Plasma Nutrient Biomarkers Are Associated with Waist-to-Height Ratio in Youth with Type 1 Diabetes[1–4]

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Abstract

Background: Plasma fatty acids (FAs) and micronutrients have been associated with central obesity in adults; however, previous studies of these associations in adults have yielded mixed results. In addition, no comparable research has been conducted among youth with type 1 diabetes (T1D).

Objective: We investigated the cross-sectional and longitudinal associations between plasma nutrient biomarkers and waist-to-height ratio (WHtR) in youth with T1D.

Methods: These analyses included 1324 youth aged 3–20 y at T1D diagnosis with a baseline visit in the SEARCH (Search for Diabetes in Youth) Study and a subset of 1178 of these youth with a follow-up visit an average of 23 mo (range: 16–40 mo) after their baseline visit. Plasma phospholipid FAs and vitamins were measured, and estimated desaturase activities were calculated at baseline. Anthropometric measurements and diabetes-related assessments were collected at each visit. Multiple linear regression was used to examine the association between plasma nutrient biomarkers and WHtR.

Results: In cross-sectional analysis, plasma palmitic acid ($P = 0.004$), dihomo-γ-linolenic acid (DGLA; $P = 0.017$) and Δ6 desaturase (D6D; $P = 0.006$) were positively correlated with WHtR after adjustment of confounders. Oleic acid (OA; $P = 0.002$), linoleic acid (LA; $P = 0.015$), Δ9 desaturase 18 (D9D-18; $P = 0.027$), and vitamin D ($P < 0.0001$) were negatively correlated with WHtR after adjustment. Weight status was an effect modifier ($P < 0.05$). In normal-weight youth, vitamin D ($P = 0.003$) was negatively associated with WHtR. In obese youth, stearic acid ($P = 0.037$), DGLA ($P < 0.0001$), and D6D ($P < 0.0001$) were positively associated and OA ($P = 0.0008$), D9D-18 ($P = 0.0006$), and vitamin D ($P < 0.0001$) were negatively associated with WHtR. In longitudinal analysis, baseline linoleic acid ($P = 0.018$), n–6:n–3 (ω-3:ω-6) FA ratio ($P = 0.029$), vitamin D ($P = 0.003$), and vitamin E ($P < 0.0001$) were negatively correlated with WHtR at follow-up only in obese participants.

Conclusions: In T1D youth, plasma FAs and vitamins are associated with WHtR and are modified by weight status. These associations are particularly marked in obese youth. *J Nutr* 2015;145:579–86.

Keywords: plasma biomarker, plasma fatty acids, central obesity, waist-to-height ratio, type 1 diabetes

Introduction

Children and adolescents with type 1 diabetes (T1D)[15] are at high risk of cardiovascular disease (1, 2). Excess adipose tissue, especially in the abdominal region, is a well-established risk factor for the development of cardiovascular disease (3) in the general population and in individuals with T1D. Waist-to-height

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ratio (WHtR), a marker of central obesity, is the strongest correlate of total cholesterol and LDL cholesterol in youth with T1D when compared with waist circumference (WC) and BMI (4). Because overweight and obesity are common in youth with T1D (5–7), prevention of excessive abdominal fat accumulation is of particular concern in youth with T1D in order to decrease the risks of associated comorbidities, such as cardiovascular and metabolic disease, in this population.

Several etiologic factors are involved in the accumulation of adiposity, including inflammation and oxidative stress. Plasma FA composition reflects both dietary consumption and desaturase activities (8) and has been associated with metabolic syndrome and inflammation in youth. Specifically, higher proportions of plasma n–6 PUFAs are associated with more favorable blood lipid profiles than those with lower proportions in T1D youth (9) and with lower concentrations of 2 markers of low-grade inflammation (i.e., IL-6 and CRP) in overweight adolescents without diabetes (10). Further evidence suggests that deficiencies of certain micronutrients are also related to greater central obesity. Higher plasma vitamin D concentrations were associated with lower amounts of abdominal subcutaneous and visceral adipose tissue in Hispanics and African Americans (11). As a blood antioxidant, vitamin E was related to oxidative stress, which starts early in life (12) and can worsen with age (13). In overweight and obese individuals, higher serum concentration of vitamin E was also reported to be associated with lower WC (14). Despite the growing evidence to support these associations in the general population, data quantifying associations between plasma FA composition or concentrations of vitamins D and E with amounts of central obesity are limited in populations at high risk of cardiovascular disease, such as individuals with T1D.

As part of the Search for Diabetes in Youth (SEARCH) Nutrition Ancillary Study (SNAS), we investigated the cross-sectional and longitudinal association of nutritional plasma biomarkers with central obesity among youth with T1D. We hypothesized that plasma FAs, estimated desaturase activities, and vitamins D and E would be associated with WHtR and these associations would be modified by weight status. Understanding these associations in the T1D population can provide insight on strategies to prevent central obesity in this population already at risk of cardiovascular disease.

Methods

Population

The SEARCH for Diabetes in Youth Study is an ongoing observational study with 5 research centers designed to describe the epidemiology of childhood diabetes. The SNAS was derived from the SEARCH study, with the aim to examine the associations of nutritional factors with diabetes-related health outcomes among youth with T1D. The SEARCH study has ascertained cases of incident T1D in youth younger than 20 since 2002, with follow-up data collected at ~1 and 2 y post–baseline visit. Both SEARCH and SNAS were reviewed and approved annually by the appropriate institutional review boards. Written informed consent and assent were obtained from parents of participants <18 y and from participants aged ≥18 y at the time of data collection.

Subject inclusion

These analyses include data from the 2002–2005 incident cohorts of SEARCH, consisting of participants who were aged 3–20 y when diagnosed. Cross-sectional analysis included participants who had at least one available nutritional plasma biomarker (FAs, vitamin D, or vitamin E) and WHtR from their baseline visit. The sample included 1324 participants, 1104 of whom had at least one measurement of anthropometry at follow-up and were included in the longitudinal analysis. (See **Supplemental Figure 1** for flowchart of subject inclusion.)

Data collection

Assessment of central obesity. Central obesity is commonly assessed as WC and WHtR in adults. WHtR, which is calculated as WC divided by height, is superior to WC alone as a marker of trunk adiposity in youth (15). Furthermore, WHtR was the strongest indicator for 3 cardiovascular risk factors (total cholesterol, LDL cholesterol, and diastolic blood pressure) in youth with T1D in SEARCH (4). Therefore, we used WHtR as the marker of central obesity in youth with T1D in the present study.

WC was assessed as the circumference just above the right iliac crest at the midaxillary line according to the NHANES protocol (16). WC and height were measured twice in centimeters by using a measuring tape and stadiometer, respectively. If the first 2 measures differed by >1.0 cm for WC or by >0.5 cm for height, a third measurement was made. WHtR was calculated by using measured waist (cm) divided by measured height (cm). Weight was determined in kilograms by an electronic scale to the nearest 0.1 kg. BMI was calculated for each subject. Overweight was defined as a BMI ≥85th and <95th percentile and obesity was defined as a BMI ≥95th percentile (7).

Assessment of nutrient biomarkers. Plasma nutrient biomarkers were measured by using frozen fasting blood samples that were collected at the time of the SEARCH baseline examination. For FA measures, total lipids were extracted from plasma by the Bligh-Dyer method, and phospholipids were separated from all other lipids by using one-dimensional thin-layer chromatography. The proportion of plasma phospholipid FAs was measured by GC after preparation that included saponification and transmethylation (17). Data were analyzed with ChemStation Firmware A.01.09 (Agilent Technologies).

On the basis of a comprehensive review of the literature, we focused our analyses on select plasma FAs previously related to cardiovascular risk factors. These included the following: *1*) SFAs [palmitic acid (PA; 16:0), stearic acid (SA; 18:0)], *2*) MUFAs [palmitoleic acid (POA; 16:1), oleic acid (OA; 18:1)], *3*) n–6 PUFAs [linoleic acid (LA; 18:2), dihomo-γ-linolenic acid (DGLA; 20:3), arachidonic acid (AA; 20:4)], *4*) n–3 PUFAs [α-linolenic acid (ALA; 18:3), EPA (20:5), and DHA (22:6)], and *5*) the n–6:n–3 FA ratio (10) [(LA + AA + DGLA)/(EPA + DHA + ALA)]. Estimated desaturase activities (18) were calculated as ratios of FAs: Δ5 desaturase (D5D) activity = AA/DGLA, Δ6 desaturase (D6D) activity = DGLA/LA, Δ9 desaturase 16 (D9D-16) activity = POA/PA, and Δ9 desaturase 18 (D9D-18) activity was calculated by OA/SA.

The plasma concentration of 25-hydroxyvitamin D [25(OH)D] was determined by the direct competitive chemiluminescence immunoassay, which measures 25-hydroxyergocalciferol and 25-hydroxycholecalciferol (17) (interassay CV: 11.0%). The concentration of vitamin E (α-tocopherol) in plasma was assayed by HPLC according the method of Cheng et al. (19) (interassay CV <5%).

Covariates

The following demographic and diabetes-related data were collected at the baseline visit: sex, self-reported race/ethnicity, age, season (only for vitamin D), parental education, household income, and clinic site. Data on diabetes duration and treatment regimen, including type of insulin, total daily insulin dose (units/kg), frequency of insulin injections, or use of continuous subcutaneous insulin infusion (insulin pump) were

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[4] Supplemental Figure 1 and Supplemental Tables 1 and 2 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.
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[15] Abbreviations used: AA, arachidonic acid; ALA, α-linolenic acid; DGLA, dihomo-γ-linolenic acid; D5D, Δ5 desaturase; D6D, Δ6 desaturase; D9D-16, Δ9 desaturase 16; D9D-18, Δ9 desaturase 18; LA, linoleic acid; LOD, limit of detection; OA, oleic acid; PA, palmitic acid; POA, palmitoleic acid; SA, stearic acid; SEARCH, Search for Diabetes in Youth; SNAS, SEARCH Nutrition Ancillary Study; T1D, type 1 diabetes; WC, waist circumference; WHtR, waist-to-height ratio; 25(OH)D, 25-hydroxyvitamin D.

collected from the parent for participants <18 y or from the participants who were ≥18 y. Fasting blood samples were obtained under conditions of metabolic stability (i.e., no episode of diabetic ketoacidosis during the previous month). Glycated hemoglobin was measured in whole blood with an automated, nonporous ion-exchange HPLC system (model G-7; Tosoh Bioscience).

Statistical analysis

Of the 944 participants whose plasma samples were assayed for FAs, 7 were missing POA, 23 were missing ALA, and 7 were missing EPA. No other FA data were missing. Missing FA percentages may result from an undetected peak (referred to as "nondetects"), which is likely indicative of a value lower than the detectable limit. Omission of these values can bias results, and the literature suggests that when the number of nondetects is small (Environmental Protection Agency guidelines state <15%), it is appropriate to perform simple imputation, replacing missing values with small values. The small value chosen is commonly based on the limit of detection (LOD), such as LOD/2 or LOD/$\sqrt{2}$. The units of the FAs are a "percentage of total," and the LOD is not well defined in these units, so we replaced the nondetects with half the lowest observed value. As a sensitivity analysis, the results were compared with models with no imputation. No differences were found for POA, ALA, and EPA in models without and with imputation.

Because of the possibility that associations of plasma nutrient biomarkers with WHtR might differ according to weight status, the sample was stratified by BMI category. Descriptive analyses were conducted to examine the distribution of demographic measures and baseline nutritional biomarkers across the 3 BMI categories (underweight/normal weight, overweight, and obese). Chi-square tests and general linear models were used to compare the 3 groups for categorical data and continuous data, respectively. Comparison of plasma biomarkers between the different groups were made with post hoc tests.

Multiple linear regression was used to examine baseline associations between each nutritional biomarker and WHtR. Models adjusted for the following potential confounders: *1*) demographic variables [age, sex, race/ethnicity, season (only for vitamin D), highest level of parental education, clinic site], *2*) diabetes-related variables (diabetes duration, insulin regimen, insulin dose per kilogram, glycated hemoglobin), and *3*) BMI group. Model 1 was unadjusted, model 2 adjusted for demographic and diabetes-related variables, and model 3 further adjusted for BMI. Because weight status may modify the association between plasma biomarkers and central obesity, the interaction between BMI group and each plasma biomarker was further tested (model 4). A statistically significant interaction indicated that the relation differed across weight status.

Multiple linear regression was again used to examine the relation between baseline plasma nutritional biomarkers and WHtR at follow-up. These models adjusted for the same potential confounders as in the cross-sectional models, with additional adjustment for baseline WHtR and time between baseline and follow-up measurements.

Logistic regression was used to predict the odds of incident central obesity at follow-up from baseline plasma nutrient biomarkers. Central obesity was defined as measured WC at or above the NHANES-based age- and sex- specific 90th percentile (20). Incident central obesity was defined as occurring in participants who were not centrally obese at baseline but became centrally obese at follow-up. Models adjusted for the same potential confounders as in the longitudinal multiple regression models. For the stability of logistic models, some subgroups of categorical confounders were combined. Model results are described by using estimated ORs for the incidence of central obesity. All analyses were performed by using SAS (version 9.2; SAS Institute), with $P < 0.05$ as the significance level.

Results

Characteristics of participants at baseline. Characteristics of participants at the time of the baseline visit stratified by weight status are shown in **Table 1**. In this sample of youth with T1D (n = 1324), all ages and both sexes were similarly distributed across weight status groups. However, overweight and obese participants were more likely to be non-Hispanic black, to have parents with lower education, to have lower income, or to take any combination of insulin excluding long insulin (≥3 times/d); and they were less likely to be using pump therapy. In overweight and obese participants, the prevalence of central obesity was 25.2% and 78.0%, respectively.

Several of the plasma nutrient biomarkers varied substantially by weight status. Compared with normal-weight participants, overweight youth had higher DGLA and lower OA, D9D-18 activity, and vitamin D; obese youth had higher SA, DGLA, AA, and D6D activity and lower OA, LA, D9D-18 activity, and vitamin D.

Cross-sectional association between plasma nutrient biomarkers and WHtR. The unadjusted baseline associations between nutrient biomarkers and WHtR and the associations after adjustment for potential confounders and weight status are shown in **Table 2**. Across all levels of adjustment, PA, DGLA, and D6D activity were consistently positively associated with WHtR; OA, LA, D9D-18 activity, and vitamin D were inversely associated with WHtR. Other associations did not persist across all levels of adjustment. Specifically, SA and AA were positively associated with WHtR in the unadjusted model (model 1). With additional adjustment for demographic characteristics and diabetes-related confounders (model 2), EPA was positively and D5D was negatively associated with WHtR, respectively. However, these associations were no longer significant after further adjustment for weight status (model 3).

When the biomarker-WHtR relations were examined according to weight status (Table 2, model 4), we found evidence of an interaction between SA, OA, DGLA, D6D activity, D9D-18 activity, vitamin D, and weight status. The positive association of WHtR with SA, DGLA, and D6D activity was only significant in the obese group. In both the normal-weight and obese group, but not in the overweight group, vitamin D was negatively related to WHtR. In the overweight and obese group, OA and D9D-18 activity were negatively associated with WHtR.

Longitudinal association between baseline plasma nutrient biomarkers and WHtR at follow-up. The relations between baseline nutritional biomarkers and follow-up WHtR are shown in **Table 3**. Higher vitamin D was associated with lower WHtR at follow-up in models 1 and 3, but no other biomarkers were significantly related to WHtR at follow-up. The interaction between the biomarkers and weight status at follow-up was significant for LA, the n–6:n–3 FA ratio, vitamin D, and vitamin E. Lower LA, n–6:n–3 FA ratio, vitamin D, and vitamin E at baseline were found to be associated with higher WHtR at follow-up only in obese participants.

Odds of central obesity at follow-up. During the follow-up period, 70 new cases of central obesity among the 923 participants who were initially free of central obesity (**Supplemental Table 1**) were observed. Incident central obesity was more common in males, in participants aged ≥15 y at follow-up, and with family incomes of <$50,000/y. A potential protective effect of SA (model 3) and vitamin D (model 1) against the occurrence of central obesity was observed (**Supplemental Table 2**).

Discussion

In the present cross-sectional and longitudinal analyses, several plasma nutrient biomarkers (PA, SA, OA, LA, DGLA, D6D

TABLE 1 Baseline characteristics of SEARCH 2002–2005 incident type 1 diabetes cases according to weight status[1]

	All	Normal weight	Overweight	Obese	*P*
n	1324	883	262	177	
Age category, *n* (%)					0.61
2–4 y	66 (5.0)	46 (5.2)	15 (5.7)	5 (2.8)	
5–9 y	423 (32.0)	288 (32.6)	75 (28.6)	60 (33.9)	
10–14 y	597 (45.2)	389 (44.1)	128 (48.9)	80 (45.2)	
≥15 y	236 (17.9)	160 (18.1)	44 (16.8)	32 (18.1)	
Sex, *n* (%)					0.25
Female	652 (49.3)	435 (49.3)	138 (52.7)	79 (44.6)	
Male	670 (50.7)	448 (50.7)	124 (47.3)	98 (55.4)	
Race, *n* (%)					<0.0001
Non-Hispanic black	126 (9.5)	59 (6.7)	27 (10.3)	40 (22.6)	
Non-Hispanic white	1031 (78.0)	733 (83.0)	190 (72.5)	108 (61.0)	
Other	165 (12.5)	91 (1.03)	45 (17.2)	29 (16.4)	
Parental education, *n* (%)					<0.0001
Less than high school	61 (4.6)	33 (3.8)	14 (5.4)	14 (8.0)	
High school graduate	194 (14.7)	119 (13.5)	40 (15.3)	35 (19.9)	
Some college/associate's degree	442 (33.6)	274 (31.2)	90 (34.5)	78 (44.3)	
Bachelor's degree or more	619 (47.0)	453 (51.5)	117 (44.83)	49 (27.8)	
Income, *n* (%)					<0.0001
Don't know/refused	87 (6.6)	69 (7.9)	8 (3.1)	10 (5.7)	
<$25,000	160 (12.2)	89 (10.1)	37 (14.1)	34 (19.3)	
$25,000–$49,999	299 (22.7)	179 (20.4)	65 (24.8)	55 (31.3)	
$50,000–$74,999	261 (19.8)	168 (19.1)	56 (21.4)	37 (21.0)	
≥$75,000	510 (38.7)	374 (42.6)	96 (36.6)	40 (22.7)	
Season of visit, *n* (%)					0.68
Spring	326 (24.7)	225 (25.5)	64 (24.4)	37 (20.9)	
Summer	369 (27.9)	249 (28.2)	70 (26.7)	50 (28.3)	
Autumn	288 (21.8)	187 (21.2)	64 (24.4)	37 (20.9)	
Winter	339 (25.6)	222 (25.1)	64 (24.4)	53 (29.9)	
Insulin regimen, *n* (%)					<0.01
Pump	121 (9.3)	80 (9.1)	31 (12.1)	10 (5.9)	
Long + short/rapid insulin (≥3 times/d)	413 (31.7)	290 (33.1)	71 (27.7)	52 (30.4)	
Long + any other combination (≥2 times/d)	90 (6.9)	74 (8.5)	12 (4.7)	4 (2.3)	
Any combination of insulin excluding long (≥3 times/d)	188 (14.4)	108 (12.3)	44 (17.2)	36 (21.1)	
Any insulin taken 1×/d or any insulin combination excluding long 2×/d	490 (37.6)	323 (36.9)	98 (38.3)	69 (40.4)	
Other[2]					
Duration of diabetes, mo	10.0 ± 6.4 (1324)	10.2 ± 6.5 (883)	10.0 ± 6.4 (262)	9.1 ± 6.1 (177)	0.10
Insulin dose, units/kg	0.6 ± 0.4 (1293)	0.6 ± 0.4 (868)	0.7 ± 0.4 (256)	0.7 ± 0.3 (169)	0.04
Outcome					
WHtR[2]	0.48 ± 0.06 (1416)	0.45 ± 0.03 (883)	0.52 ± 0.04 (262)	0.59 ± 0.07 (177)	<0.0001
Central obesity, *n* (%)	231 (16.3)	10 (1.1)	71 (25.5)	150 (77.7)	<0.0001
Nutrient biomarkers					
n	944	659	173	111	
Plasma FAs, %					
PA (16:0)	25.7 ± 1.72	25.7 ± 1.8	25.7 ± 1.6	26.0 ± 1.7	0.23
SA (18:0)	15.0 ± 1.10	15.0 ± 1.1	15.0 ± 1.0	15.4 ± 1.2*,¶	<0.01
POA (16:1)	0.4 ± 0.3	0.4 ± 0.4	0.4 ± 0.2	0.4 ± 0.2	0.66
OA (18:1)	10.0 ± 1.2	10.1 ± 1.2	9.7 ± 1.12*	9.6 ± 1.2*	<0.0001
LA (18:2)	25.4 ± 2.8	25.5 ± 2.8	25.6 ± 2.8	24.4 ± 2.6*,¶	<0.01
DGLA (20:3)	3.1 ± 0.7	3.0 ± 0.7	3.2 ± 0.7*	3.3 ± 0.6*	<0.01
AA (20:4)	13.0 ± 1.9	13.0 ± 1.9	13.1 ± 2.0	13.5 ± 2.0*	0.01
ALA (18:3)	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.27
EPA (20:5)	0.4 ± 0.3	0.4 ± 0.3	0.4 ± 0.2	0.5 ± 0.3*,¶	0.06
DHA (22:6)	2.5 ± 0.9	2.5 ± 0.9	2.5 ± 0.7	2.5 ± 0.9	0.88
n–6:n–3	14.8 ± 4.3	14.9 ± 4.2	14.7 ± 3.9	14.5 ± 5.6	0.58
D5D	4.5 ± 1.7	4.5 ± 1.9	4.4 ± 1.4	4.3 ± 1.1	0.38
D6D	0.12 ± 0.03	0.12 ± 0.03	0.13 ± 0.04	0.14 ± 0.03*,¶	<0.01
D9D-16	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.76
D9D-18	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.1*	0.6 ± 0.1*,¶	<0.0001

(Continued)

TABLE 1 *Continued*

	All	Normal weight	Overweight	Obese	*P*
Plasma vitamins[2]					
25(OH)D, nmol/L	57.4 ± 33.4 (1306)	60.6 ± 34.7 (873)	52.8 ± 30.1* (258)	48.0 ± 29.1* (173)	<0.0001
α-Tocopherol, mg/mL	6.2 ± 3.0 (1141)	6.3 ± 3.1 (765)	6.1 ± 2.8 (225)	5.9 ± 2.6 (151)	0.21

[1] Values are means ± SDs unless otherwise indicated. There were 2 missing values for BMI. *Different from normal-weight participants, $P < 0.05$; ¶Different from overweight participants, $P < 0.05$. AA, arachidonic acid; ALA, α-linolenic acid; DGLA, dihomo-γ-linolenic acid; D5D, Δ5 desaturase; D6D, Δ6 desaturase; D9D-16, Δ9 desaturase 16; D9D-18, Δ9 desaturase 18; LA, linoleic acid; OA, oleic acid; PA, palmitic acid; POA, palmitoleic acid; SA, stearic acid; WHtR, waist-to-height ratio; 25(OH)D, 25-hydroxyvitamin D.
[2] *n* in parentheses.

activity, D9D-18 activity, and vitamins D and E) were found to be associated with WHtR among youth with T1D. Specifically, higher PA, SA, and DGLA proportions and D6D activity and lower proportions of OA and LA, and concentrations of vitamins D and E and D9D-18 activity were associated with higher WHtR. Several of these associations were modified by weight status, such that stronger associations were observed in obese youth than in normal-weight and overweight youth.

The mechanism underlying the link between plasma FAs and central obesity is not clear. However, there are 2 possible mechanisms by which plasma FAs may associated with central obesity. First, certain plasma FAs may directly influence the accumulation of abdominal adiposity. A diet rich in n–3 PUFAs has been suggested to have antiobesity effects by modulating satiety (21) and increasing fat oxidation and energy expenditure (22). Studies in animals showed consistent evidence of an impact of n–3 PUFA intake on body composition; however, support in humans is less certain (23). Studies examining the role of plasma n–3 FAs in the prevention of central obesity are scarce; however, Micallef et al. (24) reported that greater concentrations of plasma phospholipid EPA and DHA were negatively associated with WC in obese adults, although the reported associations were limited by weak associations and a lack of controlling for potential confounders. In the present study, our data showed no evidence of a relation between n–3 PUFAs and WHtR in youth with T1D after accounting for several major confounders associated with both exposures and outcomes of interest.

A second mechanism might be that the plasma FAs are directly related to insulin resistance and inflammation. If this is the case, the association observed between plasma FAs and central obesity would be an indirect association and result from the strong correlation between WHtR and its metabolic consequences. n–6 FAs may be associated with central obesity through this mechanism. In the current study, a positive association between DGLA and WHtR and a negative association between LA and WHtR were identified in obese participants. The direction of these associations are consistent with results of

TABLE 2 Multiple regression analysis examining the unadjusted and adjusted associations between plasma nutrient biomarkers and WHtR at baseline in youth with type 1 diabetes[1]

	β Coefficients for WHtR at baseline						
				Model 4[5]			
Nutrient biomarker	Model 1[2]	Model 2[3]	Model 3[4]	Normal	Overweight	Obese	*P*-interaction
PA (16:0)	0.004 ± 0.001**	0.003 ± 0.001**	0.002 ± 0.001**				NS
SA (18:0)	0.004 ± 0.002*	0.003 ± 0.002	−0.0002 ± 0.0012	−0.002 ± 0.001	0.001 ± 0.003	0.007 ± 0.003*	0.042
POA (16:1)	0.01 ± 0.01	0.01 ± 0.01	0.007 ± 0.004				NS
OA (18:1)	−0.009 ± 0.002**	−0.008 ± 0.002**	−0.003 ± 0.001**	−0.002 ± 0.001	−0.006 ± 0.003*	−0.01 ± 0.01**	0.020
LA (18:2)	−0.003 ± 0.001**	−0.003 ± 0.001**	−0.001 ± 0.001*				NS
DGLA (20:3)	0.01 ± 0.01**	0.01 ± 0.01**	0.005 ± 0.002*	0.003 ± 0.002	0.001 ± 0.004	0.02 ± 0.01**	<0.01
AA (20:4)	0.002 ± 0.001*	0.002 ± 0.001	0.001 ± 0.001				NS
ALA (18:3)	−0.05 ± 0.03	−0.05 ± 0.03	−0.01 ± 0.02				NS
EPA (20:5)	0.01 ± 0.01	0.02 ± 0.01**	0.006 ± 0.004				NS
DHA (22:6)	0.002 ± 0.002	0.002 ± 0.002	0.001 ± 0.001				NS
n–6:n–3 FAs	−0.0006 ± 0.0005	−0.0004 ± 0.0004	−0.0002 ± 0.0003				NS
D5D	−0.001 ± 0.001	−0.003 ± 0.001*	−0.0003 ± 0.0008				NS
D6D	0.24 ± 0.06**	0.31 ± 0.06**	0.11 ± 0.04**	0.07 ± 0.05	0.05 ± 0.08	0.45 ± 0.11**	<0.01
D9D-16	0.23 ± 0.16	0.25 ± 0.15	0.16 ± 0.10				NS
D9D-18	−0.12 ± 0.02**	−0.09 ± 0.02**	−0.03 ± 0.01*	−0.004 ± 0.016	−0.06 ± 0.03*	−0.12 ± 0.04**	<0.01
Vitamin D	−0.0003 ± 0.0001**	−0.0002 ± 0.0001**	−0.0001 ± 0.0001**	−0.0001 ± 0.0001*	−0.0001 ± 0.0001	−0.0005 ± 0.0001**	<0.01
Vitamin E	−0.0009 ± 0.0006	−0.0005 ± 0.0006	−0.0001 ± 0.0004				NS

[1] Values are β estimates ± SEs. *$P < 0.05$, **$P < 0.01$. AA, arachidonic acid; ALA, α-linolenic acid; DGLA, dihomo-γ-linolenic acid; D5D, Δ5 desaturase; D6D, Δ6 desaturase; D9D-16, Δ9 desaturase 16; D9D-18, Δ9 desaturase 18; LA, linoleic acid; OA, oleic acid; PA, palmitic acid; POA, palmitoleic acid; SA, stearic acid; WHtR, waist-to-height ratio.
[2] Model 1 was unadjusted.
[3] Model 2 adjusted for demographic variables [age, sex, race/ethnicity, season (only for vitamin D), parental education, household income, clinic site] and diabetes-related variables (diabetes duration, insulin regimen, insulin dose, and glycated hemoglobin).
[4] Model 3 further adjusted for BMI group.
[5] Model 4 further included an interaction between biomarker and BMI group.

TABLE 3 Multiple regression analysis examining the unadjusted and adjusted associations between plasma nutrient biomarkers and WHtR at follow-up in youth with type 1 diabetes[1]

	β Coefficients for WHtR at follow-up						
				Model 4[5]			
Nutrient biomarker	Model 1[2]	Model 2[3]	Model 3[4]	Normal	Overweight	Obese	*P*- interaction
PA (16:0)	0.001 ± 0.001	0.0006 ± 0.0008	−0.0001 ± 0.0007				NS
SA (18:0)	−0.001 ± 0.001	−0.0005 ± 0.0013	−0.001 ± 0.001				NS
POA (16:1)	−0.005 ± 0.004	−0.003 ± 0.006	−0.004 ± 0.005				NS
OA (18:1)	−0.001 ± 0.001	−0.0005 ± 0.0012	0.0001 ± 0.0010				NS
LA (18:2)	0.0008 ± 0.0005	−0.0001 ± 0.0005	0.0004 ± 0.0004	0.0009 ± 0.0005	0.001 ± 0.001	−0.003 ± 0.001*	0.012
DGLA (20:3)	−0.003 ± 0.002	−0.003 ± 0.002	−0.003 ± 0.002				NS
AA (20:4)	−0.0008 ± 0.0007	0.0005 ± 0.0007	−0.0001 ± 0.0006				NS
ALA (18:3)	0.003 ± 0.020	−0.02 ± 0.02	−0.02 ± 0.02				NS
EPA (20:5)	0.002 ± 0.005	0.002 ± 0.005	−0.0007 ± 0.0045				NS
DHA (22:6)	0.0001 ± 0.0015	−0.0003 ± 0.0016	−0.0005 ± 0.0013				NS
n–6:n–3 FAs	−0.0002 ± 0.0003	−0.0001 ± 0.0003	0.0001 ± 0.0003	0.0004 ± 0.0003	0.0008 ± 0.0007	−0.001 ± 0.001*	0.021
D5D	0.001 ± 0.001	0.002 ± 0.001	0.001 ± 0.001				NS
D6D	−0.06 ± 0.04	−0.04 ± 0.04	−0.05 ± 0.03				NS
D9D-16	−0.1 ± 0.1	−0.1 ± 0.2	−0.1 ± 0.1				NS
D9D-18	−0.004 ± 0.014	−0.0001 ± 0.015	0.01 ± 0.01				NS
Vitamin D	−0.0001 ± 0.0001**	−0.0001 ± 0.0001	−0.0001 ± 0.0001*	−0.0001 ± 0.0001	−0.0001 ± 0.0001	−0.0003 ± 0.0001**	0.029
Vitamin E	0.0001 ± 0.0004	−0.0004 ± 0.0004	−0.0007 ± 0.0004	−0.0001 ± 0.0004	−0.0001 ± 0.0010	−0.005 ± 0.001**	<0.01

[1] Values are β estimates ± SEs. *$P < 0.05$, **$P < 0.01$. AA, arachidonic acid; ALA, α-linolenic acid; DGLA, dihomo-γ-linolenic acid; D5D, Δ5 desaturase; D6D, Δ6 desaturase; D9D-16, Δ9 desaturase 16; D9D-18, Δ9 desaturase 18; LA, linoleic acid; OA, oleic acid; PA, palmitic acid; POA, palmitoleic acid; SA, stearic acid; WHtR, waist-to-height ratio.
[2] Model 1 adjusted for baseline WHtR and time between the baseline and the follow-up examinations.
[3] Model 2 further adjusted for demographic variables [age at follow-up, sex, race/ethnicity, season (only for vitamin D), parental education, household income, clinical site] and diabetes-related variables (diabetes duration, insulin regimen, insulin dose, and glycated hemoglobin at follow-up).
[4] Model 3 further adjusted for BMI group at follow-up.
[5] Model 4 further included an interaction between biomarker and BMI group.

previous studies that examined associations of plasma FAs with markers of inflammation and endothelial activation (25, 26), or insulin resistance (27, 28), as outcomes. Obesity has been confirmed as a state of chronic inflammation, which is related to chronic excessive macronutrient intake (29). Increased inflammation-sensitive plasma proteins such as fibrinogen and orosomucoid were shown to be predictive of weight gain (30). Thus, it is probable that n–6 FAs are related to adipose tissue accumulation through mechanisms involved in modifying insulin sensitivity or inflammation. However, more clinical trials are needed to fully explore the causal relations of the associations between these biomarkers.

Current dietary recommendations advise replacing SFAs, which is considered "bad" fat, with "good" fat such as MUFAs. In our study, higher concentrations of SA was related to higher WHtR in obese participants. However, a potential protective effect of SA was observed in participants who were not centrally obese at baseline. These findings indicate that the association between SA and WHtR depends on participants' obese status. In addition, higher PA and lower OA were found to be related to higher WHtR. The administration of OA has been suggested to inhibit gluconeogenesis and suppress appetite through central nervous system signaling mechanisms (31). Thus, our results supported current national nutrition guidelines related to recommended dietary fat type in the T1D population.

Desaturase activities, which regulate the degree of unsaturation of lipids, determine plasma FA profile together with dietary fat intake (28). Previous studies reported that high activity of D6D and D9D-16 and low activity of D5D were related to abdominal adiposity (32, 33), insulin resistance (28, 34), and the development of metabolic syndrome (35). In line with these observations, we found that higher D6D activity, which related to higher DGLA, was associated with higher WHtR at baseline. However, no significant association of activity of D5D and D9D-16 with WHtR was observed in the present study. In addition, we found that higher activity of D9D-18 was associated with lower WHtR at baseline in obese youth, which may be because more OA was produced by higher activity of D9D-18.

Several cross-sectional studies showed that higher concentrations of plasma vitamin D is associated with lower amounts of abdominal adiposity (11, 36), but no significant longitudinal associations were identified (11). In the present study, plasma vitamin D was negatively associated with WHtR at baseline in normal-weight and obese youth and with WHtR at follow-up in youth who were obese at baseline. It has been hypothesized that obesity may be responsible for decreased bioavailability of cholecalciferol (vitamin D_3) from cutaneous and dietary sources (37). Furthermore, vitamin D_3 has been shown to be a powerful inhibitor of leptin secretion, which regulates adipose deposition (38). However, our vitamin D assay does not separately quantify ergocalciferol (vitamin D_2) and vitamin D_3, so we were unable to test these hypotheses on vitamin D_3 alone. As with vitamin D, higher baseline plasma vitamin E was associated with lower WHtR longitudinally in obese youth in our study. This is in accordance with previous data suggesting that vitamin E is negatively related to central obesity in both serum (39) and adipose tissue (40). Furthermore, all longitudinal associations existed only in participants who were obese, suggesting that weight status may influence associations between plasma biomarkers and obesity. The mechanism underlying these associations might be that suboptimal vitamin E concentrations may contribute to inadequate antioxidant defenses, which further contributes to accumulation of body fat (12).

A limitation of our study is that we used WHtR as a marker of central obesity in children and adolescents instead of DXA or MRI, which are more accurate in assessing visceral adipose tissue. Future studies would benefit from the use of DXA or MRI to assess fat distribution or body composition. However, WHtR, as an established predictor of many cardiovascular risk factors, is also a rapid and effective indicator of central obesity in epidemiologic studies and is an easily measured clinical measure of central obesity (41). We also acknowledge the small sample sizes of the obese group and incident cases of central obesity, which may have resulted in limited power to detect significant interactions in the multiple regression analyses or significant ORs in the logistic regression.

The strengths of our study are noteworthy. First, the SNAS is a multicenter prospective study with a larger sample size than previous cross-sectional studies (24, 42). Second, our study is novel in that it explores the association between individual plasma FAs and central obesity in youth with T1D. Most previous studies in this area focused on FA classes among healthy individuals or in those with type 2 diabetes, so existing findings obtained from other populations are needed to be confirmed in a T1D population. Third, blood FA biomarkers of dietary intake, which can serve as independent measures of diet not subject to the measurement errors of dietary surveys, have the potential to be used more quantitatively (43). An additional strength of this study is our large sample size, which allowed us to control for desired potential confounders and to include an analysis of effect modification.

In conclusion, several plasma nutrient biomarkers were associated with WHtR at baseline and follow-up in youth with T1D, independent of BMI. The favorable plasma nutrient profile associated with optimal fat distribution included higher proportions of OA, LA, and vitamins D and E concentrations and D9D-18 activity and lower proportions of PA, SA, and DGLA and D6D activity. Of these, some associations are particularly marked in obese youth. These findings raise the possibility that a diet of high nutritional quality, such as a Mediterranean-type diet, would likely reduce central adiposity by increasing amounts of beneficial plasma biomarkers in youth with T1D. However, this hypothesis needs to be confirmed in future studies. In addition, the exact mechanisms of these associations are unclear; more feeding studies and dietary interventions are needed to explore the mechanisms, particularly related to the potential enhancement of effects among obese individuals.

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SW and EJM-D designed the research and had primary responsibility for the final content of the manuscript; SW, JLC, SCC, IBK, JML, DD, APL, GK, RAB, SZ, and EJM-D conducted the research; SW and JLC analyzed the data; and SW, JLC, SCC, and EJM-D interpreted the results and wrote the manuscript. All authors read and approved the final manuscript.

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