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Maternal and fetal factors affecting cord plasma leptin and adiponectin levels and their ratio in preterm and term newborns: New insight on fetal origins of metabolic dysfunction

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Abstract

Background: Understanding of maternal and fetal factors affecting leptin, adiponectin, and adiponectin:leptin ratio at birth may provide valuable insights into potential future risk of metabolic alterations and inform primordial prevention and precision nutrition strategies. The objective of this study is to identify maternal and fetal risk factors that affect leptin and adiponectin levels (markers of adiposity) and adiponectin/leptin ratio (a marker of dysfunctional adipose tissue) at birth.

Methods: We studied mother–infant pairs in the Boston Birth Cohort. Cord blood was collected at birth. We used student *t*- tests to compare log normalized cord leptin and adiponectin levels. Regression analysis was performed to examine the association of maternal and fetal factors with leptin and adiponectin levels and adiponectin:leptin ratio at birth in both term and preterm infants.

Results: We analyzed 1012 infants (245 preterm). Both cord leptin and adiponectin were higher in term infants than preterm infants (10.2 ± 0.9 *vs.* 9.2 ± 1.3, $P < 0.0001$ and 9.5 ± 0.7 *vs.* 8.9 ± 0.8, $P < 0.0001$, respectively). Cord leptin was higher for Black infants (10.1 ± 1.1 *vs.* 9.9 ± 1.2; $P < 0.001$) although Black (ref: non-Black) infants had lower cord adiponectin levels (9.3 ± 0.8 *vs.* 9.5 ± 0.7; $P = 0.01$). Ratio of adiponectin to leptin (log normalized) was higher in preterm infants (–0.24) *vs.* term infants (–0.69). On regression analysis, cord leptin was positively associated with longer gestational age (GA), birth weight *z* score, Black race, maternal overweight and obesity, gestational diabetes and pregestational diabetes mellitus and negatively associated with male sex. Cord adiponectin was positively associated with GA, birth weight *z* score and negatively with Black race and male sex. Adiponectin:leptin ratio was positively with male sex and negatively with GA, birth weight *z* score, Black race, gestational DM, pregestational DM and maternal overweight and obesity.

Conclusions: We identified several factors that affect leptin and adiponectin levels along with adiponectin–leptin ratio at birth beyond GA and birth weight which could also play an important role in influencing the trajectory of these hormones and future cardiometabolic outcomes. This knowledge can help tailor precision nutrition interventions.

Keywords: Prematurity, Leptin, Adiponectin

Introduction

Adverse intrauterine environments may induce long-term metabolic consequences for developing fetuses. *In utero* exposures shape fetal adaptation to survive the adverse exposures and prepare fetuses for a similar metabolic environment postnatally. Yet, maladaptation occurs when the expected postnatal environment is different and the *in utero* fetal adaptations end up being deleterious for childhood metabolic health.[1] Epidemiological and animal studies have led to the firmly established concept of the Developmental Origins of Health and Disease.[2,3]

Growing evidence points to the regulatory function of adipokines in physiological and pathological processes in human metabolic health.[4] Leptin and adiponectin are two key adipokines that are involved in the etiology and prognosis of obesity, hypertension, and metabolic syndromes.[5,6] Leptin has several metabolic and immunological roles, and the state of leptin resistance is an important precursor for obesity.[6] A vicious cycle between leptin resistance and the risk of obesity—higher leptin levels promote obesity that further leads to leptin resistance—has been proposed in previous studies.[7] As for the developmental origins for leptin levels, studies have

This is a secondary data analysis of data already obtained by the Boston Birth Cohort. Informed consent was obtained at initial cohort enrollment and postnatal follow-up.

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shown small for gestational age (SGA) infants to have lower cord leptin levels, which results in rapid postnatal weight gain and leads to metabolic syndromes. Maternal cardiometabolic factors such as pre-pregnancy obesity and diabetes may also result in higher cord leptin levels, placing infants at a higher risk of metabolic syndromes.[8] Adiponectin, the most abundant adipokines, is reported to have an insulin-sensitizing role and possibly protects against the development of insulin resistance and metabolic syndrome.[9] Conversely to leptin, higher cord adiponectin levels have been found to be associated with lower degrees of childhood adiposity levels.[10,11] However, in newborns, unlike adults there is a positive correlation between both leptin and adiponectin levels, gestational age (GA), and birth weight.[11–13] An interplay between adipokines could play a role in the early programming of fetuses for the development of metabolic syndromes.

There is a particularly critical need to understand the role of maternal and fetal factors on cord adipokines among children born preterm. Premature infants are at higher risk of developing metabolic syndrome-related disorders such as obesity, type 2 diabetes, and cardiovascular diseases in later life, but the associated risk factors and pathogenic mechanisms are not well understood.[14] Preterm birth can interrupt the acquisition of energy and fat stores and limit the metabolic adaptation of premature newborns to extra-uterine life. The ensuing adipose tissue dysfunctions could explain the well-reported associations of prematurity with future adverse cardiometabolic health outcomes.[5,13] Hence, cord blood adipokines could provide metabolic clues to the adipose tissue maladaptation secondary to *in utero* influences, which could have long-term implications for a neonate's health. Knowledge of these factors will potentially allow planning of precision nutrition recommendations for the high-risk infants based on their biology and environment rather than a "one size fits all" nutritional approach.

We previously reported a dose-dependent association between GA and plasma leptin levels at birth.[15] Previous studies have identified GA and anthropometric associations with adipokines, but they were conducted in studies with smaller sample sizes.[5,16] To our knowledge, no study has been done among a cohort predominated by Black infants. Studies have also been limited in their inclusion of several biological and social factors that affect maternal health and influence fetal metabolic programming. Our study aims to further advance our understanding of a broader array of maternal and fetal determinants of leptin and adiponectin levels in both term and preterm births. It is important to understand how the concentration of adipokines in cord blood relates to fetal and infant growth and maternal biological and socio-demographic influences because, ultimately, this may affect future cardiometabolic health risk. This study tested the hypothesis that multiple maternal and fetal factors, individually and jointly, are associated with plasma adipokines levels at birth. Through this type of comprehensive analysis, we will be able to better understand the risk factors for future childhood adiposity. Such type of studies may also provide systematic assessment of individual risk profile for early childhood adiposity, *via* combination of epidemiological and clinical data. This on a broader scale will contribute to the generation of refined computer algorithms to guide postnatal nutrition and develop the field of precision nutrition in neonatology and pediatrics.

Materials and Methods

We used data from the Boston Birth Cohort (BBC), a prospective birth cohort enriched by a spectrum of preterm births and characterized by a predominately Black, urban, low-income population in the United States.[17] Institutional Review Boards of Boston Medical Center and the Johns Hopkins Bloomberg School of Public Health approved this study. Since 1998, the BBC recruited mother–infant dyads within 2 to 3 days after birth using a rolling design. Mothers who delivered singleton live infants without major birth defects were eligible for participation. Supplementary Figure, http://links.lww.com/PN9/A8, shows how participants were selected for this analysis. The final analysis included 1012 infants (recruited between 1998 and 2010) who had data on cord leptin and adiponectin levels measured at birth.

Maternal and perinatal characteristics

We collected data on maternal age at delivery, parity, race, education, drug and smoking history using a standardized postpartum questionnaire. Maternal pre-pregnancy body mass index (BMI) was calculated as pre-pregnancy weight (kg) divided by height (m) squared. We classified mothers as overweight or obese (OWO) if their BMI was ≥25 kg/m^2. Medical records were accessed for information about infant sex, type of delivery, growth status at birth, GA, birth weight, antenatal steroid use, gestational diabetes mellitus (GDM), and hypertensive disorders. GDM was diagnosed between 24 and 28 gestational weeks based on an oral glucose tolerance test (OGTT). In cases of missing OGTT information, blood glucose after 14 weeks of gestation was used to ascertain GDM status. The presence of one or more of the following during pregnancy: preeclampsia, eclampsia, chronic hypertension; hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, led to the classification of maternal hypertensive disorder.[15,18]

GA, birthweight for GA

We extracted data on birth outcomes and medical conditions from the medical records. GA was confirmed using both the first day of the last menstrual period and early (<20 weeks of gestation) ultra-sonographic results, as described previously.[17] Preterm birth was defined as GA less than 37 weeks.[19] Neonates were categorized into three groups: SGA (<10th percentile), large for gestational age (LGA, >90th percentile), and appropriate for gestational age (*AGA, 10th–90th percentile)[20] based on birth weight categories.

Plasma adipokines assays

Umbilical cord blood was collected at delivery. Plasma was processed immediately after collection and stored in a −80°C freezer. Leptin concentrations were determined using sandwich immunoassays based on flow metric xMAP technology on Luminex 200 machines (Luminex Corp., Austin, TX) with an inter-assay coefficient of variation (CV) of 4.5%. Adiponectin was measured by ELISA with an inter-assay CV of <5.8%. The immunoassay kit was obtained commercially from Millipore Corp. Each sample was run in duplicate, and the intra-assay CVs for leptin and adiponectin were 4.3% and 2.9%, respectively. Units of measurements are in pg/mL for leptin and ng/mL for adiponectin.

Statistical analysis

Our primary outcomes were cord leptin and adiponectin levels (log-transformed). We used logistic regression models to estimate the crude and adjusted associations of maternal and fetal factors with cord leptin and adiponectin levels. We adjusted for GA in model 1, birth weight in model 2, and all maternal and fetal factors (including GA and birth weight) in model 3. Maternal and fetal factors included infant sex, delivery type, growth status at birth, GA in completed weeks, maternal age (<20, 20–35, ≥35 years), maternal race (Black, non-Black including all other race in the BBC), smoking (never smoker, previous smoker, active smoker), education (below high school, high school graduate, college graduate or above), antenatal steroid use (yes, no), antenatal and index pregnancy stress (mild, average–severe), diabetes (no, gestational, pregestational), hypertensive disorders (yes, no), drug use (yes, no), and maternal OWO (yes, no), and type of preterm birth (spontaneous, medically indicated). As planned *a priori*, in the subgroup analysis for preterm infants we added "any" and "completed" antenatal steroids as additional variables in model 3. Additionally, we conducted a stepwise regression for preterm infants. Stata 15.2 (StataCorp. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP; 2015.) was used to conduct all analyses. We considered a 2-sided *P* value <0.05 as statistically significant.[21]

Results

Table 1 summarizes the characteristics of the 1012 mother–infant pairs included in this analysis; 245 (24%) children were born preterm. Mothers who delivered preterm infants were more likely to have had drug exposure in pregnancy, experienced cesarean delivery, had GDM and hypertensive disorders, and had a higher proportion of antenatal steroid use. Cord leptin (10.2 ± 0.9 *vs.* 9.2 ± 1.3) and adiponectin (9.5 ± 0.7 *vs.* 8.9 ± 0.8) levels were higher in term infants than preterm infants ($P < 0.0001$). Cord leptin was higher for Black infants (10.1 ± 1.1 *vs.* 9.9 ± 1.2; $P < 0.001$) although Black infants had lower cord adiponectin levels (9.3 ± 0.8 *vs.* 9.5 ± 0.7; $P = 0.01$). When analyzed for birth growth status, cord leptin was highest in infants born LGA (10.6 ± 1.1, $n = 109$) and lowest for SGA infants (9.2 ± 1.1, $n = 109$) as compared to AGA infants (9.9 ± 1.1, $n = 792$; $P < 0.001$), while cord adiponectin did not statistically differ by birth growth status (LGA: 9.4 ± 0.7; SGA: 9.3 ± 0.7; AGA: 9.4 ± 0.8; $P = 0.3$). Ratio of adiponectin to leptin (log normalized) was higher in preterm infants (–0.24) *vs.* term infants (–0.69).

Figure 1 depicts the distribution of cord leptin (A), adiponectin (B), and adiponectin:leptin ratio (C) tracked by GA (weekly interval). Both cord leptin and adiponectin levels were directly related to increasing GA with a major increase in the third trimester for cord leptin. On the other hand, adiponectin: leptin ratio decreased by increase in GA.

Table 2 shows the multivariable regression analysis for factors affecting cord leptin (log normalized). Factors associated positively with cord leptin in the final model (model 3) included GA, birth weight *z* score, Black race, maternal OWO, maternal GDM and diabetes mellitus (DM and male sex and SGA was found to be negatively associated with cord leptin). Stepwise regression analysis revealed GA, birth weight *z* score, maternal OWO, Black race, GDM and maternal DM, higher maternal age, average index pregnancy stress to be positively associated and male sex, SGA, average and severe general pregnancy stress, severe index pregnancy stress, vaginal delivery and *in utero* drug exposure to be negatively associated with cord leptin levels (data not shown). For preterm infants, multivariable regression (Supplementary Table 2, http://links.lww.com/PN9/A8) revealed positive association of cord leptin with GA, birth weight *z* score, and GDM and a negative association with male sex and severe general maternal stress. Stepwise regression for preterm infants revealed a positive association with GA, birth weight *z* score, GDM and maternal DM, maternal hypertension, higher maternal age, maternal OWO and average index pregnancy stress and a negative association with male sex, severe index pregnancy stress, *in utero* drug exposure and average and severe general pregnancy stress (data not shown).

Table 3 shows the multivariable regression analysis for factors affecting cord adiponectin (log normalized). Factors associated positively with cord adiponectin in the final model (model 3)

Table 1

Characteristics of the mothers and children included in this analysis (with both cord leptin and adiponectin available).

Variables, *n* (%)	Preterm (*N* = 245)	Term (*N* = 767)
Birth weight, g, mean (SD)	2255.23 (689.88)	3265.09 (521.77)
Gestational age, weeks, mean (SD)	34.04 (3.01)	39.41 (1.25)
Child sex		
Male	127 (51.84%)	383 (49.93%)
Female	118 (48.16%)	384 (50.07%)
Delivery type		
Vaginal	145 (59.18%)	518 (67.89%)
C section	100 (40.82%)	245 (32.11%)
Any antenatal steroids	74 (30.20%)	4 (0.52%)
Antenatal steroid completed	52 (29.38%)	4 (9.52%)
Maternal race		
Black	140 (57.14%)	436 (56.84%)
Non-Black	105 (42.86%)	331 (43.16%)
Maternal age		
20–35	174 (71.02%)	560 (73.01%)
<20	22 (8.98%)	71 (9.26%)
≥35	49 (20.00%)	136 (17.73%)
Maternal education		
Below high school	81 (33.33%)	221 (29.00%)
High school graduate	134 (55.14%)	425 (55.77%)
College graduate or above	28 (11.52%)	116 (15.22%)
Nulliparity	101 (41.63%)	325 (42.37%)
Smoking		
Never smoker	185 (75.82%)	636 (84.13%)
Previous smoker	21 (8.61%)	50 (6.61%)
Active smoker	38 (15.57%)	70 (9.26%)
General maternal stress		
Mild	85 (35.12%)	295 (38.76%)
Average–severe	157 (64.88%)	466 (61.24%)
Stress during index pregnancy		
Mild	87 (35.95%)	290 (38.16%)
Average–severe	155 (64.05%)	470 (61.84%)
Maternal overweight or obese	135 (57.45%)	365 (50.07%)
In utero drug exposure	18 (7.35%)	3 (0.39%)
Maternal diabetes mellitus		
No diabetes mellitus	205 (83.67%)	682 (89.15%)
Gestational diabetes mellitus	21 (8.57%)	57 (7.45%)
Diabetes mellitus	19 (7.76%)	26 (3.40%)
Hypertensive disorders	62 (25.31%)	82 (10.69%)
Log cord leptin, pg/mL, mean (SD)	9.2 (1.3)	10.2 (0.9)
Log cord adipo, ng/mL, mean (SD)	8.9 (0.8)	9.5 (0.7)
Log adipo/leptin ratio, mean (SD)	–0.24 (1.29)	–0.69 (1.09)

Numbers are reported as *n* (%) unless specified.
SD, standard deviation.

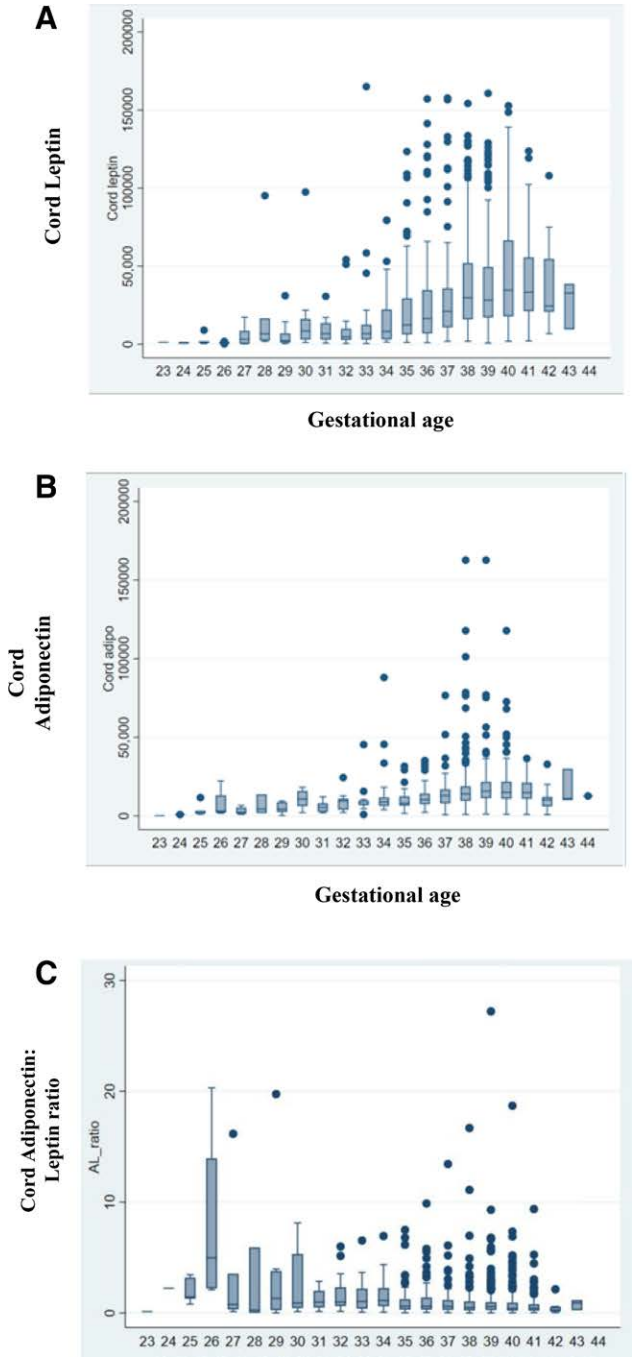

Figure 1 : (A) Distribution of cord leptin by gestational age (in weekly increments). (B) Distribution of cord adiponectin by gestational age (in weekly increments). (C) Distribution of cord adiponectin/leptin ratio by gestational age (in weekly increments).

included GA, and below high school maternal education. Male sex was the only factor showing negative association with cord adiponectin in the final model. Stepwise regression analysis for cord adiponectin revealed GA and birth weight *z* score to be positively associated and male sex, Black race, average and severe general pregnancy stress and higher maternal education to be negatively associated with cord adiponectin levels (data not shown). Multivariable regression for preterm infants (Supplementary Table 3, http://links.lww.com/PN9/A8) revealed positive association of cord adiponectin with GA and birth weight *z* score and negative association with higher maternal education (college graduate and above). Stepwise regression analysis for preterm infants revealed a positive association with GA and birth weight *z* score and a negative association with male sex, higher maternal education, Black race and LGA birth status (data not shown).

Table 4 shows the multivariable regression analysis for factors affecting cord adiponectin:leptin ratio (log normalized). Factors associated positively with cord adiponectin:leptin ratio in the final model (model 3) were male sex. Factors associated negatively with cord adiponectin:leptin ratio were birth weight *z* score, GA, Black race, GDM, and DM. Stepwise regression analysis revealed male sex, *in utero* drug exposure, and vaginal delivery to be positively associated with adiponectin:leptin ratio and birth weight *z* score, GA, Black race, average index pregnancy stress, maternal OWO, higher maternal education, GDM, and maternal DM to be negatively associated with adiponectin:leptin ratio (data not shown). Multivariable regression for the preterm subgroup (Supplementary Table 4, http://links.lww.com/PN9/A8) revealed positive association of cord adiponectin:leptin ratio with male sex and a negative association with GA and Black race in the final model (model 3). Stepwise regression for preterm infants revealed a positive association of cord adiponectin:leptin with, severe index pregnancy stress, average and severe general pregnancy stress and male sex to be positively associated and birth weight *z* score, GA, maternal hypertension, Black race, maternal OWO, higher maternal age, medically induced preterm delivery and maternal DM to be negatively associated with cord adiponectin:leptin (data not shown).

Discussion

Our study makes several novel contributions to our understanding of the fetal origins of metabolic disorders pertaining to adipokines balance at birth. We found independent associations between leptin, adiponectin, and adiponectin:leptin ratio in cord plasma and several maternal and fetal factors as summarized in Supplementary Table 1A http://links.lww.com/PN9/A8 (full cohort) and Supplementary Table 1B http://links.lww.com/PN9/A8 (preterm infants only). Findings from this study could have direct relevance to understanding and improving early risk assessment of metabolic dysfunction, paving the way to potential primordial prevention and precision nutrition strategies in this high-risk population.

Associations of cord adipokines with GA and birth weight have been reported in the literature.[16,22] Previous study from BBC also reported a dose-dependent association of leptin[15] with GA and this current study reports a positive association of GA and birth weight *z* scores with cord leptin and adiponectin in both term and preterm infants and a negative association with adiponectin:leptin ratio. Studies from non-US population have reported lower leptin levels in SGA infants and higher leptin levels in LGA infants even after adjusting for prematurity and several maternal factors.[5,23–26] In this current analysis, we found that cord adiponectin was negatively associated with LGA status only for preterm infants. LGA infants have an increased risk of obesity, cardiovascular and metabolic complications during life.[27] LGA infants even when born to non-diabetic mothers have elevated cord leptin levels compared to AGA infants suggesting a disturbance in adipokines balance.[24,27] This adipokines imbalance has been reported to be associated with subsequent central obesity in children.[24,28]

Table 2

Multivariable regression of maternal and fetal factors with cord leptin levels (log normalized).

Variables	Unadjusted Coefficient (95% CI)	Model 1: adjusted for GA Coefficient (95% CI)	Model 2: adjusted for birth weight *z* score Coefficient (95% CI)	Model 3* Coefficient (95% CI)
GA	0.19 (0.17–0.21)†	NA	0.19 (0.18–0.22)†	0.21 (0.19–0.23)†
Birth weight *z* score	0.38 (0.32–0.45)†	0.42 (0.36–0.47)†	NA	0.33 (0.24–0.42)†
Birth growth status (ref: AGA)				
SGA	−0.76 (−0.97 to −0.54)†	−0.85 (−1.03 to −0.66)†	−0.19 (−0.46 to 0.08)	−0.26 (−0.49 to −0.01)†
LGA	0.64 (0.43 to 0.86)†	0.65 (0.46 to 0.83)†	−0.02 (−0.32 to 0.27)	−0.11 (−0.36 to 0.14)
Male sex (ref: female)	−0.36 (−0.50 to −0.22)†	−0.37 (−0.49 to −0.25)†	−0.32 (−0.45 to −0.19)†	−0.37 (−0.47 to −0.26)†
Black race (ref: non-Black)	0.16 (0.02–0.30)†	0.24 (0.12–0.36)†	0.12 (−0.01 to 0.25)	0.16 (0.05–0.28)†
C section delivery (ref: vaginal)	−0.04 (−0.19 to 0.09)	0.14 (0.01–0.26)†	−0.08 (−0.22 to 0.05)	0.09 (−0.03 to 0.22)
Type of preterm birth (ref: spontaneous)	0.03 (−0.12 to 0.17)	0.02 (−0.11 to 0.14)	0.06 (−0.07 to 0.20)	0.003 (−0.12 to 0.13)
Maternal smoking (ref: never smoker)				
Previous smoker	−0.14 (−0.42 to 0.13)	−0.07 (−0.31 to 0.16)	−0.15 (−0.40 to 0.11)	−0.13 (−0.34 to 0.09)
Active smoker	−0.41 (−0.64 to −0.19)†	−0.34 (−0.54 to −0.16)†	−0.27 (−0.49 to −0.06)†	−0.11 (−0.30 to 0.07)
Maternal hypertensive disorders	−0.24 (−0.43 to −0.05)†	0.13 (−0.03 to 0.30)	−0.21 (−0.38 to −0.03)†	0.06 (−0.10 to 0.22)
Maternal overweight or obese	0.30 (0.16–0.44)†	0.35 (0.23–0.47)†	0.17 (0.04–0.31)†	0.14 (0.02–0.25)†
Maternal diabetes mellitus (ref: no maternal diabetes mellitus)				
Gestational diabetes mellitus	0.52 (0.27–0.78)†	0.57 (0.36–0.79)†	0.30 (0.05–0.54)†	0.35 (0.14–0.55)†
Diabetes mellitus	0.42 (0.08–0.75)†	0.66 (0.37–0.94)†	0.24 (−0.08 to 0.55)	0.39 (0.13–0.67)†
General maternal stress (ref: mild)				
Average	−0.09 (−0.23 to 0.06)	−0.03 (−0.15 to 0.09)	−0.08 (−0.22 to 0.06)	−0.10 (−0.29 to 0.10)
Severe	−0.37 (−0.61 to −0.13)†	−0.24 (−0.44 to −0.03)†	−0.31 (−0.53 to 0.09)†	−0.18 (−0.46 to 0.09)
Stress during index pregnancy (ref: mild)				
Average	0.03 (−0.12 to 0.18)	0.06 (−0.07 to 0.19)	0.02 (−0.13 to 0.16)	0.17 (−0.03 to 0.36)
Severe	−0.32 (−0.51 to −0.12)†	−0.19 (−0.36 to −0.03)†	−0.26 (−0.44 to −0.08)†	−0.03 (−0.27 to 0.21)
Maternal age (ref: 25–35 years)				
<20	−0.17 (−0.42 to 0.07)	−0.19 (−0.40 to 0.02)	−0.08 (−0.31 to 0.15)	0.0005 (−0.20 to 0.20)
≥35	0.13 (−0.05 to 0.31)	0.21 (0.06 to 0.37)†	0.07 (−0.09 to 0.24)	0.11 (−0.12 to 0.35)
Maternal education (ref: high school)				
Below high school	0.01 (−0.15 to 0.17)	0.01 (−0.13 to 0.15)	−0.01 (−0.16 to 0.14)	0.02 (−0.11 to 0.15)
College graduate or above	0.15 (−0.05 to 0.36)	0.05 (−0.12 to 0.23)	0.15 (−0.04 to 0.34)	0.09 (−0.07 to 0.26)
In utero drug exposure	−1.29 (−1.7 to −0.81)†	−0.71 (−1.13 to −0.29)†	−1.12 (−1.57 to −0.67)†	−0.37 (−0.78 to 0.03)

*Model 3: adjusted for the following variables: GA, birth weight *z* score, birth growth status, sex, race, type of delivery, type of preterm delivery, maternal hypertension, maternal OWO, maternal smoking status, maternal diabetes, maternal index and general stress, maternal age and education and *in utero* drug exposure.

†Statistically significant.

AGA, appropriate for gestational age; CI, confidence interval; GA, gestational age; LGA, large for gestational age; NA, not applicable; SGA, small for gestational age.

Our report of consistent associations of adipokines and GA and birth weight is important as our study covers a US population with a Black predominance. Additionally, our results are from a racial population known to be at high risk of preterm birth, early childhood obesity, and DM which has been historically underrepresented in such studies. Our work helps establish the association of cord adipokines with these variables in a US minority cohort.

We found that cord leptin levels were higher and adiponectin levels were lower in infants born to Black mothers, and these associations held in the preterm subpopulation. This finding potentially suggests racial disparities in metabolic dysfunction beyond prematurity alone. Racial disparities in early childhood obesity are well reported. Childhood obesity rates of 24.2% were reported in non-Hispanic Black children as compared to 16.1% among non-Hispanic White children.[29] Researchers have explored the role of racial differences in early childhood obesity rates,[30,31] although research on impact of racial factors at different stages of life course including early development is lacking. Adult studies have shown that relevant to racial disparities, circulating leptin levels were higher and adiponectin levels were lower in Black (*vs*. White) men taking into account differences in adiposity in a US nationally representative study.[32] One study reported a non-significant higher trend in cord blood leptin (adjusted) in Black male neonates.[33] In a large (n = 10,700) US pediatric study, the authors reported several postnatal risk factors for obesity that differed by race.[34] Additionally, obesity risk profiles for Black children were less favorable than those of white children. The racial differences in leptin and adiponectin levels observed in this analysis could possibly suggest an early metabolic sign that portends future obesity risk. Black neonates have a lower mean birth weight and a higher proportion of low and very low birth weight compared with white neonates. Even then Black infants grow faster in childhood and rapid postnatal growth has been linked to the early onset of childhood obesity.[35,36] Infant weight gain is also known to differ by race.[37] Hence these racial differences in leptin and adiponectin levels at birth could also be an early sign of rapid postnatal growth and future obesogenic risk in Black neonates. This race-specific unfavorable adipokines balance at birth; which is probably a result of unfavorable maternal influences and extends to affect several other obesogenic risk factors in early childhood could serve as an important link explaining an intergenerational risk of obesity. Early identification of these risk factors could guide the planning of interventions that can be implemented early in life and could help curb widening racial disparities in early childhood obesity.

Literature on sex-specific differences for adipokines has been conflicting especially with regards to the age at which these sex-specific differences in childhood obesity begin. These imbalances at birth reported in our study may help highlight the long-term

Table 3

Multivariable regression of maternal and fetal factors with cord adiponectin levels (log normalized).

Variable	Unadjusted Coefficient (95% CI)	Model 1: adjusted for GA Coefficient (95% CI)	Model 2: adjusted for birth weight Coefficient (95% CI)	Model 3* Coefficient (95% CI)
GA	0.10 (0.09–0.12)†	NA	0.10 (0.09–0.12)†	0.10 (0.08–0.12)†
Birth weight *z* score	0.05 (0.01–0.1)†	0.07 (0.03,0.11)†	NA	0.07 (–0.004 to 0.14)
Birth growth status (ref: AGA)				
SGA	–0.15 (–0.29 to –0.01)†	–0.19 (–0.33 to –0.07)†	–0.07 (–0.25 to 0.11)	–0.12 (–0.31 to 0.06)
LGA	0.03 (–0.12 to 0.17)	0.05 (–0.08 to 0.18)	–0.08 (–0.28 to 0.12)	–0.07 (–0.26 to 0.13)
Male sex (ref: female)	–0.12 (–0.19 to –0.02)†	–0.11 (–0.19 to –0.03)†	–0.11 (–0.20 to –0.02)†	–0.09 (–0.18 to –0.007)†
Black race (ref: non-Black)	–0.11 (–0.19 to –0.02)†	–0.09 (–0.17 to –0.01)†	–0.11 (–0.20, –0.02)†	–0.06 (–0.15 to 0.03)
C section delivery (ref: vaginal)	–0.13 (–0.22 to –0.03)†	–0.05 (–0.14 to 0.03)	–0.13 (–0.23 to –0.04)†	–0.02 (–0.12 to 0.08)
Type of preterm birth (ref: spontaneous)	–0.04 (–0.14 to 0.05)	–0.05 (–0.14 to 0.04)	–0.04 (–0.13 to 0.06)	–0.02 (–0.12 to 0.09)
Maternal smoking (ref: never smoker)				
Previous smoker	–0.12 (–0.30 to 0.05)	–0.10 (–0.26 to 0.06)	–0.12 (–0.29 to 0.05)	–0.09 (–0.27 to 0.07)
Active Smoker	–0.02 (–0.16 to 0.13)	0.03 (–0.10 to 0.17)	0.01 (–0.14 to 0.15)	0.07 (–0.08 to 0.22)
Maternal hypertensive disorders	–0.23 (–0.36 to –0.11)†	–0.08 (–0.19 to 0.04)	–0.23 (–0.35 to 0.10)†	–0.01 (–0.14 to 0.12)
Maternal OWO	–0.02 (–0.12 to 0.07)	0.002 (–0.08 to 0.09)	–0.04 (–0.13 to 0.05)	–0.01 (–0.11 to 0.08)
Maternal diabetes mellitus (ref: no maternal diabetes mellitus)				
Gestational diabetes mellitus	0.02 (–0.15 to 0.19)	0.05 (–0.10 to 0.21)	–0.02 (–0.19 to 0.15)	–0.01 (–0.17 to 0.15)
Diabetes mellitus	–0.22 (–0.44 to 0.003)	–0.08 (–0.29 to 0.13)	–0.25 (–0.48 to –0.03)†	0.01 (–0.21 to 0.23)
General maternal stress (ref: mild)				
Average	–0.12 (–0.22 to –0.03)†	–0.11 (–0.19 to –0.02)†	–0.12 (–0.22 to –0.03)†	–0.14 (–0.28 to 0.02)
Severe	–0.24 (–0.40 to –0.09)†	–0.18 (–0.32, –0.04†	–0.24 (–0.39 to –0.09)†	–0.17 (–0.38 to 0.05)
Stress during index pregnancy (ref: mild)				
Average	–0.07 (–0.17 to 0.03)	–0.07 (–0.15 to 0.03)	–0.07 (–0.16 to 0.02)	0.04 (–0.11 to 0.20)
Severe	–0.16 (–0.27 to –0.03)†	–0.11 (–0.22 to 0.01)	–0.15 (–0.27 to –0.03)†	–0.003 (–0.20 to 0.19)
Maternal age (ref: 25–35 years)				
<20	0.03 (–0.12 to 0.17)	–0.02 (–0.12 to 0.16)	0.04 (–0.11 to 0.20)	–0.01 (–0.17 to 0.14)
≥35	–0.12 (–0.23 to –0.002)†	–0.08 (–0.19 to 0.03)	–0.13 (–0.24 to –0.01)†	–0.09 (–0.27 to 0.08)
Maternal education (ref: high school)				
Below high school	0.10 (0.002–0.20)†	0.09 (–0.001 to 0.18)	0.10 (–0.004 to 0.20)	0.10 (0.002–0.21)†
College graduate or above	–0.04 (–0.17 to 0.09)	–0.08 (–0.21 to 0.03)†	–0.04 (–0.17 to –0.09)†	–0.01 (–0.19 to 0.06)
In utero drug exposure	–0.25 (–0.57 to 0.08)	0.07 (–0.23 to 0.38)	–0.22 (–0.55 to 0.10)	0.16 (–0.17 to 0.50)

*Model 3: adjusted for the following variables: GA, birth weight *z* score, birth growth status, sex, race, type of delivery, type of preterm delivery, maternal hypertension, maternal OWO, maternal smoking status, maternal diabetes, maternal index and general stress, maternal age and education and *in utero* drug exposure.

†Statistically significant.

AGA, appropriate for gestational age; CI, confidence interval; GA, gestational age; LGA, large for gestational age; NA, not applicable; OWO, overweight or obese; SGA, small for gestational age.

sexual dimorphism in childhood obesity. Some studies have reported higher levels of adiponectin and leptin in the cord blood of females.[13,37,38] This has been attributed to a higher percentage of fat in females for a similar weight[38] and is proposed by some researchers to be an indication of the sex-specific female advantage in the acquisition and functionality of adipose tissue in fetal life.[5] On the other hand, other studies have reported no sex-specific difference in adiponectin. This lack of consistent association in our and several other studies could be due to several factors like sex-based difference in adipose tissue regulation of leptin production,[38] the fact that body weight does not reflect body fat mass alone,[39] and sexual difference in leptin secretion.[40]

Our analysis also highlights an important association of GDM, maternal DM, and maternal OWO with cord adipokines. Along the lines of fetal programming, maternal diabetes and obesity have been implicated in childhood obesity.[41] Fetal exposure to high maternal glucose leads to fetal hyperinsulinemia which then leads to fetal leptin resistance. This leptin resistance can then lead to overgrowth of fat cells and eventual obesity.[41,42] It has been proposed that altered leptin signaling *in utero* may predispose the fetus for leptin resistance, which could explain the strong association between maternal obesity in pregnancy, LGA status at birth, and obesity in children.[43] Neonates born to obese mothers are prone to develop cardiovascular and metabolic disorders later in life secondary to *in utero* programing from maternal obesity. Similarly, obese mothers with GDM are three times more likely to have LGA or macrosomic babies who have increased adiposity.[44,45] Moreover, GDM diagnosis is associated with increased future risk of obesity, cardiovascular disease, and metabolic disease in both mother and child.[46,47] Maternal obesity has also been associated with low grade inflammatory state due to increased release of adipokines.[48] However, not many studies have explored the link between impaired maternal metabolic health and fetal adiposity programming and even fewer have explored the association at birth (including preterm birth) with cord leptin levels and adiponectin:leptin ratio. Additionally, most of such data stems from studies conducted on non-US population.[49–51] Our analysis highlights a similar link between maternal OWO and diabetes with higher cord leptin which could be an early signal of future obesity, which provides an important clue to a mechanistic relationship between maternal obesity, neonatal adiposity, and childhood obesity in Black neonates. It also suggests that improving the health and nutrition of women in their reproductive age may provide a primordial prevention approach to childhood obesity.

Obesity-related adipose tissue expansion is characterized by an increase in circulating leptin and a decrease in adiponectin levels and adiponectin: leptin has been proposed to be a marker of dysfunctional adipose tissue.[52,53] Adiponectin:leptin correlates negatively with BMI[54] and is a better surrogate of insulin

Table 4

Multivariable regression of maternal and fetal factors with cord adiponectin–leptin ratio (log normalized).

Variable	Unadjusted Coefficient (95% CI)	Model 1: adjusted for GA Coefficient (95% CI)	Model 2: adjusted for birth weight Coefficient (95% CI)	Model 3* Coefficient (95% CI)
GA	−0.08 (−0.10 to −0.06)†	NA	−0.09 (−0.11 to −0.06)†	−0.09 (−0.12 to −0.07)†
Birth weight *z* score	−0.34 (−0.41 to −0.27)†	−0.35 (−0.42 to −0.29)†	NA	−0.28 (−0.39 to −0.17)†
Birth growth status (ref: AGA)				
SGA	0.64 (0.41–0.86)†	0.67 (0.45–0.89)†	0.09 (−0.19 to 0.38)	0.13 (−0.16 to 0.42)
LGA	−0.55 (−0.77 to −0.33)†	−0.57 (−0.79 to −0.35)†	0.09 (−0.22 to 0.40)	0.10 (−0.21 to 0.40)
Male sex (ref: female)	0.26 (0.12–0.40)†	0.27 (0.12–0.39)†	0.22 (0.08–0.36)†	0.26 (0.12–0.39)†
Black race (ref: non-Black)	−0.33 (−0.48 to −0.19)†	−0.35 (−0.49 to −0.21)†	−0.30 (−0.44 to −0.16)†	−0.25 (−0.40 to −0.11)†
C section delivery (ref: vaginal)	−0.14 (−0.29 to 0.01)	−0.21 (−0.36 to −0.06)†	−0.11 (−0.25 to 0.04)	−0.14 (−0.29 to 0.02)
Type of preterm birth (ref: spontaneous)	−0.07 (−0.22 to 0.08)	−0.06 (−0.21 to 0.09)	−0.10 (−0.24 to 0.04)	−0.04 (−0.19 to 0.12)
Maternal smoking (ref: never smoker)				
Previous smoker	0.02 (−0.27 to 0.30)	−0.004 (−0.26 to 0.27)	−0.002 (−0.27 to 0.26)	0.04 (−0.23 to 0.32)
Active Smoker	0.40 (0.17–0.63)†	0.37 (0.14–0.60)†	0.24 (0.02–0.47)†	0.16 (−0.07 to 0.39)
Maternal hypertensive disorders	−0.02 (−0.22 to 0.19)	−0.15 (−0.35 to 0.06)	−0.03 (−0.22 to 0.17)	−0.01 (−0.22 to 0.20)
Maternal OWO	−0.28 (−0.43 to −0.14)†	−0.31 (−0.45 to −0.17)†	−0.17 (−0.31 to −0.03)†	−0.12 (−0.26 to 0.03)
Maternal diabetes mellitus (ref: no maternal diabetes mellitus)				
Gestational diabetes mellitus	−0.43 (−0.70 to −0.19)†	−0.46 (−0.71 to −0.20)†	−0.23 (−0.49 to 0.03)	−0.29 (−0.54 to −0.03)†
Diabetes mellitus	−0.57 (−0.92 to −0.22)†	−0.68 (−1.02 to −0.35)†	−0.39 (−0.73 to −0.06)†	−0.34 (−0.68 to 0.004)†
General maternal stress (ref: mild)				
Average	−0.13 (−0.29 to 0.02)	−0.15 (−0.29 to 0.005)	−0.14 (−0.29 to −0.02)	−0.04 (−0.29 to 0.19)
Severe	0.09 (−0.16 to 0.034)	0.04 (−0.20 to 0.28)	0.04 (−0.20 to 0.27)	0.03 (−0.32 to 0.37)
Stress during index pregnancy (ref: mild)				
Average	−0.18 (−0.34 to −0.02)†	−0.18 (−0.33 to −0.03)†	−0.17 (−0.32 to −0.041†	−0.17 (−0.41 to 0.08)
Severe	0.08 (−0.12 to 0.27)	0.04 (−0.15 to 0.24)	0.03 (−0.15 to 0.22)	−0.01 (−0.31 to 0.29)
Maternal age (ref: 25–35 years)				
<20	0.33 (0.08–0.57)†	0.33 (0.09–0.57)†	0.25 (0.01–0.48)†	−0.13 (−0.37 to 0.12)
≥35	−0.17 (−0.35 to 0.02)	−0.20 (−0.38 to −0.02)†	−0.12 (−0.30 to −0.06)	−0.22 (−0.51 to 0.07)
Maternal education (ref: high school)				
Below high school	0.10 (−0.06 to 0.26)	0.09 (−0.07 to 0.25)	0.11 (−0.04 to 0.27)	0.06 (−0.09 to 0.22)
College graduate or above	−0.19 (−0.40 to 0.02)	−0.16 (−0.36 to 0.05)	−0.18 (−0.38 to 0.02)	−0.18 (−0.39 to 0.02)
In utero drug exposure	1.01 (0.52–1.52)†	0.79 (0.30–1.3)†	0.84 (0.36–1.32)†	0.46 (−0.05 to 0.97)

*Model 3: adjusted for the following variables: GA, birth weight *z* score, birth growth status, sex, race, type of delivery, type of preterm delivery, maternal hypertension, maternal OWO, maternal smoking status, maternal diabetes, maternal index and general stress, maternal age and education and *in utero* drug exposure.

†Statistically significant.

AGA, appropriate for gestational age; CI, confidence interval; GA, gestational age; LGA, large for gestational age; OWO, overweight or obese; NA, not applicable; SGA, small for gestational age.

resistance and metabolic syndrome than adiponectin and leptin alone.[55,56] Since the adiponectin:leptin ratio reflects the functionality of adipose tissue, this ratio serves as a clinically useful biomarker for susceptibility to cardiometabolic diseases.[56] Early identification of factors impacting this clinically important ratio could help guide screening and intervention strategies immediately after birth. In our analysis, we reported a negative association between Black race and maternal GDM with adiponectin:leptin ratio, signifying a possible positive correlation with BMI and other obesity-related adverse outcomes in future.

Limitations of our study include the lack of several maternal factors that could affect fetal metabolic status. Maternal diet and nutritional balance before and during pregnancy have been implicated in fetal metabolic maladaptation in several animal and epidemiological studies.[8,57] We did not have data on maternal gestational weight gain, although we included maternal pre-pregnancy OWO in the model, which has been reported to be more critical than gestational weight gain in affecting obesity risk in children.[58] Second, we only examined factors affecting cord blood adipokines and did not explore other hormones like insulin. We have explored cord insulin in a previous publication[59] and we intend to study the interactions of adipokines and insulin in the future. Finally, we have not explored other adipokines in this analysis that have been associated with adiposity such as resistin and ghrelin.[5,16]

Our study adds important information on adipokines profile in preterm and term neonates in a large US-based minority sample. An important dimension of our study is the extensive study of the association with sociodemographic factors that could predict a metabolically maladapted neonate beyond prematurity and anthropometric associations. Our results may help classify neonates at risk of future adverse cardiometabolic health who could benefit from primordial prevention or postnatal interventions during a potential therapeutic window that could reverse developmental metabolic programming.[8,60] An adipokine-based stratification of neonates at risk of future adiposity could supplement development of sophisticated models for nutritional recommendations along the theme of precision nutrition. Further study of the trajectory of these adipokines, their interaction with insulin and early childhood markers of metabolic syndrome will be crucial to evaluate the possible role of adipokines in early childhood adiposity.

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Author Contributions

K.M., X.W., and M.Z. conceptualized this study, performed the statistical analyses, drafted the initial manuscript, reviewed and revised the manuscript, and take responsibility for all the contents of this manuscript. K.A. assisted with the study design and critically reviewed the manuscript for important reviewed and revised the manuscript. X.H. and G.W. performed lab assay of the cord plasma leptin and adiponectin, managed epidemiological and clinical and laboratory data, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflicts of Interest

None.

References

[1] Gluckman PD, Hanson MA, Spencer HG. Predictive adaptive responses and human evolution. Trends Ecol Evol 2005;20(10):527–533. doi:10.1016/j.tree.2005.08.001.
[2] Barker DJ. The fetal and infant origins of adult disease. BMJ 1990;301(6761):11111111.–111111111.doi:10.1136/bmj.301.6761.1111.
[3] Hales CN. Fetal and infant origins of adult disease. J Clin Pathol 1997;50(5):359. doi:10.1136/jcp.50.5.359.
[4] Martin CR. Preventing bioenergetic failure in the preterm infant. Arch Dis Child Fetal Neonatal Ed 2016;101(2):F99–F101. doi:10.1136/archdischild-2015-308221.
[5] Han L, Li B, Xu X, et al. Umbilical cord blood adiponectin, leptin, insulin, and ghrelin in premature infants and their association with birth outcomes. Front Endocrinol 2021;12:738964. doi:10.3389/fendo.2021.738964.
[6] Park HK, Ahima RS. Physiology of leptin: energy homeostasis, neuroendocrine function and metabolism. Metabolism 2015;64(1):24–34. doi:10.1016/j.metabol.2014.08.004.
[7] Zhang Y, Scarpace PJ. The role of leptin in leptin resistance and obesity. Physiol Behav 2006;88(3):249–256. doi:10.1016/j.physbeh.2006.05.038.
[8] Vickers MH. Developmental programming and adult obesity: the role of leptin. Curr Opin Endocrinol Diabetes Obes 2007;14(1):17–22. doi:10.1097/MED.0b013e328013da48.
[9] Nedvídková J, Smitka K, Kopský V, et al. Adiponectin, an adipocyte-derived protein. Physiol Res 2005;54(2):133–140. PMID: 15544426.
[10] Stefan N, Bunt JC, Salbe AD, et al. Plasma adiponectin concentrations in children: relationships with obesity and insulinemia. J Clin Endocrinol Metab 2002;87(10):4652–4656. doi:10.1210/jc.2002-020694.
[11] Martos-Moreno GA, Barrios V, Chowen JA, et al. Adipokines in childhood obesity. Vitam Horm 2013;91:107–142. doi:10.1016/B978-0-12-407766-9.00006-7.
[12] Kajantie E, Hytinantti T, Hovi P, et al. Cord plasma adiponectin: a 20-fold rise between 24 weeks gestation and term. J Clin Endocrinol Metab 2004;89(8):4031–4036. doi:10.1210/jc.2004-0018.
[13] Martos-Moreno GA, Barrios V, Sáenz de Pipaón M, et al. Influence of prematurity and growth restriction on the adipokine profile, IGF1, and ghrelin levels in cord blood: relationship with glucose metabolism. Eur J Endocrinol 2009;161(3):381–389. doi:10.1530/EJE-09-0193.
[14] Luu TM, Rehman Mian MO, Nuyt AM. Long-term impact of preterm birth: neurodevelopmental and physical health outcomes. Clin Perinatol 2017;44(2):305–314. doi:10.1016/j.clp.2017.01.003.
[15] Wang G, Divall S, Radovick S, et al. Preterm birth and random plasma insulin levels at birth and in early childhood. JAMA 2014;311(6):587–596. doi:10.1001/jama.2014.1.
[16] Ng PC, Lee CH, Lam CWK, et al. Resistin in preterm and term newborns: relation to anthropometry, leptin, and insulin. Pediatr Res 2005;58(4):725–730. doi:10.1203/01.PDR.0000180556.76864.9A.
[17] Wang X, Zuckerman B, Pearson C, et al. Maternal cigarette smoking, metabolic gene polymorphism, and infant birth weight. JAMA 2002;287(2):195–202. doi:10.1001/jama.287.2.195.
[18] Bustamante Helfrich B, Chilukuri N, He H, et al. Maternal vascular malperfusion of the placental bed associated with hypertensive disorders in the Boston Birth Cohort. Placenta 2017;52:106–113. doi:10.1016/j.placenta.2017.02.016.
[19] Engle WA; American Academy of Pediatrics Committee on Fetus and Newborn. Age terminology during the perinatal period. Pediatrics 2004;114(5):1362–1364. doi:10.1542/peds.2004-1915.
[20] Wang L, Wang X, Laird N, et al. Polymorphism in maternal LRP8 gene is associated with fetal growth. Am J Hum Genet 2006;78(5):770–777. doi:10.1086/503712.
[21] StataCorp. Stata Statistical Software: Release 14. College Station. TX: StataCorp LP; 2015.
[22] Yoshida T, Nagasaki H, Asato Y, et al. The ratio of high-molecular weight adiponectin and total adiponectin differs in preterm and term infants. Pediatr Res 2009;65(5):580–583. doi:10.1203/PDR.0b013e3181995103.
[23] Kamoda T, Saitoh H, Saito M, et al. Serum adiponectin concentrations in newborn infants in early postnatal life. Pediatr Res 2004;56(5):690–693. doi:10.1203/01.PDR.0000142711.24999.8A.
[24] Lausten-Thomsen U, Christiansen M, Hedley PL, et al. Adipokines in umbilical cord blood from children born large for gestational age. J Pediatr Endocrinol Metab 2016;29(1):33–37. doi:10.1515/jpem-2014-0502.
[25] Tsai PJ, Yu CH, Hsu SP, et al. Cord plasma concentrations of adiponectin and leptin in healthy term neonates: positive correlation with birthweight and neonatal adiposity. Clin Endocrinol 2004;61(1):88–93. doi:10.1111/j.1365-2265.2004.02057.x.
[26] Donnelly JM, Lindsay KL, Walsh JM, et al. Fetal metabolic influences of neonatal anthropometry and adiposity. BMC Pediatr 2015;15:175. doi:10.1186/s12887-015-0499-0.
[27] Viswanathan S, McNelis K, Makker K, et al. Childhood obesity and adverse cardiometabolic risk in large for gestational age infants and potential early preventive strategies: a narrative review. Pediatr Res 2021. doi:10.1038/s41390-021-01904-w. Epub ahead of print. PMID: 34916624.
[28] Dong Y, Luo ZC, Nuyt AM, et al. Large-for-gestational-age may be associated with lower fetal insulin sensitivity and β-cell function linked to leptin. J Clin Endocrinol Metab 2018;103(10):3837–3844. doi:10.1210/jc.2018-00917.
[29] Childhood Obesity Facts. 2022. Available from: https://www.cdc.gov/obesity/data/childhood.html#:~:text=Childhood%20obesity%20is%20also%20more,among%20non%2DHispanic%20Asian%20children. [Accessed June 8, 2022].
[30] Weden MM, Brownell P, Rendall MS. Prenatal, perinatal, early life, and sociodemographic factors underlying racial differences in the likelihood of high body mass index in early childhood. Am J Public Health 2012;102(11):2057–2067. doi:10.2105/AJPH.2012.300686.
[31] Guerrero AD, Mao C, Fuller B, et al. Racial and ethnic disparities in early childhood obesity: growth trajectories in body mass index. J Racial Ethn Health Disparities 2016;3(1):129–137. doi:10.1007/s40615-015-0122-y.
[32] Ruhl CE, Everhart JE. Leptin concentrations in the United States: relations with demographic and anthropometric measures. Am J Clin Nutr 2001;74(3):295–301. doi:10.1093/ajcn/74.3.295.
[33] Lai GY, Rohrmann S, Agurs-Collins T, et al. Racial variation in umbilical cord blood leptin concentration in male babies. Cancer Epidemiol Biomarkers Prev 2011;20(4):665–671. doi:10.1158/1055-9965.EPI-10-0283.
[34] Isong IA, Rao SR, Bind MA, et al. Racial and ethnic disparities in early childhood obesity. Pediatrics 2018;141(1):e20170865. doi:10.1542/peds.2017-0865.
[35] Komlos J, Breitfelder A. Differences in the physical growth of US-born black and white children and adolescents ages 2-19, born 1942-2002. Ann Hum Biol 2008;35(1):11–21. doi:10.1080/03014460701747176.
[36] Taveras EM, Gillman MW, Kleinman K, et al. Racial/ethnic differences in early-life risk factors for childhood obesity. Pediatrics 2010;125(4):686–695. doi:10.1542/peds.2009-2100.

[37] Lau SM, Hng TM, de Vries B, et al. Sexual dimorphism of high molecular weight adiponectin in cord blood. Clin Endocrinol 2009;70(3):500–501. doi:10.1111/j.1365-2265.2008.03373.x.
[38] Tome MA, Lage M, Camiña JP, et al. Sex-based differences in serum leptin concentrations from umbilical cord blood at delivery. Eur J Endocrinol 1997;137(6):655–658. doi:10.1530/eje.0.1370655.
[39] Jaquet D, Leger J, Tabone MD, et al. High serum leptin concentrations during catch-up growth of children born with intrauterine growth retardation. J Clin Endocrinol Metab 1999;84(6):1949–1953. doi:10.1210/jcem.84.6.5744.
[40] Van Harmelen V, Reynisdottir S, Eriksson P, et al. Leptin secretion from subcutaneous and visceral adipose tissue in women. Diabetes 1998;47(6):913–917. doi:10.2337/diabetes.47.6.913.
[41] Huang JS, Lee TA, Lu MC. Prenatal programming of childhood overweight and obesity. Matern Child Health J 2007;11(5):461–473. doi:10.1007/s10995-006-0141-8.
[42] Plagemann A. Perinatal programming and functional teratogenesis: impact on body weight regulation and obesity. Physiol Behav 2005;86(5):661–668. doi:10.1016/j.physbeh.2005.08.065.
[43] Bouret SG. Nutritional programming of hypothalamic development: critical periods and windows of opportunity. Int J Obes Suppl 2012;2(Suppl 2):S19–S24. doi:10.1038/ijosup.2012.17.
[44] Harper LM, Tita A, Biggio JR. The institute of medicine guidelines for gestational weight gain after a diagnosis of gestational diabetes and pregnancy outcomes. Am J Perinatol 2015;32(3):239–246. doi:10.1055/s-0034-1383846.
[45] Logan KM, Emsley RJ, Jeffries S, et al. Development of early adiposity in infants of mothers with gestational diabetes mellitus. Diabetes Care 2016;39(6):1045–1051. doi:10.2337/dc16-0030.
[46] Stang J, Huffman LG. Position of the academy of nutrition and dietetics: obesity, reproduction, and pregnancy outcomes. J Acad Nutr Diet 2016;116(4):677–691. doi:10.1016/j.jand.2016.01.008.
[47] Zhao P, Liu E, Qiao Y, et al. Maternal gestational diabetes and childhood obesity at age 9-11: results of a multinational study. Diabetologia 2016;59(11):2339–2348. doi:10.1007/s00125-016-4062-9.
[48] Howell KR, Powell TL. Effects of maternal obesity on placental function and fetal development. Reproduction 2017;153(3):R97–R108. doi:10.1530/REP-16-0495.
[49] Kampmann FB, Thuesen ACB, Hjort L, et al. Increased leptin, decreased adiponectin and FGF21 concentrations in adolescent offspring of women with gestational diabetes. Eur J Endocrinol 2019;181(6):691–700. doi:10.1530/EJE-19-0658.
[50] Lawlor DA, West J, Fairley L, et al. Pregnancy glycaemia and cord-blood levels of insulin and leptin in Pakistani and white British mother-offspring pairs: findings from a prospective pregnancy cohort. Diabetologia 2014;57(12):2492–2500. doi:10.1007/s00125-014-3386-6.
[51] Blais K, Arguin M, Allard C, et al. Maternal glucose in pregnancy is associated with child's adiposity and leptin at 5 years of age. Pediatr Obes 2021;16(9):e12788. doi:10.1111/ijpo.12788.
[52] Vega GL, Grundy SM. Metabolic risk susceptibility in men is partially related to adiponectin/leptin ratio. J Obes 2013;2013:409679. doi:10.1155/2013/409679.
[53] Frühbeck G, Catalán V, Rodríguez A, et al. Adiponectin-leptin ratio is a functional biomarker of adipose tissue inflammation. Nutrients 2019;11(2):454. doi:10.3390/nu11020454.
[54] Lee JM, Kim SR, Yoo SJ, et al. The relationship between adipokines, metabolic parameters and insulin resistance in patients with metabolic syndrome and type 2 diabetes. J Int Med Res 2009;37(6):1803–1812. doi:10.1177/147323000903700616.
[55] Frühbeck G, Catalán V, Rodríguez A, et al. Involvement of the leptin-adiponectin axis in inflammation and oxidative stress in the metabolic syndrome. Sci Rep 2017;7(1):6619. doi:10.1038/s41598-017-06997-0.
[56] Frühbeck G, Catalán V, Rodríguez A, et al. Adiponectin-leptin ratio: a promising index to estimate adipose tissue dysfunction. Relation with obesity-associated cardiometabolic risk. Adipocyte 2018;7(1):57–62. doi:10.1080/21623945.2017.1402151.
[57] McMillen IC, Edwards LJ, Duffield J, et al. Regulation of leptin synthesis and secretion before birth: implications for the early programming of adult obesity. Reproduction 2006;131(3):415–427. doi:10.1530/rep.1.00303.
[58] Voerman E, Santos S, Patro Golab B, et al. Maternal body mass index, gestational weight gain, and the risk of overweight and obesity across childhood: an individual participant data meta-analysis. PLoS Med 2019;16(2):e1002744. doi:10.1371/journal.pmed.1002744.
[59] Makker K, Zhang M, Wang G, et al. Early-life determinants of childhood plasma insulin levels: implications for primordial prevention of diabetes. Pediatr Res 2022. doi:10.1038/s41390-022-02070-3.
[60] Duncan AF, Frankfurt JA, Heyne RJ, et al. Biomarkers of adiposity are elevated in preterm very-low-birth-weight infants at 1, 2, and 3 y of age. Pediatr Res 2017;81(5):780–786. doi:10.1038/pr.2017.11.

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