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Associations of prenatal and early life dietary inflammatory potential with childhood adiposity and cardiometabolic risk in Project Viva

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Abstract

Background—Limited information exists regarding the association between early-life diet and cardiometabolic risk.

Objectives—Examine associations of Dietary Inflammatory Index (DII) in pregnancy and early childhood (3–5y) with adiposity, blood pressure and metabolic markers in mid-childhood (6–10y).

Methods—Among 992 mother-child pairs from Project Viva, a pre-birth cohort, we examined associations of DII scores with outcomes using multivariable linear regression adjusted for child age and sex and maternal age, BMI, education, parity, smoking, race and income.

Results—Mean (SD) maternal DII in pregnancy was −2.6(1.4) units and in child DII in early childhood was 0.3(0.7). Mean mid-childhood BMI z-score was 0.40(0.98) units. In boys only, DII in early childhood was associated with higher BMIz (adjusted β=0.16 units per unit DII, 95%CI 0.02, 0.29), waist circumference (0.93cm; −0.07, 1.92) and skin fold thicknesses (1.12mm; 0.01, 2.23). DII in the highest quartiles during both pregnancy and in early childhood, compared to the

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lowest quartiles, was associated with higher waist circumference (2.4 cm; 0.14, 4.6) in all children, and BMIz in boys (0.78 units; 0.34, 1.22). Associations with BP and metabolic markers were null.

Conclusions—A pro-inflammatory diet in pregnancy and early childhood may promote the development of adiposity.

Keywords

inflammation; pregnancy; childhood obesity

Introduction

Chronic inflammation, which may stem from a variety of physiologic, psychosocial, and environmental sources, including diet, has an established role in pathogenesis of obesity and cardiometabolic disease in adults. The so-called “Western diet”, which is characterized by a high intake of red meat, high-fat dairy products, refined grains and simple carbohydrates, has been positively associated with markers of inflammation, including higher levels of circulating CRP and Interleukin (IL)-6, as well as cardiometabolic disease risk (1). On the other hand, the Mediterranean and many other “non-Western” diets, which tend to be high in whole grains, fish, fruit and green vegetables and low in red meat and butter, have been associated with lower levels of inflammation (2) and cardiometabolic risk markers (1).

We have recently shown, in the Project Viva cohort, that maternal C-reactive protein (CRP) concentration, a non-specific marker of inflammation, was directly associated with mid-childhood overall and central adiposity (3). Similarly, Lourenco *et al.* reported that CRP in young Brazilian children (< 5 years old) was directly associated with change in body mass index (BMI) z-score measured 5 years later (4). These findings suggest that inflammation during early life may be associated with later obesity risk.

The Dietary Inflammatory Index (DII)™ has been developed and validated to characterize and quantify the cumulative inflammatory potential of individual diet (5). The DII score positively correlates with interval changes in high-sensitivity CRP (hsCRP) in non-pregnant and pregnant adults (5, 6). The DII is not a dietary pattern in itself, but a way to assess the pro- or anti-inflammatory potential of any diet. As such, this scoring can be applied broadly to many cultural contexts. Although diet plays a key role in modulating inflammation, the relationship between early life dietary inflammation and childhood obesity and cardiometabolic risk remains poorly understood.

Here we examined the association of a pro-inflammatory diet during pregnancy and early childhood, using the DII, with obesity and metabolic risk markers in mid-childhood. Given the role of diet in systemic inflammation, and the role of a pro-inflammatory diet in early life on later health outcomes (3–4, 7–8), we hypothesized that dietary inflammation during pregnancy and early childhood would be independently (exposure during either period) and cumulatively (exposure during both periods) associated with offspring BMI, adiposity and markers of cardiometabolic risk in mid-childhood.

Subjects and Methods

Subjects

We analyzed data from participants in Project Viva, a longitudinal cohort of mother and child pairs enrolled from 1999 to 2002 at initial prenatal visits at Atrius Harvard Vanguard Medical Associates, in urban and suburban Eastern Massachusetts. Study procedures for this cohort have been described previously (9). Our final sample consisted of 922 pairs with exposure and outcome data without type one or two diabetes or preterm birth. The Institutional Review Board of Harvard Pilgrim Health Care approved the study.

Exposure

Mothers completed validated semiquantitative food frequency questionnaires (FFQs) at the first (median 9.9 weeks gestation) and second (27.9 weeks gestation) study visits in pregnancy (10).

In early childhood (range 2.8 to 4.9 years, median age 3.1 years) mothers completed another FFQ, previously validated in children (11), for their child's diet over the prior month. We used these data to calculate DII scores for each mother during pregnancy and for each child in early childhood. In Project Viva, first and second trimester DII scores were strongly correlated (Pearson $r=0.61$, $p<0.0001$) and thus, we used the mean for these analyses.

Hebert *et al.* developed the DII to provide an aggregate assessment of dietary inflammation. It is a literature-based, population-adjusted measure of dietary inflammatory potential which we validated with various inflammatory markers, including CRP (12), tumor necrosis factor-alpha and IL-6 in non-pregnant adults (13, 14). A complete description of the DII is available elsewhere (5). Briefly, we calculated DII by first linking the cohort dietary data to a world database that provided a mean and standard deviation for each food parameter included in the DII. Next, we created a z-score by subtracting the "standard global mean" from the amount reported and dividing this value by the standard deviation. We multiplied this centered percentile score for each food parameter by the respective food parameter effect score to obtain a food parameter-specific DII score, which we summed to create the overall DII score for each participant. A higher DII score indicates a more pro-inflammatory diet.

Outcomes

Anthropometric Outcomes—Trained reseach assistants collected measures at an in-person research visit in mid-childhood (range 6–10 years, median 7.7 years) (9). Child waist circumference, weight (Tanita model TBF-300A, Tanita Corporation of America, Inc.) and height (Shorr stadiometer, Shorr Productions) were measured, from which we calculated BMI and age- and sex-specific BMI z-scores using Centers for Disease Control and Prevention 2000 reference data (15). Whole-body dual-x-ray absorptiometry (DXA) scans (Hologic,Bedford, MA) (n=775) were conducted to obtain measures of total, trunk fat mass and fat-free mass (kg) and we calculated fat mass and fat-free mass indices (kg/m^2). Skin fold thicknesses in the subscapular (SS) and triceps (Tr) regions were measured with Holtain calipers (Holtain Ltd, Crosswell, United Kingdom), which were summed (SS+Tr). Blood

pressure was measured 5 times per child and then averaged (Dinamap Pro 100, Critikon, Inc., Tampa, Florida).

Blood collection and assays—Phlebotomists collected children's blood after an overnight fast. We measured plasma fasting glucose enzymatically, and fasting insulin using an electrochemiluminescence immunoassay (Roche Diagnostics, Indianapolis, IN). We estimated insulin resistance using the Homeostatic Model of Insulin Resistance (HOMA-IR=glucose × insulin/22.5). Triglycerides and cholesterol were measured enzymatically with correction for endogenous glycerol. We measured plasma leptin concentrations with a radioimmunoassay (Linco Research, St. Charles, MO). We used an immunoturbidimetric hsCRP assay (Roche Diagnostics, Indianapolis, IN).

We calculated an overall metabolic risk score (n=481) by averaging sex- and cohort-specific internal z-scores for the following variables: systolic blood pressure, log-transformed triglycerides, waist circumference, high density lipoprotein-cholesterol (HDL, scaled inversely), and log-transformed HOMA-IR. There is no standardized definition of metabolic syndrome in children, but this and similar scores have been previously utilized, with a higher score indicating higher risk (16). We examined the score and its components as outcomes.

Covariates

Mothers reported their age, education, household income, race/ethnicity, parity and smoking history. We calculated pre-pregnancy BMI (pp BMI) from self-reported height and pre-pregnancy weight.

Statistical analysis

We first examined mean DII in pregnancy and early childhood overall and within categories of maternal characteristics. Next, using Pearson's correlations we examined bivariate associations of the DII and log transformed hsCRP with food and nutrient intake. We then conducted multivariable linear regression analyses. We sequentially adjusted for the following covariates, which were considered to be possible confounders in this analysis: child age and sex (model 1); maternal ppBMI (model 2); and maternal age, education, parity, smoking, race/ethnicity and household income (model 3). We additionally adjusted models for systolic blood pressure for child height at the time of outcome, given the strong association between height and SBP. Because we hypothesized that prenatal and early childhood DII may cumulatively affect outcomes, we categorized both maternal and early childhood DII into quartiles and examined adjusted associations of the 16 possible combinations with outcomes. Lastly, we also examined effect modification by sex for all outcomes in mid-childhood. We conducted all analyses using SAS version 9.3 software.

Results

Mean DII in pregnancy was −2.6 (standard deviation (SD) 1.4, range −5.4, 3.3) (Table 1). Mean (SD) maternal BMI was 24.7(5.0) kg/m^2. Younger maternal age, higher BMI, lower education, lower household income, black race or Hispanic ethnicity, and multiparity were associated with a more pro-inflammatory diet (higher DII) during pregnancy (Table 1). In

early childhood, the mean DII in girls was 0.21 (0.7), range −1.4 to 2.0, and in boys was 0.29 (0.7), range −1.1 to 2.1. In mid-childhood, mean BMI z-score was 0.40 (0.98), fat mass index 4.4 (1.8) kg/m^2, and metabolic risk score −0.01 (0.61).

Intake of nutrients and food groups and DII

Early childhood intake of saturated fat (r=0.34) and trans fat (r=0.29) were the nutrients most strongly correlated with child DII, and fiber (r=−0.60) and selenium (r=−0.53) were the nutrients with the strongest negative correlations. When we examined food groups, early childhood intake of sugar-sweetened beverages (r=0.06) had a positive correlation with early childhood DII, and vegetables (r=−0.61), fruits (r=−0.58) and whole grain foods (r=−0.36) had the strongest negative correlation. Consumption of these pro-inflammatory nutrients and food groups in early childhood may explain the marked difference in mean DII scores between pregnancy and early childhood. As we have previously described, during pregnancy intake of nutrients and food groups had similar associations with DII (6).

Diet and Systemic Inflammation

As we previously reported (6), intakes of specific nutrients and food groups during pregnancy were minimally associated with second trimester hsCRP. Mean first and second trimester DII was directly but modestly associated with maternal hsCRP in the second trimester (r=0.13, p<0.01) (6).

Early childhood intake of individual nutrients and food groups also were minimally associated with log transformed hsCRP in mid-childhood. N-3 and n-6 fatty acids had the strongest (r=0.12 and 0.11, respectively) pro-inflammatory association and vitamin D had the strongest (r=−0.14) anti-inflammatory association with hsCRP. DII in early childhood was not associated with offspring hsCRP in mid-childhood (r=−0.06, p=0.20) (Supplementary table 1).

Pregnancy DII and mid-childhood outcomes

In unadjusted models, maternal DII in pregnancy was directly associated with offspring size in mid-childhood, including BMI z-score (β=0.09 units per point increase in DII, 95%CI 0.04, 0.13), fat-free mass index (β=0.10 kg/m^2, 95%CI 0.04, 0.16) and waist circumference (β=0.41 cm per point increase in DII, 95%CI 0.07, 0.74), as well as more direct measures of adiposity and dysmetabolism, including fat mass index (β=0.12 kg/m^2, 95%CI 0.04, 0.21), trunk fat mass index (β=0.05 kg/m^2, 95%CI 0.01, 0.09), SS+Tr (β=0.71mm, 95%CI 0.31, 1.1) and fasting insulin (β=0.57uU/ml, 95%CI 0.24, 0.91). Associations were similar in both boys and girls (Table 2, all interaction p values ≥0.15). After adjustment for maternal ppBMI, associations of pregnancy DII with waist circumference, fat mass index and trunk fat mass index results were completely attenuated, and associations of pregnancy DII with BMI z-score, fat-free mass index, SS+Tr and fasting insulin were attenuated after additional adjustment for maternal sociodemographics (Table 2). Pregnancy DII was not associated with leptin, hsCRP, LDL cholesterol, metabolic risk score or HDL cholesterol, HOMA-IR, systolic blood pressure or triglycerides (components of the metabolic risk score, data not shown), in mid-childhood in adjusted analyses.

Early childhood DII and mid-childhood outcomes

Although the p-value for interaction values for sex were not statistically significant (all p>0.22) for the association between early childhood DII and mid-childhood outcomes, we observed substantially different results between the sexes. Thus, all results in table 3 are presented stratified by sex.

In girls, there was no association between DII in early childhood and any anthropometric or cardiometabolic outcomes in mid-childhood in either unadjusted or adjusted models. In boys, in all models including model 3 (adjusted for child age and sex, and maternal ppBMI and sociodemographics), higher early childhood DII, indicating a more pro-inflammatory diet, was associated with larger child size (mid-childhood BMI z-score β=0.16 units per point DII, 95%CI 0.02, 0.29) and greater adiposity by SS+Tr (β=1.12mm, 95%CI 0.01, 2.23). Early childhood DII was also associated with fat-free mass index (β=0.23 kg/m^2, 95%CI 0.03, 0.42) after adjustment for child age and sex and maternal ppBMI. However, these associations were modestly attenuated after additional adjustment for maternal sociodemographics (β=0.19 kg/m^2, 95%CI −0.01, 0.39). There was no association between early childhood DII with fat mass index, trunk fat mass index, leptin, hsCRP, fasting insulin, total cholesterol, the metabolic risk score or any of its components (data not shown) in mid-childhood.

Prenatal and Early Life Exposure to Pro-inflammatory diet

DII in pregnancy and early childhood were positively correlated (r=0.31, p<0.0001), with 34% of dyads falling in the same quartile of pregnancy and early childhood DII. In boys only, after adjustment for child age, maternal ppBMI and maternal sociodemographics, exposure to the highest quartile of pro-inflammatory diet *in utero* (pregnancy DII) and in early childhood compared to exposure to the lowest quartile of pro-inflammatory diet at both time points, was associated with higher BMI z-score in mid-childhood (Q4-Q4 0.78 BMI z-score units per unit DII, 95% CI 0.34, 1.22, vs. Q1-Q1 as referent) (Supplementary figure 1). Additionally, among boys who consumed the highest quartile of DII in early childhood, exposure to the highest quartile of pro-inflammatory diet *in utero* (pregnancy DII) was associated with an approximately 18% higher BMI z-score in mid-childhood compared to exposure to the lowest quartile of pregnancy DII (Q1-Q4 vs. Q4-Q4, supplementary figure 1). In boys and girls, exposure to the highest quartile of pro-inflammatory diet *in utero* (pregnancy DII) and in early childhood compared to exposure to the lowest quartile of pro-inflammatory diet at both time points was associated with higher fat mass index (Q4-Q4 β=0.67 kg/m^2 per unit DII, 95% CI 0.06, 1.27 vs. Q1-Q1) and waist circumference in mid-childhood (WC Q4-Q4 β=2.36 cm per unit DII, 95% CI 0.14, 4.59 vs. Q1-Q1 as referent) after adjustment for child age, maternal ppBMI and maternal sociodemographics.

Discussion

In this US pre-birth cohort, a pro-inflammatory diet in early childhood was associated with higher BMI z-score, waist circumference and adiposity as measured by SS+Tr skin fold thickness, but only among boys. Additionally, we found that combined exposure to a pro-inflammatory diet *in utero* and in early childhood may be associated with higher adiposity in

all children and higher BMI in boys. These results provide evidence that exposure to a pro-inflammatory diet in early life may affect offspring size and adiposity in childhood.

Here we use the DII, which we have previously shown to be associated with systemic inflammation during pregnancy and pregnancy outcomes in the same cohort, to provide a novel aggregate assessment of dietary inflammatory potential during childhood. The advantage of this dietary measure is that it comprehensively measures the standardized contribution of a wide variety of foods and nutrients based on their pro- or anti-inflammatory effect in cell, animal or human studies. Interestingly, we did not find an association between DII in early childhood and hsCRP in mid-childhood. This may be related to the timing of our exposure and outcome, with our exposure assessment approximately four years before outcome assessment. Dietary habits and preferences have been shown to change rapidly in childhood (17), which may affect this association. Also, CRP was available in only a subset of children.

Studies examining the relationship between diet quality during pregnancy and offspring BMI and adiposity are few, and have compared a variety of dietary exposures. Maternal fat intake during pregnancy was positively correlated with offspring adiposity and BMI in adulthood in a Danish cohort (18). An earlier British study (19) measured maternal intake of fat, protein and carbohydrates during pregnancy and, in contrast to the previous Danish study, did not find that intake of any of these dietary components were associated with offspring adiposity or lean mass. However, macronutrient composition of a diet alone does not adequately reflect its cumulative health effects. More recently, Fernandez-Barres *et al* found an association between maternal adherence to the Mediterranean diet during pregnancy and lower offspring waist circumference at four years of age in a Spanish cohort (20) and Vidakovic *et al* reported that higher maternal n-6 to n-3 fatty acid ratio during pregnancy is associated with higher total and central adiposity at six years in children (21). Importantly, these studies evaluate either cultural dietary traditions or isolated nutrients. By contrast, the DII is a way to classify many food components that can be incorporated into any diet, alone or in combination.

We found that dietary inflammation in early childhood was associated with later adiposity in boys only, despite similar overall DII scores and caloric intake in girls and boys. Human data supporting sex differences in fetal programming is limited, but there is mounting evidence from animal models that males are more susceptible to the effects of both fetal and early-life overnutrition than females. Both hormonal and epigenetic mechanisms have been proposed to explain this association (22–24). Few epidemiologic studies in the pre-pubertal period have looked for sex differences. Our novel findings suggest the need for further investigation of mechanisms underlying this divergence, as well as follow-up into adolescence and beyond.

We further describe a “cumulative effect” of a pro-inflammatory diet during pregnancy and early childhood on mid-childhood BMI and adiposity. Although this phenomenon has been described in animal models, with pups exposed to a “Western” diet (high saturated fat and high simple carbohydrate) *in utero* and postnatally having more profound obesity and cardiometabolic risk than pups exposed to a “Western” diet *in utero* only (25, 26), there is

scarce epidemiologic evidence supporting this effect. We speculate that although a pro-inflammatory diet during pregnancy was not independently associated with offspring adiposity or BMI, exposure during the critical fetal window may allow greater susceptibility to the effects of dietary inflammation in early childhood. We and others have found a strong correlation between maternal and early childhood diet, which may be related to programming of taste preference or the social and environmental determinants of food choices. These factors may be primary or additional drivers of intergenerational obesity and metabolic dysregulation in high-risk dyads (19).

Our analysis has several limitations. Although adiposity and insulin resistance in mid-childhood have a strong association with adult obesity and metabolic syndrome (27), the implications of our findings for long-term health are unclear. Follow-up in our cohort is ongoing which will allow future analyses at older ages. Additionally, our cohort was relatively well educated and drawn from a single practice in Massachusetts, with relatively low rates of childhood obesity (12.2% with BMI z-score>95th percentile) compared to the general US population (19.6% of 6–11 year olds in 2007–2008) (28). Thus, the generalizability of our findings to other populations may be limited.

In this cohort, a pro-inflammatory diet in early childhood was associated with later adiposity in boys. Additionally, children who were exposed to the highest dietary inflammation during both pregnancy and early childhood were at the highest risk for obesity in mid-childhood. This study may provide early insight into potential mechanisms underlying early-life programming of obesity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

DII	dietary inflammatory index
BMI	body mass index
hsCRP	high sensitivity C reactive protein
IL	Interleukin
FFQ	food frequency questionnaire
SS+Tr	Subscpular+Triceps Skin Fold Thickness
HDL and LDL	High and Low Density Lipoprotein Cholesterol
ppBMI	Pre-pregnancy BMI

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What is already known about this subject

- Pro-inflammatory diet in adults is associated with systemic inflammation and cardiometabolic risk
- Nutrition during pregnancy and early childhood can have lifelong effects on offspring growth and health
- Pro-inflammatory diet during pregnancy is associated with adverse perinatal outcomes

What this study adds

- A pro-inflammatory diet in early childhood is associated with higher BMI and adiposity in mid-childhood in boys
- A pro-inflammatory diet both in pregnancy and early childhood may be cumulatively associated with increased risk for childhood obesity

Table 1

Maternal characteristics and mean (SD) pregnancy and early childhood DII among 992 mothers in the Project Viva cohort, recruited 1999–2002.

		Pregnancy DII[1]	Early childhood DII[2]
	N (%)	Mean (SD)	
Total	**N=992**	**−2.6 (1.4) Range −5.4 to 3.3**	**0.3 (0.7) Range −1.4 to 2.1**
Age at enrollment, years			
<25	85 (8.6)	−1.5 (1.7)	0.4 (0.8)
25–<35	594 (59.9)	−2.6 (1.4)	0.3 (0.7)
>=35	313 (31.6)	−2.9 (1.2)	0.2 (0.7)
Maternal BMI, kg/m^2			
18.5–<25	641 (64.6)	−2.7 (1.4)	0.2 (0.7)
25–<30	220 (22.2)	−2.4 (1.5)	0.3 (0.7)
≥30	131 (13.2)	−2.2 (1.5)	0.3 (0.8)
College graduate			
No	295 (29.7)	−1.9 (1.6)	0.3 (0.7)
Yes	697 (70.3)	−2.9 (1.2)	0.2 (0.7)
Household income >$70,000 during pregnancy			
No	322 (34.7)	−2.3 (1.6)	0.3 (0.7)
Yes	605 (65.3)	−2.8 (1.2)	0.2 (0.7)
Race/ethnicity			
Black	140 (14.1)	−2.0 (1.8)	0.3 (0.8)
Hispanic	63 (6.4)	−1.8 (1.8)	0.3 (0.8)
Asian	44 (4.4)	−3.1 (1.2)	0.3 (0.8)
White	700 (70.6)	−2.8 (1.2)	0.2 (0.7)
Other	45 (4.5)	−2.0 (1.8)	0.4 (0.8)
Smoking Status			
Never	693 (70.0)	−2.6 (1.5)	0.2 (0.7)
Former	202 (20.4)	−2.8 (1.2)	0.2 (0.7)
During pregnancy	95 (9.6)	−2.0 (1.4)	0.4 (0.7)
Nulliparous			
No	516 (52.0)	−2.4 (1.5)	0.2 (0.7)
Yes	476 (48.0)	−2.8 (1.3)	0.3 (0.7)

[1] Pregnancy DII was the mean of first and second trimester DII,

[2] Median age at early childhood was 3.1 years

Table 2

Associations of maternal prenatal DII with mid-childhood (median age 7.7 years) adiposity and cardiometabolic outcomes separately among girls and boys

Outcomes in girls	**Mean (S.D)**	**β (95% CI) per 1 point increment in pregnancy DII**		
Size		Model 1	Model 2	Model 3
Body mass index z-score	0.40 (0.97)	0.08 (0.02, 0.14)	0.05 (0.00, 0.11)	0.01 (−0.05, 0.07)
Fat-free mass index, kg/m^2	12.7 (1.4)	0.09 (0.00, 0.17)	0.05 (−0.03, 0.14)	−0.02 (−0.11, 0.07)
Waist Circumference, cm	60.1 (8.1)	0.57 (0.11, 1.04)	0.35 (−0.09, 0.79)	0.00 (−0.48, 0.48)
Adiposity				
Fat mass index, kg/m^2	4.8 (1.9)	0.14 (0.02, 0.26)	0.09 (−0.02, 0.21)	0.02 (−0.11, 0.15)
Trunk fat mass index, kg/m^2	1.7 (0.80)	0.05 (0.00, 0.11)	0.03 (−0.02, 0.09)	0.00 (−0.06, 0.06)
SS+Tr, mm	21.6 (9.8)	0.74 (0.16, 1.32)	0.50 (−0.06, 1.06)	0.11 (−0.51, 0.72)
Metabolic Markers				
Leptin, ng/mL	6.8 (7.4)	0.08 (−0.48, 0.65)	0.08 (−0.49, 0.64)	−0.10 (−0.73, 0.53)
hsCRP mg/L *	1.1 (3.2)	7.61 (−5.82,22.95)	6.28 (−6.76,21.15)	1.41 (−12.3,17.26)
Fasting insulin uU/ml	8.8 (6.7)	0.53 (0.02, 1.04)	0.49 (−0.02, 0.99)	0.26 (−0.26, 0.78)
LDL cholesterol, mg/dL	92.6 (21.4)	−0.15 (−1.80, 1.50)	−0.21 (−1.86, 1.45)	−0.49 (−2.34, 1.37)
Composite Metabolic Outcome				
Mid-childhood metabolic risk score	−0.00 (0.64)	0.06 (0.00, 0.11)	0.05 (−0.01, 0.10)	0.03 (−0.03, 0.09)
Outcomes in boys				
Size				
Body mass index z-score	0.4 (0.98)	0.10 (0.03, 0.16)	0.06 (0.00, 0.12)	0.04 (−0.03, 0.11)
Fat-free mass index, kg/m^2	13.3 (1.3)	0.12 (0.02, 0.21)	0.08 (−0.02, 0.17)	0.04 (−0.07, 0.15)
Waist Circumference, cm	59.7 (7.8)	0.21 (−0.26, 0.69)	−0.07 (−0.54, 0.40)	−0.11 (−0.64, 0.42)
Adiposity				
Fat mass index, kg/m^2	4.0 (1.7)	0.11 (−0.02, 0.24)	0.04 (−0.08, 0.17)	0.04 (−0.11, 0.19)
Trunk fat mass index, kg/m^2	1.3 (0.80)	0.04 (−0.02, 0.10)	0.01 (−0.04, 0.07)	0.01 (−0.05, 0.08)
SS+Tr, mm	17.9 (8.5)	0.68 (0.13, 1.23)	0.34 (−0.21, 0.88)	0.08 (−0.51, 0.68)
Metabolic Markers				
Leptin, ng/mL	4.8 (5.7)	0.55 (0.07, 1.04)	0.36 (−0.13, 0.86)	0.25 (−0.32, 0.82)
hsCRP mg/L *	0.6 (2.0)	1.85 (−10.8,16.27)	−1.51 (−14.0,12.84)	−6.40 (−20.2, 9.72)
Fasting insulin uU/ml	6.8 (5.2)	0.61 (0.18, 1.05)	0.43 (−0.01, 0.87)	0.45 (−0.07, 0.98)
LDL cholesterol, mg/dL	89.8 (23.8)	−1.98 (−4.01, 0.06)	−1.57 (−3.66, 0.52)	−1.84 (−4.22, 0.54)
Composite Metabolic Outcome				
Metabolic risk score	−0.02 (0.58)	0.00 (−0.06, 0.05)	−0.02 (−0.07, 0.04)	−0.01 (−0.07, 0.06)

Model 1. Adjusted for child age and sex; Model 2. Model 1 + maternal pre-pregnancy BMI; Model 3. Model 2 + maternal age, education, parity, smoking during pregnancy, race/ethnicity and household income. hsCRP=high sensitivity C Reactive Protein, LDL-C=Low density lipoprotein cholesterol, SS+Tr=subscapular+triceps skinfold thickness, SS:Tr=ratio of subscapular to triceps skin fold thickness.

* We used log transformed hsCRP and presented results as % change calculated as: % change = (exp(beta) - 1)*100.

** Metabolic risk score is a mean of five sex- and cohort-specific z-scores for waist circumference, systolic blood pressure, HDL cholesterol (scaled inversely), and log-transformed triglycerides and HOMA-IR; higher scores indicate higher risk.

Table 3

Associations of early childhood (median age 3.2 years) DII with mid-childhood (median age 7.7 years) adiposity and cardiometabolic outcomes in girls and boys

Outcomes in girls	**β (95% CI) per 1 point increment in DII**		
Size	Model 1	Model 2	Model 3
Body mass index z-score	0.05 (−0.08, 0.18)	0.04 (−0.08, 0.17)	0.04 (−0.09, 0.17)
Fat-free mass index, kg/m^2	0.11 (−0.09, 0.31)	0.08 (−0.11, 0.27)	0.06 (−0.13, 0.24)
Waist Circumference, cm	0.33 (−0.70, 1.36)	0.23 (−0.75, 1.20)	0.21 (−0.77, 1.19)
Adiposity			
Fat mass index, kg/m^2	0.23 (−0.05, 0.50)	0.18 (−0.08, 0.44)	0.14 (−0.13, 0.40)
Trunk fat mass index, kg/m^2	0.11 (−0.02, 0.23)	0.09 (−0.03, 0.21)	0.06 (−0.05, 0.18)
SS+Tr, mm	0.56 (−0.73, 1.85)	0.44 (−0.78, 1.67)	0.31 (−0.92, 1.53)
Metabolic Markers			
Leptin, ng/mL	−0.74 (−1.97, 0.49)	−0.75 (−1.99, 0.49)	−0.82 (−2.09, 0.44)
hsCRP mg/L *	−14.0 (−36.1, 15.77)	−14.8 (−36.1,13.46)	−20.5 (−41.0, 7.17)
Fasting insulin uU/ml	0.12 (−0.95, 1.20)	0.08 (−0.98, 1.14)	−0.06 (−1.10, 0.97)
LDL cholesterol, mg/dL	−0.41 (−4.28, 3.47)	−0.44 (−4.31, 3.44)	−0.17 (−4.11, 3.77)
Composite Metabolic Outcome			
Mid-childhood metabolic risk score	0.06 (−0.06, 0.18)	0.05 (−0.07, 0.17)	0.04 (−0.08, 0.16)
Outcomes in boys			
Size			
Body mass index z-score	0.19 (0.06, 0.33)	0.17 (0.04, 0.30)	0.16 (0.02, 0.29)
Fat-free mass index, kg/m^2	0.25 (0.05, 0.44)	0.23 (0.03, 0.42)	0.19 (−0.01, 0.39)
Waist Circumference, cm	0.89 (−0.09, 1.87)	0.69 (−0.28, 1.65)	0.93 (−0.07, 1.92)
Adiposity			
Fat mass index, kg/m^2	0.17 (−0.10, 0.43)	0.13 (−0.13, 0.39)	0.13 (−0.14, 0.41)
Trunk fat mass index, kg/m^2	0.07 (−0.05, 0.19)	0.05 (−0.06, 0.17)	0.06 (−0.06, 0.19)
SS+Tr, mm	1.07 (−0.04, 2.18)	0.81 (−0.28, 1.90)	1.12 (0.01, 2.23)
Metabolic Markers			
Leptin, ng/mL	−0.23 (−1.30, 0.84)	−0.35 (−1.41, 0.70)	−0.68 (−1.84, 0.47)
hsCRP mg/L *	−11.2 (−33.2,18.21)	−13.3 (−34.8,15.44)	−12.2 (−35.6,19.66)
Fasting insulin uU/ml	−0.34 (−1.33, 0.64)	−0.52 (−1.49, 0.45)	−0.80 (−1.85, 0.24)
LDL cholesterol, mg/dL	−1.78 (−6.18, 2.61)	−1.43 (−5.83, 2.96)	−3.19 (−7.82, 1.44)
Composite Metabolic Outcome			
Metabolic risk score	0.04 (−0.07, 0.15)	0.03 (−0.08, 0.14)	0.02 (−0.10, 0.14)

Model 1. Adjusted for child age and sex; Model 2. Model 1 + maternal pre-pregnancy BMI; Model 3. Model 2 + maternal age, education, parity, smoking during pregnancy, race/ethnicity and household income. hsCRP=high sensitivity C Reactive Protein, LDL-C=Low density lipoprotein cholesterol, SS+Tr=subscapular+triceps skinfold thickness, SS:Tr=ratio of subscapular to triceps skin fold thickness.

* We used log transformed hsCRP and presented results as % change calculated as: % change = (exp(beta) - 1)*100.

** Metabolic risk score is a mean of five sex- and cohort-specific z-scores for waist circumference, systolic blood pressure, HDL cholesterol (scaled inversely), and log-transformed triglycerides and HOMA-IR; higher scores indicate higher risk.