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ORIGINAL ARTICLE

Pediatric Obesity

Childhood nutrient intakes are differentially associated with hepatic and abdominal fats in adolescence: The EPOCH study

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Abstract

Objective: The aim of this study was to examine whether nutrient intakes in childhood are associated with abdominal and hepatic fat depots later in adolescence.

Methods: Using data from 302 participants in the longitudinal Exploring Perinatal Outcomes among CHildren (EPOCH) study, energy partition and nutrient density models were constructed to examine associations of nutrient intakes in childhood (~10 years of age), assessed by food frequency questionnaire, with abdominal subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), and hepatic fat in adolescence (~16 years of age).

Results: In energy partition models (energy intake not held constant), total, monounsaturated, and polyunsaturated fat intakes in childhood were associated with higher SAT in adolescence (β [95% CI]: 8.5 [0.1-17.1], 25.1 [2.1-48.1], and 59.7 [16.1-103.3] mm^2 per 100 kcal/d), higher starch intake was associated with log-hepatic fat (back-transformed β [95% CI]: 1.07 [1.01-1.15] per 100 kcal/d), and, in boys only, higher animal protein intake was associated with VAT (β [95% CI]: 5.3 [0.3-10.3] mm^2 per 100 kcal/d). Most associations were unchanged when adjusted for energy intake in nutrient density models.

Conclusions: Childhood nutrient intakes were differentially associated with adolescent body fats; specifically, unsaturated fat intake predicted abdominal SAT, animal protein intake predicted VAT, and starch intake predicted hepatic fat. These nutrient intakes may, therefore, be targets for intervention studies aiming to modify adolescent body fat distribution.

INTRODUCTION

The high prevalence of childhood obesity, defined by BMI-for-age greater than the 95th percentile, is an alarming public health issue with associated cardiometabolic risks (1,2). However, it has also been shown that children with obesity can vary considerably in terms of metabolic dysfunction, despite similar BMI (3). One factor that may explain this heterogeneity is underlying patterns of body fat partitioning. Specifically, studies have shown that greater abdominal fat deposition, especially visceral fat, and hepatic fat deposition are strong risk factors for insulin resistance and other cardiometabolic risk factors in youth, independent of total adiposity (4-6). These associations may be particularly relevant during adolescence, a period of development characterized by rapid growth, including changes in body composition (7), and a higher incidence of cardiometabolic diseases, such as type 2 diabetes mellitus (DM) (8) and nonalcoholic fatty liver disease (NAFLD) (9), compared with younger children.

Currently, the etiology of body fat partitioning is poorly understood, but lifestyle behaviors, including diet, are likely involved. Of particular interest is the role of diet quantity versus quality. Overfeeding studies have shown that excess energy intake is associated with increases in abdominal and hepatic fats but often with considerable interindividual differences (10), which may, in part, be explained by qualitative aspects of diet that have also been shown to influence body composition (11-13). For example, short-term treatment studies (ranging from 9 days to 8 weeks) among youth with obesity or clinical NAFLD have shown that isoenergetic modifications to macronutrient composition, particularly reductions in carbohydrate/sugar intake, are associated with lower visceral fat (14) and/or hepatic fat (15). While these findings may be critical in informing treatment strategies among youth with clinical disease, it remains unclear the extent to which macronutrient composition may prevent the accumulation of metabolically adverse body fat depots in settings that are representative of the general pediatric population. Thus, there is a need for additional prospective studies aiming to understand whether nutrient intakes earlier in life, especially among healthy children, are predictive of body fat partitioning patterns later in adolescence, as such findings would be critical in informing primordial prevention strategies.

Our objective was to examine associations of nutrient intakes in childhood (~10 years) with abdominal fat (subcutaneous adipose tissue [SAT] and visceral adipose tissue [VAT]) and hepatic fat deposition in adolescence (~16 years), using data from the Exploring Perinatal Outcomes among CHildren (EPOCH) study, a longitudinal cohort study in Colorado. We also tested whether associations were independent of total energy intake (TEI) in childhood, given potential correlations between energy and nutrient intakes (16), or were modified by sex, given established differences in nutrient metabolism (17) and body fat distribution phenotypes (18) for boys versus girls.

Study importance

What is already known?

- Regional body fat distribution, especially as abdominal and/or ectopic fat, appears to be a strong risk factor for cardiometabolic dysfunction in youth.
- Diet and nutrition in childhood may be predictive of adverse body fat distribution later in life, but few studies have assessed this using a prospective study design and more sophisticated measures of body composition.

What does this study add?

- Using data from a longitudinal cohort in Colorado, we showed that nutrient intakes in childhood (~10 years of age) were differentially associated with different types of abdominal and ectopic fat deposition later in adolescence (~16 years of age).
- Specifically, higher unsaturated fat intake in childhood predicted higher abdominal subcutaneous fat, higher animal protein intake in childhood predicted higher abdominal visceral fat, and higher starch intake in childhood predicted higher hepatic fat in adolescence.

How might these results change the direction of research or the focus of clinical practice?

- This study provides insight into the potential influence of nutrient intakes earlier in childhood on future abdominal and hepatic fat deposition in adolescence and may, therefore, be used to inform interventions aiming to modify body fat distribution patterns in youth.

METHODS

Study population

The EPOCH study is a prospective, multiethnic pediatric cohort based in Colorado. Eligible participants were offspring of singleton pregnancies at a single hospital between 1992 and 2002, whose biological mothers were members of the Kaiser Permanente of Colorado Health Plan at the child's delivery. Eligible participants were invited to two research visits, which were timed approximately 6 years apart (childhood visit = 6–14 years old; adolescence visit = 12–19 years old) (19,20). The study was approved by the Colorado Multiple Institutional Review Board. Mothers provided written informed consent, and children older than 8 years provided written assent. A flowchart of participant selection for this study is shown in Figure 1. Among the 604 participants enrolled in childhood, 417 returned for a second visit in adolescence. Of those, 18 participants who did not complete the magnetic resonance imaging (MRI) procedure in adolescence (to assess abdominal and hepatic fat depots), 2 participants with missing dietary data at visit 1, and 5 participants with extreme TEI at visit 1 (<800 or >4,000 kcal for boys and <500 kcal or >3,500 kcal for girls) (21) were excluded, resulting in an eligible sample of 392 participants. We further excluded 90 participants categorized as TEI underreporters at visit 1 based on the Goldberg method, resulting in an analytical sample of 302 participants. In Supporting Information Table S1, we compared the characteristics of this analytical sample at visit 1 ($n = 302$) to the full EPOCH cohort of children enrolled at visit 1 ($n = 604$).

Dietary intake assessments

Dietary intake was assessed at both visits using a modified version of the Block Kids Questionnaire, a semiquantitative food frequency questionnaire (FFQ) that has been validated in children as young as 8 years old (22,23), which was developed for the SEARCH for Diabetes in Youth Study (24). Briefly, the questionnaire followed

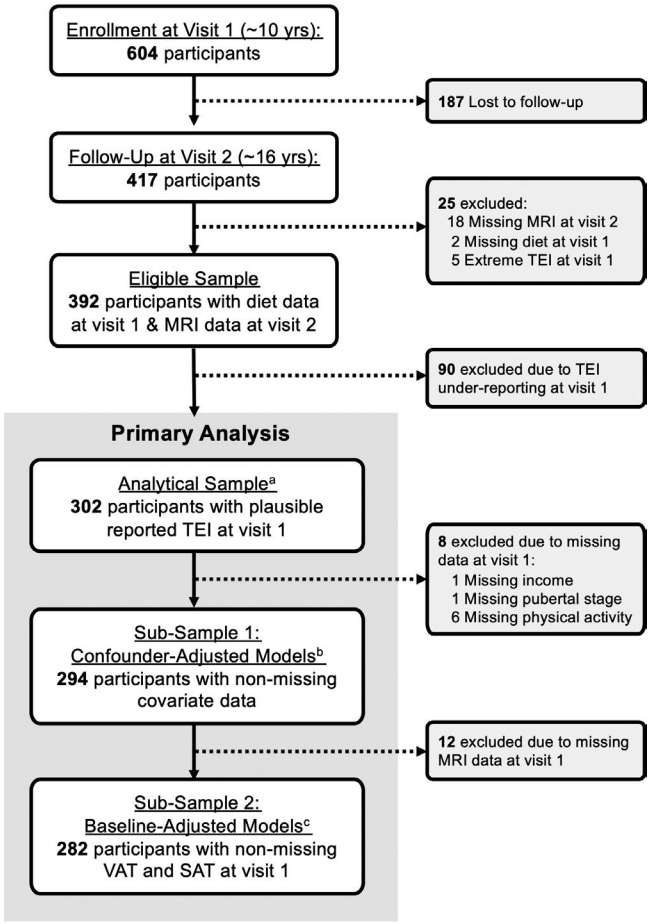

FIGURE 1 Flowchart of the selection of participants from the Exploring Perinatal Outcomes among CHildren (EPOCH) cohort study for this prospective analysis examining associations between childhood nutrient intakes and adolescent abdominal and hepatic fats. [a]Analytical sample included in Model 1 regression analyses (unadjusted). [b]Subsample included in Model 2 regression analyses (adjusted for potential confounders). [c]Subsample included in Model 3 regression analyses (adjusted for abdominal SAT or VAT in childhood). MRI, magnetic resonance imaging; SAT, subcutaneous adipose tissue; TEI, total energy intake; VAT, visceral adipose tissue

the same general format as the original Block Kids Questionnaire, whereby respondents were asked how many days and the average portion size that an item was consumed over the past week, but in the SEARCH questionnaire, the number of foods queried was expanded, particularly focusing on additional foods with regional and/or local importance, and the number of nutrients and food groups available for analysis was expanded. In EPOCH, the questionnaires were administered by trained research staff either using a self-administered format or a structured interview format if the staff member determined the participant was having difficulty completing the form. All questionnaires were analyzed using the Nutrition Data System for Research (University of Minnesota, Minneapolis, Minnesota) to estimate TEI in kilocalories per day and macronutrient intakes in grams per day. Nutrient intakes of interest for this analysis included total carbohydrates, protein, and fat, as well as their subtypes (starch and sugar, animal protein and vegetable protein, and saturated fat [SFA], monounsaturated fat [MUFA], and polyunsaturated fat [PUFA]). Dietary intake data were also used to calculate Healthy Eating Index-2010 (HEI-2010) total scores as a measure of overall diet quality (25).

Assessment of energy intake underreporting

We assessed TEI underreporting at visit 1 in childhood using the Goldberg method (26,27). Briefly, we calculated participant-specific ratios of reported TEI (rTEI) to basal metabolic rate (BMR, calculated using Schofield equations) and compared this ratio to a physical activity level (PAL) constant. We chose a PAL constant of 1.55, based on World Health Organization (WHO) recommendations for light activity (26). The cutoff for TEI underreporting was set as the lower confidence limit for this PAL constant calculated based on the equation described by Black (26). Participants with an rTEI:BMR ratio below this threshold (rTEI:BMR <1.10) were categorized as underreporters (n = 90) and excluded from analyses. Characteristics of the excluded TEI underreporters compared with acceptable reporters at visit 1 are shown in Supporting Information Table S2. Underreporters were older and had higher BMI z scores, abdominal SAT, and abdominal VAT at both visits. Underreporters also reported lower intakes of energy (as expected), total protein, and animal protein but higher intakes of starch, vegetable protein, and fiber as a percentage of TEI.

Hepatic and abdominal fat assessments

MRI was performed at both visits by trained technicians and research staff at the University of Colorado Anschutz Medical Campus. Abdominal SAT and VAT were assessed at both visits by abdominal MRI using a 3-T HDx Imager (General Electric, Waukesha, Wisconsin), as previously described (19). Briefly, participants were placed in a supine position on the scanner and a series of T1-weighted coronal images were taken to locate the L4-L5 plane. Abdominal SAT and VAT areas (millimeters squared) were determined by analyzing one axial T1-weighted image at the umbilicus or L4-L5 vertebrae. All images were analyzed by a single reader who was blinded to each participant's identity and other measures/assessments. Hepatic fat was also assessed by MRI but only in adolescence (visit 2), using a breath-hold, six-point MRI-proton density fat fraction technique (20), whereby hepatic fat fraction was calculated from the mean pixel signal intensity data for each flip angle acquisition using the OsiriX Lipoquant plug-in (28).

Other covariate assessments

Participant sex, race/ethnicity, and household income were self-reported at the first research visit. Height and weight were

measured at both visits, and age- and sex-adjusted BMI *z* scores were calculated using the WHO growth reference (29). The pubertal stage of participants was assessed by self-reported Tanner staging of pubic hair for boys and breast development for girls. When adjusting for pubertal stage in models, we categorized participants as prepubertal (Stage I) or pubertal (Stages II-IV) at visit 1 and as pubertal or postpubertal (Stage V) at visit 2. Physical activity was assessed by a validated 3-day physical activity questionnaire (30,31), which was used to calculate average energy expenditure over 3 days in metabolic equivalents (METs). Participants were categorized as having exposure to maternal DM during pregnancy if the mother had a physician diagnosis of gestational DM during pregnancy or type 2 DM before pregnancy, which was ascertained from medical records as previously described (19).

Statistical analysis

Descriptive and univariate analyses

Descriptive statistics were performed to summarize characteristics of the sample using means and standard deviations or medians and interquartile ranges for continuous variables and counts and frequencies for categorical variables. Prior to analyses, we natural log-transformed all hepatic fat values to meet model assumptions of normality in the residuals. Residuals for abdominal SAT and VAT were sufficiently normal and were analyzed without transformation (in millimeters squared).

Multivariable analyses

We constructed two types of linear regression models to examine associations of childhood nutrient intakes with adolescent abdominal SAT, VAT, and hepatic fat, with and without holding energy intake constant. The first type was an energy partition model, which estimates both the energy and nonenergy effects of each nutrient intake on the dependent variable. For this model, nutrient intakes were converted from grams per day to kilocalories per day, and energy intake from all other nutrients was adjusted for as a separate covariate in models. The second type was a multivariate nutrient density model, which estimates the isocaloric effect of an increase in each nutrient intake, offset by a concomitant drop in all other nutrient intakes. For this model, nutrient intakes were converted to nutrient densities, expressed either as a percentage of TEI (%TEI) or g/1,000 kcal for fiber, and TEI (kilocalories per day) was adjusted for as a separate covariate in models. We also adjusted for potential confounders in a stepwise manner to assess whether results were altered: Model 1 was adjusted for energy intake from all other nutrients (energy partition models) or TEI (nutrient density models); Model 2 was adjusted for age, sex, Hispanic ethnicity, household income (<$50,000, $50,000–$74,999, ≥$75,000), pubertal stage (prepubertal vs. pubertal), physical activity (average METs/d), BMI *z* score category (normal/underweight vs. overweight/obesity) at visit 1, maternal DM exposure during pregnancy, and diet quality at visit (HEI-2010 total score); and Model 3 was adjusted for Model 2 covariates plus abdominal SAT or VAT in childhood (only for models with abdominal SAT or VAT in adolescence as the dependent variable). Model 3 results were not reported for hepatic fat, which was only assessed at visit 2. In unadjusted models, we also tested for effect modification by sex using product terms and reported stratified estimates if $p < 0.05$ for the interaction effect. Results were reported as β-coefficients and 95% CIs for associations of a 100-kcal/d increase in each nutrient for energy partition models or a 5% increase in each nutrient for nutrient density models with each outcome in adolescence. For hepatic fat, all estimates were also back-transformed to reflect the ratio of geometric means. To account for multiple testing, we also reported whether *p* values were below a Bonferroni-corrected $\alpha = 0.0167$ ($\alpha = 0.05/3$ outcomes). In a sensitivity analysis, we assessed whether results differed if we used the residual method (16) to adjust for energy intake instead of the nutrient density method and found that findings were similar; thus, we reported results only from nutrient density models. All analyses were carried out using SAS statistical software version 9.4 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Characteristics of the analytical sample of 302 participants overall and stratified by sex are shown in Table 1. Collectively, 48% (n = 145) were boys, and 33.8% (n = 102) were Hispanic. At visit 2 in adolescence, mean levels of abdominal SAT and VAT were 183.5 ± 137.6 mm^2 and 30.8 ± 19.1 mm^2, respectively, and the median (interquartile range) for hepatic fat was 1.8% (1.3%–2.5%). Mean nutrient intakes in the sample overall and stratified by sex are shown in Supporting Information Table S3.

Associations of childhood nutrient intakes with adolescent abdominal fat

Associations of childhood nutrient intakes with abdominal SAT later in adolescence, based on stepwise-adjusted energy partition models and nutrient density models, are shown in Table 2. In energy partition models (energy intake not held constant), higher total fat, MUFA, and PUFA intakes in childhood were positively associated with higher abdominal SAT in adolescence, both in unadjusted models (Model 1) and confounder-adjusted models (Model 2); however, additionally adjusting for childhood SAT (Model 3) attenuated all associations to the null (Table 2). In nutrient density models adjusted for TEI, associations of childhood MUFA and PUFA intakes with adolescent SAT remained significant in unadjusted models (Model 1) and confounder-adjusted models (Model

TABLE 1 Characteristics of the analytical sample of youth ($n = 302$) at both visits, overall and stratified by sex

	Overall ($n = 302$)		Boys ($n = 145$)		Girls ($n = 157$)		
	Mean or *n*	SD or %	Mean or *n*	SD or %	Mean or *n*	SD or %	p[a]
Visit 1 characteristics							
Age (y), mean (SD)	10.3	1.5	10.3	1.6	10.2	1.5	0.56
Race/ethnicity, *n* (%)							0.44
Non-Hispanic White	162	53.6%	78	53.8%	84	53.5%	
Hispanic	102	33.8%	52	35.9%	50	31.9%	
Non-Hispanic Black	22	7.3%	7	4.8%	15	9.6%	
Non-hispanic other	16	5.3%	8	5.5%	8	5.1%	
Household income, *n* (%)							0.74
<$50,000	75	24.9%	39	26.9%	36	23.1%	
$50,000–$74,999	48	16.0%	23	15.9%	25	16.0%	
≥$75,000	178	59.1%	83	57.2%	95	60.9%	
Pubertal stage,[b] *n* (%)							**<0.001**
Prepubertal (Tanner = I)	139	46.2%	81	56.3%	58	36.9%	
Pubertal (Tanner = II to IV)	162	53.8%	63	43.8%	99	63.1%	
Physical activity,[c] mean (SD)	1.9	0.3	1.9	0.3	1.9	0.3	0.20
BMI z score, mean (SD)	0.04	1.1	0.08	1.2	0.00	1.1	0.55
BMI category, *n* (%)							0.52
Normal weight	234	77.5%	110	75.9%	124	79.0%	
Overweight/obesity	68	22.5%	35	24.1%	33	24.1%	
SAT area (mm^2),[d] mean (SD)	98.3	86.0	89.0	78.0	107.2	92.4	0.07
VAT area (mm^2),[d] mean (SD)	19.8	13.2	19.2	11.5	20.4	14.7	0.41
VAT/SAT, mean (SD)	0.26	0.12	0.28	0.14	0.23	0.10	**<0.001**
Visit 2 characteristics							
Age (y), mean (SD)	16.6	1.2	16.6	1.2	16.6	1.3	0.67
Pubertal stage, *n* (%)							
Pubertal (Tanner = II to IV)	139	46%	58	40%	81	52%	**0.04**
Postpubertal (Tanner = V)	163	54%	87	60%	76	48%	
Physical activity,[c] mean (SD)	1.9	0.4	2.0	0.5	1.9	0.3	0.22
BMI *z* score, mean (SD)	0.28	1.1	0.24	1.1	0.31	1.0	0.57
BMI category, *n* (%)							0.91
Normal weight	222	73.5%	107	73.8%	115	73.3%	
Overweight/obesity	80	26.5%	38	26.2%	42	26.8%	
SAT area (mm^2), mean (SD)	183.5	137.6	141.6	118.0	222.1	143.3	**<0.001**
VAT area (mm^2), mean (SD)	30.8	19.1	29.5	20.8	31.9	17.4	0.27
VAT/SAT, mean (SD)	0.21	0.11	0.26	0.13	0.16	0.06	**<0.001**
Hepatic fat (%), median (IQR)	1.8	1.3–2.5	1.9	1.3–2.7	1.79	1.3–2.3	0.18

Abbreviations: IQR, interquartile range; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue.

[a] p values calculated by two-tailed Student test or Mann–Whitney U test for continuous variables and χ^2 test for continuous variables. Bolding indicates $p < 0.05$.

[b] Data on pubertal stage was missing for one participant at visit 1.

[c] Physical activity was measured as the average energy expenditure over 3 days in metabolic equivalents (METs). Data were missing on physical activity for six participants at visit 1 and six participants at visit 2.

[d] Data on abdominal SAT and VAT were missing for 12 participants at visit 1.

2), but they were again attenuated to the null after adjusting for childhood SAT in Model 3 (Table 2). In comparison, for abdominal VAT in adolescence, in both types of models (energy partition or nutrient density models), there were no associations between nutrient intakes in childhood and abdominal VAT later in adolescence in the full sample (Table 3).

TABLE 2 Associations of nutrient intakes in childhood with abdominal SAT in adolescence

	Model 1: Unadjusted[a] ($n = 302$)		Model 2: + Confounders[b] ($n = 294$)		Model 3: + Childhood SAT[c] ($n = 282$)	
Energy partition models	β (95% CI)[d]	p[f]	β (95% CI)[d]	p[f]	β (95% CI)[d]	p[f]
Nutrient (kcal/d)						
Energy	3.3 (−0.2, 6.8)	0.07	1.6 (−1.2, 4.4)	0.26	−0.3 (−2.5, 2.0)	0.81
Carbohydrates	−3.5 (−11.5, 4.6)	0.40	−2.1 (−8.2, 4.0)	0.49	−3.2 (−8.1, 1.7)	0.19
Starch	−1.9 (−22.6, 18.9)	0.86	0.7 (−15.2, 16.7)	0.93	0.2 (−12.5, 12.9)	0.98
Sugar	−5.9 (−16.9, 5.1)	0.29	−4.1 (−12.4, 4.2)	0.33	−4.8 (−11.5, 1.8)	0.16
Protein	−1.9 (−36.3, 32.4)	0.91	1.2 (−25.5, 27.8)	0.93	4.4 (−17.0, 25.8)	0.68
Animal protein	3.1 (−27.6, 33.8)	0.84	−0.9 (−24.5, 22.8)	0.94	3.5 (−15.5, 22.6)	0.72
Total fat	15.7 (4.6, 26.9)	**0.006***	8.5 (0.1, 17.1)	**0.049**	4.4 (−2.5, 11.2)	0.21
SFA	8.4 (−25.9, 42.8)	0.63	−3.6 (−30.2, 23.0)	0.79	1.2 (−20.1, 22.4)	0.91
MUFA	36.3 (6.0, 66.5)	**0.019**	25.1 (2.1, 48.1)	**0.032**	14.4 (−4.1, 33.0)	0.13
PUFA	92.6 (37.0, 148.2)	**0.001***	59.7 (16.1, 103.3)	**0.008***	29.3 (−6.3, 64.8)	0.11
Nutrient density models	β (95% CI)[e]	p[f]	β (95% CI)[d]	p[f]	β (95% CI)[d]	p[f]
Nutrient (%TEI)						
Carbohydrates	−15.4 (−29.2, −1.7)	**0.028**	−7.5 (−18.0, 2.9)	0.16	−6.5 (−15.0, 1.9)	0.13
Starch	−7.6 (−30.6, 15.4)	0.52	−0.4 (−18.0, 17.3)	0.97	1.4 (−12.6, 15.5)	0.84
Sugar	−14.1 (−28.4, 0.2)	0.05	−8.1 (−18.9, 2.7)	0.14	−7.2 (−15.9, 1.4)	0.10
Protein	4.1 (−35.2, 43.4)	0.84	2.0 (−28.4, 32.4)	0.90	5.7 (−18.8, 30.1)	0.65
Animal protein	7.9 (−25.1, 41.0)	0.64	−0.2 (−25.6, 25.1)	0.99	4.1 (−16.2, 24.5)	0.69
Total fat	21.8 (5.1, 38.5)	**0.011***	11.1 (−1.6, 23.9)	0.09	8.6 (−1.6, 18.9)	0.10
SFA	15.8 (−23, 54.5)	0.42	−3.4 (−33.5, 26.8)	0.83	3.9 (−20.2, 28.0)	0.75
MUFA	41.7 (7.1, 76.3)	**0.018**	26.7 (0.3, 53.0)	**0.047**	19.2 (−2.0, 40.4)	0.08
PUFA	90.4 (30.7, 150.1)	**0.003***	64.0 (17.0, 110.9)	**0.008***	37.5 (−0.6, 75.7)	0.05
Fiber	16.5 (−29.0, 62.0)	0.48	1.8 (−35.3, 38.9)	0.92	−6.8 (−36.8, 23.3)	0.66

Abbreviations: MUFA, monounsaturated fat; PUFA, polyunsaturated fat; SAT, subcutaneous adipose tissue; SFA, saturated fat; TEI, total energy intake.

[a] Model 1: adjusted for energy intake from all other nutrients (energy partition models) or TEI (nutrient density models).

[b] Model 2: adjusted for Model 1 covariates plus sex, age, race/ethnicity, household income, pubertal stage, physical activity, BMI category at visit 1, maternal diabetes mellitus exposure, and Healthy Eating Index-2010 total score at visit 1. Eight participants excluded because of missing data for household income ($n = 1$), pubertal stage ($n = 1$), or physical activity ($n = 6$).

[c] Model 3: adjusted for Model 2 covariates plus abdominal VAT in childhood. Twelve participants excluded because of missing data for abdominal SAT at visit 1.

[d] Estimated per 100-kcal/d increase in each nutrient.

[e] Estimated per 5% increase in each nutrient (except fiber, per 5 g/1,000 kcal increase).

[f] Bolding indicates $p < 0.05$. Asterisk (*) indicates if below Bonferroni-adjusted $p < 0.017$ (0.05/3 outcomes).

Associations of childhood nutrient intakes with adolescent hepatic fat

We next examined associations of childhood nutrient intakes with log-transformed hepatic fat in adolescence using the same modeling approach; however, we did not report the results from Model 3 (adjusted for childhood hepatic fat), because hepatic fat was assessed only at visit 2 in adolescence. In energy partition models, higher starch intake in childhood was associated with higher adolescent hepatic fat, but this reached significance only in confounder-adjusted models (Model 2) (Table 4). In nutrient density models adjusted for TEI, the positive association of childhood starch intake with adolescent hepatic fat followed a similar pattern and remained significant in confounder-adjusted models (Table 4).

Sex-specific findings

We found evidence of effect modification by sex on associations of total and animal protein intakes in childhood with abdominal VAT in adolescence, both in energy partition models ($p = 0.024$ for sex*total protein interaction and $p = 0.024$ for sex*animal protein interaction) and nutrient density models ($p = 0.013$ for sex*total protein interaction and $p = 0.020$ for sex*animal protein interaction). Sex-stratified estimates are shown in Table 5. In all models, intakes of total and

TABLE 3 Associations of nutrient intakes in childhood with abdominal VAT in adolescence

	Model 1: Unadjusted[a] (n = 302)		Model 2: + Confounders[b] (n = 294)		Model 3: + Childhood VAT[c] (n = 282)	
Energy partition models	β (95% CI)[d]	p	β (95% CI)[d]	p	β (95% CI)[d]	p
Nutrient (kcal/d)						
Energy	0.4 (−0.1, 0.9)	0.07	0.1 (−0.3, 0.6)	0.56	0.1 (−0.3, 0.5)	0.56
Carbohydrates	−0.2 (−1.3, 0.9)	0.69	−0.2 (−1.2, 0.8)	0.70	−0.2 (−1.0, 0.7)	0.72
Starch	0.5 (−2.4, 3.4)	0.72	0.5 (−2.2, 3.2)	0.73	0.3 (−1.9, 2.6)	0.76
Sugar	−0.5 (−2.0, 1.0)	0.51	−0.4 (−1.8, 1.0)	0.59	−0.3 (−1.5, 0.9)	0.66
Protein	2.6 (−2.2, 7.3)	0.29	2.3 (−2.2, 6.8)	0.32	3.6 (−0.2, 7.4)	0.07
Animal protein	2.8 (−1.5, 7.0)	0.20	2.0 (−2.0, 6.0)	0.32	2.7 (−0.7, 6.1)	0.12
Total fat	1.2 (−0.4, 2.7)	0.14	0.4 (−1.1, 1.8)	0.63	0.1 (−1.1, 1.3)	0.89
SFA	0.1 (−4.7, 4.8)	0.98	−1.6 (−6.1, 2.9)	0.50	−1.3 (−5.0, 2.5)	0.52
MUFA	3.0 (−1.3, 7.2)	0.17	1.7 (−2.2, 5.6)	0.40	0.7 (−2.7, 4.0)	0.69
PUFA	5.1 (−2.8, 12.9)	0.20	2.8 (−4.6, 10.3)	0.45	1.1 (−5.2, 7.5)	0.72
Nutrient density models	β (95% CI)[e]	p	β (95% CI)[d]	p	β (95% CI)[d]	p
Nutrient (%TEI)						
Carbohydrates	−1.5 (−3.5, 0.4)	0.12	−0.7 (−2.5, 1.1)	0.43	−0.6 (−2.1, 0.9)	0.46
Starch	−0.4 (−3.6, 2.8)	0.82	0.1 (−2.8, 3.1)	0.93	0.2 (−2.3, 2.7)	0.89
Sugar	−1.3 (−3.3, 0.7)	0.19	−0.6 (−2.5, 1.2)	0.50	−0.5 (−2.0, 1.1)	0.54
Protein	3.0 (−2.5, 8.4)	0.28	2.3 (−2.8, 7.4)	0.38	3.7 (−0.7, 8.0)	0.10
Animal protein	3.0 (−1.5, 7.6)	0.19	2.1 (−2.2, 6.4)	0.34	2.7 (−0.9, 6.3)	0.14
Total fat	1.5 (−0.9, 3.8)	0.22	0.5 (−1.7, 2.6)	0.67	0.1 (−1.8, 1.9)	0.94
SFA	0.9 (−4.5, 6.3)	0.74	−1.1 (−6.2, 4.0)	0.66	−0.9 (−5.2, 3.4)	0.69
MUFA	3.3 (−1.5, 8.2)	0.18	1.8 (−2.7, 6.3)	0.43	0.7 (−3.1, 4.5)	0.71
PUFA	4.6 (−3.8, 13)	0.28	2.9 (−5.1, 10.9)	0.48	1.0 (−5.8, 7.8)	0.78
Fiber	−2.1 (−8.4, 4.2)	0.51	−4.4 (−10.7, 1.8)	0.17	−3.8 (−9.1, 1.6)	0.17

Abbreviations: MUFA, monounsaturated fat; PUFA, polyunsaturated fat; SFA, saturated fat; TEI, total energy intake; VAT, visceral adipose tissue.

[a]Model 1: adjusted for energy intake from all other nutrients (energy partition models) or TEI (nutrient density models).

[b]Model 2: adjusted for Model 1 covariates plus sex, age, race/ethnicity, household income, pubertal stage, physical activity, BMI category at visit 1, maternal diabetes mellitus exposure, and Healthy Eating Index-2010 total score at visit 1. Eight participants excluded because of missing data for household income (n = 1), pubertal stage (n = 1), or physical activity (n = 6).

[c]Model 3: adjusted for Model 2 covariates plus abdominal VAT in childhood. Twelve participants excluded because of missing data for abdominal VAT at visit 1.

[d]Estimated per 100-kcal/d increase in each nutrient.

[e]Estimated per 5% increase in each nutrient (except fiber, per 5 g/1,000 kcal increase).

animal protein in childhood were associated with higher VAT in adolescence in boys but not girls (Table 5).

Post hoc analyses

Because the associations between total fat, MUFA, and PUFA intakes in childhood and abdominal SAT in adolescence were attenuated after adjusting for childhood SAT, we performed a post hoc analysis to examine associations between nutrient intakes in childhood with change in SAT from childhood to adolescence to assess whether the associations reflected an increase in SAT from childhood or reflected an association already present in childhood. As shown in Supporting Information Table S3, higher PUFA intake in childhood was associated with an increase in SAT from childhood to adolescence but only in nutrient density models (β [95% CI]: 39.4 [2.8-76.0] mm^2 per 5% TEI). There were no other associations between total fat intake or MUFA intake with change in abdominal SAT from childhood to adolescence (Table S3), suggesting most associations between these nutrient intakes and abdominal SAT were already present earlier in childhood.

DISCUSSION

The etiology of body fat partitioning in youth is complex and multifactorial, but lifestyle factors—including diet—are likely important contributors to interindividual differences. In this study, we examined

TABLE 4 Associations of nutrient intakes in childhood with log-transformed hepatic fat in adolescence

	Model 1: Unadjusted[a] ($n = 302$)		Model 2: + Confounders[b] ($n = 294$)	
Energy partition models	β (95% CI)[c]	p[e]	β (95% CI)[c]	p[e]
Nutrient (kcal/d)				
Energy	1.01 (0.99, 1.02)	0.14	1.00 (0.99, 1.02)	0.53
Carbohydrates	1.00 (0.98, 1.03)	0.76	1.01 (0.98, 1.03)	0.71
Starch	1.07 (0.99, 1.14)	0.05	1.07 (1.01, 1.15)	**0.039**
Sugar	0.98 (0.95, 1.02)	0.33	0.98 (0.95, 1.02)	0.39
Protein	0.96 (0.86, 1.08)	0.53	0.91 (0.82, 1.02)	0.12
Animal protein	0.99 (0.89, 1.09)	0.80	0.94 (0.85, 1.04)	0.26
Total fat	1.02 (0.98, 1.06)	0.27	1.01 (0.98, 1.05)	0.51
SFA	0.98 (0.87, 1.09)	0.68	0.96 (0.86, 1.08)	0.48
MUFA	1.06 (0.96, 1.18)	0.22	1.05 (0.95, 1.16)	0.31
PUFA	1.09 (0.91, 1.31)	0.36	1.10 (0.91, 1.33)	0.32
Nutrient density models	β (95% CI)[c]	p[e]	β (95% CI)[c]	p[e]
Nutrient (%TEI)				
Carbohydrates	1.00 (0.95, 1.04)	0.85	1.01 (0.96, 1.06)	0.71
Starch	1.07 (0.99, 1.15)	0.08	1.09 (1.01, 1.17)	**0.025**
Sugar	0.97 (0.92, 1.01)	0.17	0.98 (0.93, 1.02)	0.31
Protein	0.96 (0.85, 1.09)	0.53	0.90 (0.79, 1.02)	0.10
Animal protein	0.98 (0.88, 1.09)	0.75	0.93 (0.84, 1.04)	0.22
Total fat	1.01 (0.96, 1.07)	0.71	1.00 (0.95, 1.06)	0.89
SFA	0.95 (0.84, 1.08)	0.43	0.93 (0.82, 1.06)	0.28
MUFA	1.05 (0.94, 1.17)	0.42	1.04 (0.93, 1.16)	0.51
PUFA	1.07 (0.88, 1.30)	0.50	1.09 (0.89, 1.34)	0.42
Fiber	1.00 (0.86, 1.16)	0.99	0.96 (0.82, 1.13)	0.65

Abbreviations: MUFA, monounsaturated fat; PUFA, polyunsaturated fat; SFA, saturated fat; TEI, total energy intake.

[a]Model 1: adjusted for energy intake from all other nutrients (energy partition models) or TEI (nutrient density models).

[b]Model 2: adjusted for Model 1 covariates plus sex, age, race/ethnicity, household income, pubertal stage, physical activity, BMI category at visit 1, maternal diabetes mellitus exposure, and Healthy Eating Index-2010 total score at visit 1. Twelve participants excluded because of missing data for household income ($n = 1$), pubertal stage ($n = 1$), or physical activity ($n = 6$).

[c]Estimated per 100-kcal/d increase in each nutrient. Beta-coefficients have been back-transformed and reflect the ratio of geometric means for hepatic fat.

[d]Estimated per 5% increase in each nutrient (except fiber, per 5 g/1,000 kcal increase). Beta-coefficients have been back-transformed and reflect the ratio of geometric means for hepatic fat.

[e]Bolding indicates $p < 0.05$.

the influence of dietary intake in childhood on future body fat deposition in adolescence, particularly in terms of abdominal and ectopic liver fats measured by MRI. Our analyses revealed that certain nutrient intakes in childhood exhibit differential associations with abdominal and hepatic fat deposition later in adolescence. Specifically, we found that childhood MUFA and PUFA intakes were associated with higher abdominal SAT in adolescence, and childhood starch intake was associated with higher hepatic fat in adolescence. In boys only, we also found that childhood total protein intake, particularly as animal protein, was associated with higher abdominal VAT in adolescence. Importantly, most findings were similar when adjusted for potential confounders, including TEI in nutrient density models, supporting independent pathways linking these nutrient intakes to specific body fat depots. However, associations of childhood MUFA and PUFA intakes with adolescent abdominal SAT were markedly attenuated after adjusting for childhood abdominal SAT, which suggests that associations were partially already present in childhood and that interventions aiming to reduce abdominal SAT may need to target these intakes even earlier in childhood. It should also be noted that these findings were based on estimates and 95% CIs, and only a few associations survived multiple hypothesis testing corrections. Thus, most associations we found between childhood nutrient intakes and adolescent abdominal or hepatic fat should be considered modest and will need to be confirmed in other prospective studies.

Although many studies have examined the nutritional determinants of childhood obesity in general, far fewer have examined the

TABLE 5 Sex-specific associations of total protein and animal protein intakes in childhood with abdominal VAT in adolescence in the analytical sample ($n = 302$)

		Model 1: Unadjusted[a] ($n = 302$)		Model 2: + Confounders[b] ($n = 294$)		Model 3: + Childhood VAT[c] ($n = 282$)	
Energy partition models	Sex	β (95% CI)[d]	p[f]	β (95% CI)[d]	p[f]	β (95% CI)[d]	p[f]
Nutrient (kcal/d)							
Total protein	Girls	−0.9 (−6.8, 4.9)	0.75	−1.3 (−6.9, 4.2)	0.64	−0.6 (−5.3, 4.0)	0.79
	Boys	5.8 (0.5, 11.2)	**0.033**	4.8 (−0.2, 9.8)	0.06	6.4 (2.2, 10.6)	**0.003***
Animal protein	Girls	−0.9 (−6.5, 4.6)	0.74	−2.0 (−7.4, 3.4)	0.46	−2.3 (−6.8, 2.3)	0.33
	Boys	6.9 (1.6, 12.2)	**0.011***	5.3 (0.3, 10.3)	**0.036**	6.7 (2.6, 10.8)	**0.002***
Nutrient density models	Sex	β (95% CI)[d]	p[f]	β (95% CI)[d]	p[f]	β (95% CI)[d]	p[f]
Nutrient (%TEI)							
Total protein	Girls	−3.6 (−11.2, 4.1)	0.36	−4.1 (−11.2, 3.0)	0.26	−1.9 (−8.0, 4.1)	0.53
	Boys	10.2 (2.5, 17.8)	**0.009***	8.8 (1.6, 15.9)	**0.016***	9.2 (3.2, 15.1)	**0.003***
Animal protein	Girls	−1.5 (−7.6, 4.6)	0.64	−2.5 (−8.2, 3.3)	0.40	−2.0 (−6.9, 2.8)	0.41
	Boys	9.4 (2.6, 16.3)	**0.007***	7.7 (1.3, 14.0)	**0.018**	8.3 (3.0, 13.6)	**0.002***

Abbreviations: TEI, total energy intake; VAT, visceral adipose tissue.

[a]Model 1: adjusted for energy intake from all other nutrients (energy partition models) or TEI (nutrient density models).

[b]Model 2: adjusted for Model 1 covariates plus sex, age, race/ethnicity, household income, pubertal stage, physical activity, BMI category at visit 1, maternal diabetes mellitus exposure, and Healthy Eating Index-2010 total score at visit 1. Eight participants excluded because of missing data for household income ($n = 1$), pubertal stage ($n = 1$), or physical activity ($n = 6$).

[c]Model 3: adjusted for Model 2 covariates plus abdominal VAT in childhood. Twelve participants excluded because of missing data for abdominal VAT at visit 1.

[d]Estimated per 100-kcal/d increase in each nutrient.

[e]Estimated per 5% increase in each nutrient (except fiber, per 5 g/1,000 kcal increase).

[f]Bolding indicates $p < 0.05$. Asterisk (*) indicates if below Bonferroni-adjusted $p < 0.017$ (0.05/3 outcomes).

determinants of body fat partitioning in youth. This is particularly true for large, prospective cohort studies, because of the cost and time requirements of the imaging techniques (such as MRI) needed to accurately measure specific body fat depots. Regarding abdominal fat deposition, we found a novel association between childhood unsaturated fat intake and adolescent abdominal SAT in this study. This effect was particularly strong for PUFA intake, which predicted an increase in abdominal SAT from childhood to adolescence, and may relate to the pro-inflammatory and adipogenic potential of *n*-6 PUFAs (32), especially in the context of a high dietary ratio of *n*-6 to *n*-3 PUFAs, which is characteristic of a Western diet. Future studies will be needed to fully elucidate the underlying mechanisms at play, as well as to determine whether the effect of PUFAs on adolescent SAT depends on the nutrient being substituted (i.e., carbohydrates vs. fat).

We also found that higher childhood protein intake, especially from animal sources, was associated with higher adolescent VAT but only in boys. Although the literature on animal protein intake and VAT is limited, other studies in children (33,34) and adults (35,36) have also observed an association between higher intakes of animal protein and/or certain amino acid-derived metabolites with abdominal adiposity measured by anthropometrics (i.e., waist circumference or waist-to-height ratio). Our findings, therefore, add to this body of literature by showing that animal protein intake in childhood may be specifically associated with MRI-measured abdominal VAT in boys. One proposed mechanism for these associations is the ability of animal protein to upregulate insulin and insulin-like growth factor-1 (37), which stimulates adipocyte proliferation and differentiation (38) and interacts with growth hormone to regulate energy metabolism in both the liver and adipose tissue (39). Our finding that this association was only in boys may reflect the established sexual dimorphism of visceral adiposity and suggests that animal protein intake may interact with mechanisms that predispose boys to more VAT compared with girls, including differential levels of reproductive and growth hormones, differential distribution of estrogen receptors in abdominal versus peripheral fat, and/or differential expression of lipolytic (β1-2) and antilipolytic (α2) adrenergic receptors in VAT (18).

Regarding adolescent hepatic fat, we found a positive association with childhood starch intake, which is also difficult to interpret given many different foods contain starch. Because we did not find an association between childhood fiber intake and adolescent hepatic fat, we hypothesize that this association was more likely driven by high-starch foods that are low in fiber, such as refined grains, but this will need to be tested in the future. Unexpectedly, we found no associations between childhood total sugar intake and adolescent abdominal VAT or hepatic fat, which conflicts with experimental studies in children showing that dietary sugar restriction is associated with reductions in these body fat depots (14,15), as noted in the introduction. We also found no associations with childhood fiber

intake, despite dietary fiber often being associated with a more optimal body fat distribution in adolescence (40,41). These discrepant findings may be due to differences in sample characteristics, because most other studies in this area have focused on youth with obesity, compared with the generally healthy sample of youth in EPOCH. It may also be due to the prospective nature of this study, with approximately 6 years of follow-up between exposure and outcome assessments, suggesting that intakes of these nutrients (i.e., sugar, fiber) more proximal to adolescence may be more relevant to body fat partitioning patterns than intakes earlier in childhood.

Another potential explanation for some null findings is that, even after excluding TEI under-reporters, there was still some degree of under-reporting in the sample. A limitation of this study is, therefore, our reliance on self-reported dietary intake data, which can be prone to social desirability bias, particularly in individuals with obesity (42), and may contribute to dietary under-reporting, resulting in attenuated associations. Thus, our findings may be conservative estimates of true associations. There may also be measurement error specifically associated with data derived from FFQ due to incomplete food lists or inaccuracies in frequency or portion size estimations (43). At the same time, a FFQ is the most common and feasible approach for large epidemiological studies, such as EPOCH, due to their low respondent burden and ability to rank individuals according to longer-term, habitual intake, which is most relevant to the development of chronic diseases, such as NAFLD. In addition, the FFQ used in EPOCH was modified for and validated in children (22,23), and we took several additional steps to limit error, such as excluding under-reporters and adjusting for energy intake in nutrient density models (44).

Other limitations include the observational nature of this study, which limits causal inference. We did not measure hepatic fat at visit 1 in childhood; therefore, we were unable to adjust for childhood levels of hepatic fat, similar to the modeling approach used for abdominal SAT and VAT. We relied on other self-reported variables, as well, such as for pubertal stage and physical activity, which may be prone to measurement error. The sample was from one geographic region in the United States (Colorado), and participants were selected based on exposure to maternal DM during pregnancy; although we adjusted for the latter exposure in models, this may reduce the generalizability. In addition, we mainly interpreted our findings based on raw estimates and 95% CIs to avoid type 1 error (45), but it should be noted that several associations did not survive Bonferroni-correction and should be interpreted with caution.

Strengths include the use of complementary modeling strategies to examine associations between nutrient intakes and body fat deposition before and after adjusting for energy intake. Specifically, using energy partition models, we were able to evaluate the effect of an absolute increase in each nutrient, and using multivariate nutrient density models, we were able to evaluate the isocaloric effect of each nutrient holding TEI constant. We used state-of-the-art MRI technology to accurately assess abdominal SAT and VAT depots and hepatic fat in adolescence, the primary outcomes of interest, ensuring the reliability and reproducibility of findings. The longitudinal nature of the cohort enabled us to better establish temporality in evaluating associations between childhood nutrient intakes and future adiposity outcomes in adolescence, which not only limited potential reverse causality but also provided insights that may be used to inform future prevention efforts. Lastly, the EPOCH cohort was well-characterized in terms of anthropometric, lifestyle, behavioral, and biological variables; multiethnic; and included both lean individuals and individuals with overweight or obesity. Thus, as a general risk population, our findings represent associations that are present before the development of severe body fat distribution phenotypes and may be used to inform dietary guidelines.

In conclusion, the results from this prospective analysis suggest that childhood nutrient intakes exhibit differential associations with adolescent abdominal and hepatic fats; PUFA and MUFA intakes were associated with adolescent abdominal SAT, total and animal protein intakes were associated with adolescent abdominal VAT in boys, and starch intake was associated with adolescent hepatic fat. These findings may be used to inform dietary interventions aiming to promote a healthier body fat distribution in youth. Because some associations, especially between childhood fat intake and abdominal SAT, were attenuated after adjusting for childhood adiposity, this suggests that such interventions may be particularly effective if implemented earlier in childhood, before the progression of body composition phenotypes into adolescence.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS

CCC and DD conceptualized the study. CCC performed data analyses and wrote the manuscript. WP, TAB, and KS contributed to study design and data interpretation. BMR assisted with data curation. AS contributed to study design and conducted imaging analyses. DD established the cohort and acquired funding. All authors critically reviewed and revised the manuscript. All authors have read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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