Published in final edited form as:

Clin Nutr. 2010 October ; 29(5): 622–626. doi:10.1016/j.clnu.2010.03.004.

Maternal diet and cord blood leptin and adiponectin concentrations at birth

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Abstract

Background & Aims—The purpose of this study was to determine the effects of total energy intake, macronutrient intake, and maternal adherence to Mediterranean diet or Alternative Healthy Eating Index (AHEI) on cord blood leptin and adiponectin levels, which have been associated with childhood adiposity.

Methods—We used multivariable linear regression to assess associations of maternal diet, averaged over 1st and 2nd trimesters, with cord blood adipokines of 780 women from the prospective cohort study Project Viva.

Results—Mean (SD) energy intake during pregnancy was 2135 (596) kcal. Mean (SD) cord blood levels of leptin and adiponectin were 9.0 (6.6) ng/ml and 28.6 (6.7) µg/ml, respectively. Neither closer adherence to a Mediterranean/AHEI pattern diet nor energy intake was associated with either cord blood leptin or adiponectin. Protein intake was associated with both marginally lower leptin (−0.22 ng/ml [95% CI −0.41, −0.02] for each 1% of energy) and adiponectin (−0.25 µg/ml [95% CI −0.48, −0.02]).

Conclusions—Closer adherence to a Mediterranean/AHEI pattern diet during pregnancy was not associated with cord blood leptin or adiponectin. Maternal protein intake was weakly but significantly associated with lower cord blood leptin and adiponectin.

Keywords

leptin; adiponectin; Mediterranean diet; Alternative healthy eating index (AHEI); Protein intake

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CONFLICT OF INTEREST STATEMENT

None of the authors had any financial or personal conflict of interest, including work, employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding that could inappropriately bias their work.

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INTRODUCTION

Adiponectin and leptin, adipocyte-secreted hormones, are regulators of energy homeostasis, insulin resistance, glucose and lipid metabolism, atherosclerosis, and inflammation^{1, 2}. Both of these hormones play critical roles in energy homeostasis and metabolism in children and adults^{1, 3}.

We and others have reported that adiponectin and leptin levels in umbilical cord blood directly correlate with fetal weight and adiposity at birth^{4–8}. These findings are of potential physiological importance since both increased and decreased fetal growth are associated with an increased risk of childhood obesity and insulin resistance, diabetes, and cardiovascular disease later in life⁹. We have recently shown that lower levels of cord blood leptin predict higher BMI at the age of 3 years, while higher cord blood adiponectin was associated with higher central adiposity¹⁰. Thus, it is important to examine predictors of these cord blood adipokines, including maternal diet during pregnancy.

Dietary intake affects serum leptin and adiponectin levels in adults. Decreasing energy intake reduces circulating leptin concentrations¹¹. Leptin levels may be affected by both altered caloric intake and, in some studies, macronutrient (especially fat and possibly protein) intake of the diet^{11–13}. Also diets high in fiber or with a lower dietary glycemic index have been associated with lower levels of plasma adiponectin¹³. In addition, we have recently demonstrated that closer adherence to a Mediterranean diet pattern is directly associated with plasma adiponectin concentrations in diabetic women and well as men^{2, 13}.

In addition to the Mediterranean diet, another measure of diet quality, the Alternative Healthy Eating Index (AHEI), is associated with adiponectin concentrations^{13–15}. Both dietary patterns are associated with risk for cardiovascular disease in adults^{14–16}. It is thus possible that maternal adherence to these eating patterns during pregnancy could affect the levels of cord blood adiponectin and leptin.

The aim of this study was to determine the extent to which total energy intake, variation in macronutrient intake, and adherence to a Mediterranean diet or the AHEI during pregnancy are associated with levels of cord blood adiponectin and/or leptin.

METHODS

Subjects

The subjects for this study were participants in Project Viva, a prospective, observational cohort study of gestational factors, pregnancy outcomes, and offspring health. We recruited women who were attending their initial prenatal visit at 8 urban and suburban obstetrical offices of a multi-specialty group practice in eastern Massachusetts during 1999 to 2003. Eligibility criteria included fluency in English, gestational age less than 22 weeks at the initial prenatal clinical appointment, and singleton pregnancy. Details of recruitment and retention procedures are available elsewhere¹⁷. Institutional review boards of participating institutions approved the study. All procedures were in accordance with the ethical standards for human experimentation established by the Declaration of Helsinki.

Of the 2128 women who delivered a live infant, 1622 delivered at one of the two hospitals where we collected umbilical cord blood. At that hospital we obtained cord blood samples from 1022 of 1622 (63%) deliveries. The reasons for not collecting cord blood include participant refusal, hospital staffing, and complicated or preterm deliveries where the infant went right to the neonatal intensive care unit (NICU). Of the 1022 participants, we analyzed cord blood

leptin and adiponectin on 838 participants. For this analysis, we excluded 58 participants who did not complete prenatal nutritional assessments, leaving a cohort for analysis of 780 mother-child pairs. Comparison of the 780 participants in this analysis with the 242 excluded participants showed a higher proportion of maternal white race (74 v. 54%), college or graduate education (68 v. 43%), and annual household income exceeding \$70,000 (63 v. 48%) and lower mean maternal pre-pregnancy BMI (24.7 v. 25.9 kg/m²) and higher mean offspring birth weight (3.54 v. 3.46 kg) but did not differ on mean gestational age at birth (39.7 v. 39.6 weeks).

After obtaining informed consent, we performed in-person study visits with the mother at the end of the 1st and 2nd trimesters of pregnancy and with both mother and child immediately after delivery. Using a combination of questionnaires and interviews, we collected information about a range of sociodemographic factors, lifestyle habits, and medical and reproductive history¹⁸. Mothers reported paternal weight and height. We calculated gestational weight gain as the pre-pregnancy weight subtracted from the last clinically recorded weight before delivery. Infant birth weight was determined from the hospital clinical record. Gestational age was calculated from the last menstrual period, and if the estimate of gestational age from the 2nd trimester ultrasound differed by >10 days, we used that value instead. We calculated birth weight for gestational age z-score as a measure of fetal growth using United States national reference data¹⁸.

Dietary data collection

Maternal diet assessment at both the first and second visits was performed using a semi-quantitative food frequency questionnaire (SFFQ), slightly modified for use in pregnancy and validated from the extensively validated SFFQ used in the Nurses' Health Study and other large cohort studies, as described previously¹⁹. Since reported intakes were comparable between 1st and 2nd trimester visits we used mean responses over both trimesters to reduce variability of the data. Using dietary data from the SFFQ, we developed a modified version of the Mediterranean dietary pattern score^{19, 20}. We calculated the median values of intake of each of 9 food groups that contribute to the score. Participants received a point on the scale if they measured above the median consumption for each of dairy, fish, fruit, legumes, nuts, unsaturated-to-saturated fat ratio, vegetables, and whole grains. They also received a point if intake of red and processed meats was below the median value. Since alcohol consumption is not recommended for pregnant women, this variable was excluded from the score. Thus, Mediterranean dietary pattern scores ranged from 0 to 9, with higher scores indicating closer adherence to a Mediterranean-type diet. Individual components of the score were also analyzed in servings per day, as calculated from the SFFQ.

We also used the Alternate Healthy Eating Index (AHEI), slightly modified for pregnancy (AHEI-P), to measure diet quality on a 90-point scale with each of the following 9 components contributing 10 possible points: vegetables, fruit, ratio of white to red meat, fiber, *trans* fat, ratio of polyunsaturated to saturated fatty acids, and folate, calcium, and iron from foods²¹. We and others previously showed that higher AHEI scores were associated with lower disease and mortality risk in epidemiological and clinical studies^{21, 22}. In Project Viva, the AHEI-P was associated with lower screening blood glucose level during pregnancy and slightly lower risk of developing preeclampsia²¹.

We also assessed macronutrient intakes, expressed as percent of energy. Nutrient intakes were determined using the Harvard nutrient composition database used for the Nurses' Health Study and other large cohort studies¹⁹.

Cord blood measurements

We collected cord blood samples by needle/syringe from the umbilical vein immediately after delivery. We refrigerated whole blood for less than 24 hours and then spun and aliquoted samples for storage in liquid nitrogen (-80°C). We measured cord blood concentrations of leptin and adiponectin on heparin-preserved plasma using radioimmunoassay (RIA; Linco Research Inc, St. Charles, MO, USA) as previously described²³.

Statistical Analyses

We first examined characteristics of participants by Mediterranean diet score categories (low: 0 to 3, middle: 4 to 5, and high: 6 to 9). To calculate unadjusted trend *P* values across Mediterranean dietary score categories, we used Mantel-Haenszel Chi-Square for categorical characteristics and linear regression for continuous characteristics with categories coded as 1 to 3. In multivariate linear models, we used continuous cord blood leptin and adiponectin as dependent variables and Mediterranean diet score as well as the AHEI-P as independent variables. We also assessed total energy intake and intake of macronutrients and each of the components of the Mediterranean diet score as independent variables. To ensure approximate linearity, we first examined independent variables in categories. Since the associations appeared linear, we included these variables as continuous exposures in regression models. We adjusted our multivariate models for maternal race/ethnicity, age, education and pre-pregnancy BMI; glycemic status, hypertension, smoking, energy intake, physical activity, and weight gain during pregnancy; paternal BMI; household income; and child sex, duration of gestation and fetal growth z-score. We conducted all analyses SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

Mean (SD) cord blood leptin and adiponectin concentrations were 9.0 (6.6) ng/ml and 28.6 (6.7) $\mu\text{g/ml}$, respectively. Mean (SD, range) AHEI-P score was 60 (10, 36–85). Mean (SD) maternal Mediterranean dietary pattern score was 4.5 (2.1); 35% scored 0 to 3, 33% scored 4 to 5, and 31% scored 6 to 9. Closer adherence to a Mediterranean dietary pattern in the 1st and 2nd trimesters of pregnancy was associated with healthful maternal health habits and higher socioeconomic status (Table 1), as has been reported previously^{19, 20}. For example, maternal Mediterranean diet score was directly associated with age and inversely associated with both maternal and paternal BMI. Mothers more closely following a Mediterranean diet were less likely to smoke or be inactive and were more likely to be currently married, have a college education, have a family income greater than \$70,000/yr, and be of white race (Table 1). Higher scores were also associated with increased total energy, and percent of energy from carbohydrates and protein, and decreased percent of energy from total fat, mono-unsaturated fat, saturated fat, and total n3 and n6 fatty acids. (Table 1) Mediterranean diet score was not associated with gestational age at birth or fetal growth z-score.

In multivariable analysis, categorical Mediterranean diet score was not associated with concentrations of cord blood leptin (trend *p*-value=0.38) or adiponectin (trend *p*-value=0.93) (Table 2). As shown in Table 3, continuous Mediterranean diet score was not associated with concentrations of cord blood leptin (-0.04 [95% CI $-0.31, 0.22$] for each point; *p* = 0.75) or adiponectin (-0.06 [95% CI $-0.37, 0.25$]; *p* = 0.95). Similarly, continuous AHEI-P was not associated with concentrations of cord blood leptin (0.01 [95% CI $-0.26, 0.27$] for each 5 points; *p* = 0.69) or adiponectin (-0.03 [95% CI $-0.34, 0.28$]; *p* = 0.85).

Regression estimates of cord blood leptin and adiponectin on continuous intake of macronutrients and components of the Mediterranean diet score showed that higher intake of protein was associated with lower cord blood leptin (-0.22 ng/ml [95% CI $-0.41, -0.02$] for

each additional 1% of energy; $p = 0.03$) and lower cord blood adiponectin ($-0.25 \mu\text{g/ml}$ 95% CI $-0.48, -0.02$]; $p = 0.03$) (Table 3). We saw similar results after log transforming cord blood leptin levels to fully normalize leptin (data not shown). Total energy intake, and intake of other macronutrients and components of the Mediterranean diet score were not associated with either cord blood leptin or adiponectin (Table 3).

DISCUSSION

We found that closer adherence to a Mediterranean dietary pattern was associated with better maternal health status and higher socioeconomic status, as has been previously reported^{19, 20}. Neither adherence to a Mediterranean type diet or AHEI-P, however, nor intake of fat or carbohydrates was associated with concentrations of cord blood leptin or adiponectin.

Maternal protein intake was weakly but significantly associated with lower cord blood leptin and adiponectin levels. A recent observational study in adults indicates that a diet rich in protein is associated with decreased leptin and adiponectin levels²⁴. An interventional study of sequential design has also demonstrated that a high protein diet may also decrease plasma leptin concentrations²⁵. In both studies, a high protein diet from lean meat and vegetables reduced appetite and ad libitum caloric intake and thus the decreased leptin was considered to be not a direct effect of high protein diet but a compensatory response. In our study, total energy intake was not associated with leptin level. Adiponectin levels were not examined in these previously published studies.

Our null findings in relation to dietary patterns as predictors of leptin and adiponectin levels are in contrast to findings in observational studies in adult women, where adherence to the Mediterranean diet is associated with plasma levels of adiponectin²⁰. A recent study found that women with a high adherence to the AHEI had 24% higher median total adiponectin¹⁴. Our findings are consistent with prior analyses showing that dietary patterns during pregnancy are not associated with risk of gestational diabetes mellitus or pre-eclampsia²⁶. Adipokine concentrations in the maternal circulation do not correspond directly with cord blood adipokine concentrations due to fetal and/or placental contributions to the respective cord blood levels. Since both the fetus and the placenta contribute to the total amount of cord blood leptin²⁷ and adiponectin²⁸, with the majority of leptin contributed by the placenta^{29, 30}, the above stated findings from prior studies are not mutually exclusive. It is possible that maternal dietary factors appear not to be strongly associated with cord blood levels of leptin or adiponectin because a large percentage of their circulating levels derives from the placenta. Our results do not rule out effects of maternal diet during pregnancy on child obesity-related outcomes, through pathways other than cord blood adipokine levels.

Strengths of the current study include its large size and state of the art methodology used. Although multiple comparisons were performed, the hypotheses tested herein are independent from each other and results reported should not have been materially affected. In addition, we performed multivariate adjustments to control for potential confounding. Finally, our statistically significant data confirm prior observations in adults and extend these observations to cord blood levels of leptin and adiponectin. In contrast to findings in adults, our findings on dietary patterns fail to confirm a role for dietary patterns in determining cord blood adiponectin and leptin levels.

Acknowledgments

This work was supported by NIH grants DK58785, DK79929, DK 081913, DK58845, HD 034568, HL 64925, HL 68041, a discretionary grant from Beth Israel Deaconess Medical Center and by grants from Harvard Medical School and the Harvard Pilgrim Health Care Foundation.

The authors' responsibilities were as follows—LS: drafted the introduction and discussion sections of the manuscript with CSM's input and finalized the manuscript along with CSM; CJW and SLRS: analyzed the data, drafted the methods and results sections of the manuscript with input from CSM; TK: conducted laboratory measurements; EO and MG: collected data and obtained funding for Project Viva and contributed to final manuscript; CSM: conceived the overall study plan, supervised laboratory measurements, guided the statistical analysis, wrote an outline of the draft of the manuscript and revised all subsequent versions and coordinated the entire study; all authors: participated in manuscript revision and approved the final version.

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Bivariate associations between category of maternal Mediterranean diet score during pregnancy and participant characteristics, among 780 mother-infant pairs participating in Project Viva

Table 1

	Total	Scores 0–3 (n=275)	Scores 4–5 (n=260)	Scores 6–9 (n=245)	Trend p-value ^A
	Mean (SD)				
Mediterranean diet score	4.5 (2.1)	2.2 (0.9)	4.5 (0.5)	6.9 (0.9)	<0.0001
Maternal variables					
Age at enrollment (y)	32.2 (5.0)	31.4 (5.3)	32.0 (5.1)	33.3 (4.3)	<0.0001
Pre-pregnancy BMI (kg/m ²)	24.7 (5.3)	25.5 (5.8)	24.7 (5.1)	23.7 (4.7)	<0.0001
Gestational weight gain (kg)	15.7(5.5)	15.4 (5.7)	16.1 (6.0)	15.7 (4.8)	0.55
Physical activity during 2 nd trimester (h/w)	7.0 (7.6)	6.7 (9.5)	7.3 (7.3)	7.0 (5.2)	0.64
	N (%)				
		N (Column %)			
Impaired glucose tolerance or gestational diabetes	136 (18)	43 (16)	49 (19)	44 (18)	0.49
Hypertension before pregnancy	31 (4)	13 (5)	8 (3)	10 (4)	0.68
Smoking during pregnancy	83 (11)	41 (15)	30 (12)	12 (5)	<0.0001
Education, ≥ college degree	531 (68)	146 (53)	186 (72)	199 (81)	<0.0001
Married or cohabitating	731 (94)	244 (89)	247 (95)	240 (98)	<0.0001
Race/ethnicity, white	575 (74)	197 (72)	183 (70)	195 (80)	0.05
Household and paternal variables					
Household income, >\$70,000	452 (63)	144 (56)	159 (69)	149 (63)	0.09
	Mean (SD)				
		Mean (SD)			
Paternal BMI (kg/m ²)	26.5 (4.0)	27.2 (4.2)	26.2 (3.4)	26.0 (4.2)	<0.0001
Maternal diet					
Total energy intake, kcal	2135 (596)	1864 (511)	2159 (567)	2412 (583)	<0.0001
Nutrient intake (% Energy)					
Carbohydrates	54.8 (6.5)	53.1 (7.0)	54.6 (6.3)	57.0 (5.5)	<0.0001
Protein	17.4 (2.6)	17.1 (2.7)	17.5 (2.6)	17.7 (2.3)	0.01
Total fat	29.2 (5.0)	30.9 (5.2)	29.2 (4.6)	27.2 (4.4)	<0.0001
Mono-unsaturated fat	11.0 (2.2)	11.6 (2.3)	11.1 (2.1)	10.3 (2.1)	<0.0001
Poly-unsaturated fat	6.2 (1.4)	6.3 (1.6)	6.2 (1.5)	6.1 (1.2)	0.11

	Total	Scores 0–3 (n=275)	Scores 4–5 (n=260)	Scores 6–9 (n=245)	Trend p-value ^A
Saturated fat	10.9 (2.3)	12.0 (2.3)	10.9 (1.9)	9.8 (2.0)	<0.0001
Total n3 fatty acids	0.52 (0.18)	0.53 (0.18)	0.51 (0.16)	0.50 (0.19)	0.10
Total n6 fatty acids	5.4 (1.3)	5.5 (1.4)	5.5 (1.3)	5.3 (1.1)	0.07
Mediterranean diet score component intake (servings/day)					
Dairy	2.27 (1.36)	1.95 (1.32)	2.21 (1.28)	2.69 (1.38)	<0.0001
Fish	0.23 (0.19)	0.15 (0.13)	0.23 (0.18)	0.33 (0.21)	<0.0001
Fruit	3.03 (1.63)	2.10 (1.10)	2.94 (1.29)	4.18 (1.73)	<0.0001
Legumes	0.19 (0.36)	0.06 (0.11)	0.16 (0.28)	0.37 (0.50)	<0.0001
Nuts	0.43 (0.43)	0.25 (0.31)	0.44 (0.45)	0.62 (0.46)	<0.0001
Red and processed meats	0.65 (0.46)	0.72 (0.41)	0.70 (0.47)	0.52 (0.46)	<0.0001
Vegetables	2.98 (1.59)	2.06 (1.06)	2.93 (1.29)	4.06 (1.70)	<0.0001
Whole grains	1.58 (1.15)	1.02 (0.81)	1.50 (1.09)	2.30 (1.15)	<0.0001
Unsaturated:saturated fat ratio	1.61 (0.30)	1.52 (0.25)	1.61 (0.28)	1.72 (0.34)	<0.0001
Newborn variables					
	Mean (SD)	Mean (SD)			
Cord blood leptin (ng/ml)	9.0 (6.6)	9.4 (6.6)	8.7 (6.1)	9.1 (7.1)	0.58
Cord blood leptin adjusted for fetal growth (ng/ml)	9.0 (6.2)	9.2 (6.3)	8.8 (5.6)	9.1 (6.6)	0.74
Cord blood adiponectin (µg/ml)	28.6 (6.7)	28.9 (6.3)	28.0 (7.2)	28.8 (6.6)	0.90
Gestational age at birth (wk)	39.7 (1.6)	39.7 (1.6)	39.7 (1.6)	39.6 (1.6)	0.98
Fetal growth (bw/ga z-score)	0.27 (0.94)	0.33 (0.94)	0.22 (0.93)	0.28 (0.95)	0.51
Male, n (%)	402 (52)	144 (52)	142 (55)	116 (47)	0.27

^ABased on Mantel-Haenszel chi-square test for categorical variables and linear regression for continuous variables.

Table 2

Multivariable adjusted regression estimates (95% CI) of cord blood leptin and adiponectin on categorical Mediterranean diet score. Data from 780 mother-infant pairs participating in Project Viva^A

	Score 0 to 3	Score 4 to 5 Estimate (95% CI)	Score 6 to 9	Trend p-value
Cord blood leptin, ng/ml	0.0 (Ref)	−0.63 (−1.80, 0.55)	−0.59 (−1.88, 0.70)	0.38
Cord blood adiponectin, µg/ml	0.0 (Ref)	−1.32 (−2.70, 0.05)	−0.09 (−1.60, 1.42)	0.93

^A Adjusted for maternal race/ethnicity, age, education, glycemic status, hypertension, pregnancy smoking, energy intake, physical activity, pre-pregnancy BMI, gestational weight gain; paternal BMI and household income; and child gender, duration of gestation and fetal growth z-score.

Table 3

Multivariable adjusted regression estimates (95% CI) of cord blood leptin and adiponectin on continuous maternal dietary pattern, macronutrient intake, and food group variables. Data from 780 mother-infant pairs participating in Project Viva^A

	Cord blood leptin, ng/ml		Cord blood adiponectin, µg/ml	
	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
Mediterranean diet score (1 point)	−0.04 (−0.31, 0.22)	0.75	−0.06 (−0.37, 0.25)	0.69
AHEI-P (5 points)	0.01 (−0.26, 0.27)	0.95	−0.03 (−0.34, 0.28)	0.85
Total energy intake (100 kcal)	0.00 (−0.08, 0.08)	0.95	0.00 (−0.10, 0.09)	0.92
Nutrient intake (%Energy)				
Carbohydrates	0.04 (−0.03, 0.12)	0.26	0.05 (−0.04, 0.14)	0.32
Protein	−0.22 (−0.41, −0.02)	0.03	−0.25 (−0.48, −0.02)	0.03
Total fat	−0.02 (−0.12, 0.08)	0.71	−0.01 (−0.13, 0.10)	0.83
Mono-unsaturated fat	−0.11 (−0.33, 0.11)	0.31	−0.03 (−0.29, 0.23)	0.83
Poly-unsaturated fat	0.12 (−0.21, 0.46)	0.47	0.11 (−0.28, 0.50)	0.58
Saturated fat	−0.05 (−0.26, 0.17)	0.68	−0.11 (−0.36, 0.15)	0.41
Total n3 fatty acids	1.36 (−1.22, 3.94)	0.30	1.10 (−1.93, 4.13)	0.48
Total n6 fatty acids	0.13 (−0.25, 0.50)	0.50	0.12 (−0.32, 0.56)	0.60
Mediterranean diet score component intake (servings/day)				
Dairy	−0.05 (−0.44, 0.33)	0.78	−0.10 (−0.55, 0.35)	0.66
Fish	−2.33 (−5.11, 0.45)	0.10	−2.14 (−5.41, 1.13)	0.20
Fruit	0.01 (−0.35, 0.38)	0.94	0.09 (−0.34, 0.52)	0.68
Legumes	0.45 (−1.06, 1.95)	0.56	0.19 (−1.58, 1.95)	0.84
Nuts	−0.99 (−2.15, 0.16)	0.09	−0.28 (−1.63, 1.08)	0.69
Red and processed meats	−0.20 (−1.41, 1.01)	0.74	−0.26 (−1.68, 1.15)	0.71
Vegetables	−0.08 (−0.45, 0.29)	0.68	0.36 (−0.08, 0.79)	0.11
Whole grains	−0.19 (−0.65, 0.27)	0.42	−0.39 (−0.92, 0.15)	0.15
Unsaturated:saturated fat ratio	−0.24 (−1.78, 1.29)	0.75	0.63 (−1.18, 2.43)	0.50

^A Adjusted for maternal race/ethnicity, age, education, glycemic status, hypertension, pregnancy smoking, energy intake, physical activity, pre-pregnancy BMI, gestational weight gain; paternal BMI and household income; and child gender, duration of gestation and fetal growth z-score.