-score, units	Q1	0.03 (−0.18, 0.23)	0.03 (0.01, 0.05)	−0.24 (−0.46, −0.03)	0.03 (0.01, 0.05)	−0.27 (−0.48, −0.05)
	Q2	−0.08 (−0.29, 0.13)	0.01 (−0.01, 0.03)	−0.16 (−0.37, 0.05)	0.01 (−0.01, 0.03)	−0.19 (−0.40, 0.03)
	Q3	0.11 (−0.09, 0.30)	−0.01 (−0.03, 0.01)	0.10 (−0.09, 0.30)	−0.01 (−0.03, 0.01)	0.09 (−0.10, 0.29)
	Q4	Reference	Reference	Reference	Reference	Reference
Fat measures						
Waist Cir., cm	Q1	−1.2 (−2.2, −0.3)	0.4 (0.2, 0.6)	−1.7 (−2.7, −0.8)	0.4 (0.2, 0.6)	−1.7 (−2.7, −0.6)
	Q2	−0.4 (−1.2, 0.5)	0.1 (−0.1, 0.2)	−0.5 (−1.4, 0.4)	0.05 (−0.1, 0.2)	−0.6 (−1.5, 0.4)
	Q3	−0.1 (−0.9, 0.7)	0.03 (−0.2, 0.2)	−0.1 (−0.9, 0.7)	0.03 (−0.2, 0.2)	−0.2 (−1.1, 0.6)
	Q4	Reference	Reference	Reference	Reference	Reference
Hip Cir., cm	Q1	−0.6 (−1.7, 0.5)	0.2 (0.1, 0.4)	−1.4 (−2.5, −0.3)	0.2 (0.1, 0.4)	−1.4 (−2.6, −0.2)
	Q2	−0.3 (−1.3, 0.7)	0.01 (−0.2, 0.2)	−0.5 (−1.5, 0.5)	0.002 (−0.2, 0.2)	−0.5 (−1.6, 0.5)

2nd Tri-Maternal Adiponectin in quartiles (Q1/Q2/Q3 vs. Q4)

	Model 1			Model 2			Model 3		
	Main effect β (95% CI)	Interaction β (95% CI)	Main effect β (95% CI)	Interaction β (95% CI)	Main effect β (95% CI)	Interaction β (95% CI)	Main effect β (95% CI)	Interaction β (95% CI)	
Q3	-0.5 (-1.5, 0.4)	0.01 (-0.2, 0.2)	-0.5 (-1.5, 0.4)	0.01 (-0.2, 0.2)	-0.6(-1.6, 0.4)	0.03 (-0.1, 0.2)			
Q4	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	
Waist-to-Hip ratio									
Q1	-0.01 (-0.02, 0.01)	0.002 (0.00, 0.003)	-0.01 (-0.03, 0.00)	0.002 (0.000, 0.003)	-0.01 (-0.02, 0.01)	0.002 (0.000, 0.004)			
Q2	0.000 (-0.01, 0.01)	0.000 (-0.001, 0.002)	0.00 (-0.01, 0.01)	0.000 (-0.001, 0.002)	0.00 (-0.01, 0.01)	0.000 (-0.001, 0.002)			
Q3	0.01 (-0.01, 0.02)	0.000 (-0.002, 0.002)	0.01 (-0.01, 0.02)	0.000 (-0.002, 0.003)	0.01 (-0.01, 0.02)	0.001 (-0.001, 0.003)			
Q4	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	
SS+TR, mm									
Q1	-1.6 (-2.7, -0.4)	0.4 (0.2, 0.7)	-2.1 (-3.3, -0.9)	0.4 (0.2, 0.7)	-1.8 (-3.1, -0.5)	0.5 (0.2, 0.7)			
Q2	-0.8 (-1.9, 0.2)	0.1 (-0.2, 0.3)	-1.0 (-2.1, 0.1)	0.1 (-0.2, 0.3)	-1.0 (-2.1, 0.2)	0.1 (-0.2, 0.3)			
Q3	0.1 (-1.0, 1.1)	-0.1 (-0.3, 0.2)	0.1 (-1.0, 1.1)	-0.05 (-0.3, 0.2)	0.1 (-1.0, 1.2)	-0.04 (-0.3, 0.2)			
Q4	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	
SS/TR									
Q1	0.00 (-0.04, 0.03)	0.01 (0.004, 0.01)	-0.01 (-0.05, 0.02)	0.01 (0.004, 0.01)	-0.03 (-0.07, 0.00)	0.01 (0.004, 0.01)			
Q2	0.03 (-0.01, 0.06)	0.001 (-0.004, 0.01)	0.02 (-0.01, 0.06)	0.001 (-0.004, 0.01)	0.02 (-0.02, 0.06)	0.001 (-0.003, 0.01)			
Q3	0.01 (-0.02, 0.05)	0.002 (-0.003, 0.01)	0.01 (-0.02, 0.05)	0.002 (-0.003, 0.01)	0.02 (-0.02, 0.05)	0.001 (-0.003, 0.01)			
Q4	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	<u>Reference</u>	

Abbreviation: BMI, body mass index; Waist Cir-, waist circumference; Hip Cir-, hip circumference; SS + TR, sum of skinfolds, SS/TR, ratio of skinfolds.

Interaction: Maternal 2nd-trimester adiponectin in quartiles*Child age

Model 1. Child age;

Model 2. Model 1 + maternal pre-pregnancy BMI;

Model 3. Model 2 + maternal age at enrollment, college degree (yes or no), smoking during pregnancy (never, former, during pregnancy), gestational weight gain up to exposure, the other adipokine at exposure, paternal BMI, child sex and race/ethnicity (Black, Hispanic, White, Asian, others).

Table 5

Multiple linear regression of association between perinatal adipokines and early adolescence adiposity measures

Early adolescence adiposity Measures									
Perinatal adipokines	BMI z-score, units		Waist Cir ⁺ , cm	SS+TR, mm	DXA percent fat, %	DXA total fat mass index, kg/m ²	DXA total lean mass index, kg/m ²	DXA trunk fat mass index, kg/m ²	
		β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	
	Model 1	Q4							
2 nd tri-maternal leptin	Model 1	Q4	0.6 (0.4, 0.8)	7.1 (5.0, 9.2)	8.6 (6.0, 11.1)	5.0 (3.3, 6.7)	2.1 (1.4, 2.7)	0.8 (0.3, 1.2)	0.9 (0.6, 1.2)
	Model 2	Q4	-0.02 (-0.2, 0.2)	1.2 (-1.2, 3.6)	2.3 (-0.6, 5.2)	2.2 (0.3, 4.1)	0.5 (-0.3, 1.2)	-0.4 (-0.8, 0.1)	0.2 (-0.2, 0.5)
	Model 3	Q4	-0.2 (-0.4, 0.0)	-0.7 (-3.2, 1.8)	0.1 (-2.9, 3.1)	1.5 (-0.5, 3.5)	0.00 (-0.8, 0.8)	-0.9 (-1.4, -0.4)	-0.05 (-0.4, 0.3)
Cord blood leptin	Model 1	Q4	0.2 (-0.1, 0.5)	2.8 (-0.4, 6.0)	5.8 (2.2, 9.4)	4.1 (1.8, 6.3)	1.5 (0.6, 2.5)	0.2 (-0.4, 0.8)	0.7 (0.2, 1.2)
	Model 2	Q4	-0.01 (-0.3, 0.2)	0.5 (-2.4, 3.5)	3.4 (0.04, 6.8)	3.0 (0.8, 5.1)	0.9 (0.04, 1.8)	-0.3 (-0.8, 0.3)	0.4 (-0.02, 0.8)
	Model 4	Q4	-0.2 (-0.6, 0.1)	-2.0 (-5.5, 1.4)	0.2 (-3.8, 4.3)	0.9 (-1.7, 3.6)	0.00 (-1.1, 1.1)	-0.7 (-1.3, -0.03)	0.01 (-0.1, 0.5)
2 nd tri-maternal adiponectin	Model 1	Q1	0.3 (0.1, 0.5)	3.0 (0.8, 5.2)	3.6 (1.0, 6.2)	1.6 (-0.1, 3.3)	1.0 (0.3, 1.6)	0.8 (0.4, 1.2)	0.5 (0.2, 0.8)
	Model 2	Q1	0.00 (-0.2, 0.2)	-0.6 (-2.8, 1.5)	-0.3 (-2.9, 2.2)	-0.3 (-2.0, 1.4)	0.05 (-0.6, 0.7)	0.3 (-0.1, 0.7)	0.05 (-0.3, 0.4)
	Model 3	Q1	0.03 (-0.2, 0.2)	0.1 (-2.1, 2.3)	0.1 (-2.5, 2.7)	0.2 (-1.5, 1.9)	0.03 (-0.6, 0.7)	0.02 (-0.4, 0.4)	0.04 (-0.3, 0.4)
Cord blood adiponectin	Model 1	Q1	-0.03 (-0.3, 0.3)	-1.0 (-4.2, 2.1)	-0.8 (-4.4, 2.8)	-2.0(-4.3, 0.4)	-0.7 (-1.6, 0.3)	0.1 (-0.6, 0.7)	-0.3 (-0.8, 0.2)
	Model 2	Q1	-0.03 (-0.3, 0.2)	-1.2 (-4.1, 1.7)	-0.9 (-4.3, 2.4)	-2.0(-4.2, 0.2)	-0.6 (-1.5, 0.2)	0.1 (-0.5, 0.7)	-0.3 (-0.7, 0.2)
	Model 4	Q1	-0.1 (-0.4, 0.1)	-2.2 (-5.3, 0.8)	-0.9 (-4.5, 2.6)	-1.7(-4.0, 0.7)	-0.7 (-1.6, 0.2)	-0.2 (-0.8, 0.3)	-0.3 (-0.8, 0.2)

Abbreviation: BMI, body mass index; Waist Cir., waist circumference; Hip Cir., hip circumference; SS + TR, sum of skinfolds, SS/TR, ratio of skinfolds.

Model 1. Child age.

Model 2. Model 1 + maternal pre-pregnancy BMI.

Model 3. Model 2 + maternal age at enrollment, college degree (yes or no), smoking during pregnancy (never, former, during pregnancy), gestational weight gain up to exposure, the other adipokine at exposure, paternal BMI, child sex and race/ethnicity (Black, Hispanic, White, Asian, other).

Model 4. Model 3 + birth weight for gestational age z-score (for cord blood adipokines model only).