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Greater Fructose Consumption Is Associated with Cardiometabolic Risk Markers and Visceral Adiposity in Adolescents[1–3]

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Abstract

Though adolescents consume more fructose than any other age group, the relationship between fructose consumption and markers of cardiometabolic risk has not been established in this population. We determined associations of total fructose intake (free fructose plus one-half the intake of free sucrose) with cardiometabolic risk factors and type of adiposity in 559 adolescents aged 14–18 y. Fasting blood samples were measured for glucose, insulin, lipids, adiponectin, and C-reactive protein. Diet was assessed with 4–7 24-h recalls and physical activity (PA) was determined by accelerometry. Fat-free soft tissue (FFST) mass and fat mass were measured by DXA. The s.c. abdominal adipose tissue (SAAT) and visceral adipose tissue (VAT) were assessed using MRI. Multiple linear regression, adjusting for age, sex, race, Tanner stage, FFST mass, fat mass, PA, energy intake, fiber intake, and socioeconomic status, revealed that fructose intake was associated with VAT (β = 0.13; P = 0.03) but not SAAT (P = 0.15). Significant linear upward trends across tertiles of fructose intake were observed for systolic blood pressure, fasting glucose, HOMA-IR, and C-reactive protein after adjusting for the same covariates (all P-trend < 0.04). Conversely, significant linear downward trends across tertiles of fructose intake were observed for plasma HDL-cholesterol and adiponectin (both P-trend < 0.03). When SAAT was added as a covariate, these trends persisted (all P-trend < 0.05). However, when VAT was included as a covariate, it attenuated these trends (all P-trend > 0.05). In adolescents, higher fructose consumption is associated with multiple markers of cardiometabolic risk, but it appears that these relationships are mediated by visceral obesity. J. Nutr. 142: 251–257, 2012.

Introduction

Between 1977 and 2004, U.S. consumption of fructose increased on average 32% across all gender and age groups (1,2). This trend has been accredited to the increasing use of HFCS[7] as the predominate sweetener in processed foods and soft drinks by industry (3). There has been a growing concern that increased fructose consumption may be related to factors known to increase risk for cardiovascular disease and type 2 diabetes (4), because animal studies suggest that high fructose consumption promotes obesity, elevated blood pressure, insulin resistance, inflammation, and dyslipidemia (5–7). However, the extent to which increased fructose consumption is related to adiposity and metabolic dysregulation in humans is uncertain. Whereas some authors report that greater fructose consumption may increase body fatness and blood pressure (8–11), others report no relations between fructose intake and adiposity or blood pressure (12,13). Disparate findings also exist between fructose intake and other markers of cardiometabolic risk, including lipids, insulin resistance, and inflammatory-related cytokines (9,14–20).

The discrepancies in the aforementioned dietary fructose and cardiometabolic risk factor investigations can be attributed in part to differences in the populations studied and the study designs and instruments used. However, it is also likely that the half-portion of fructose from sucrose could be an additional confounding factor (1). Because absorbed sucrose is hydrolyzed into free fructose and free glucose before it arrives at the liver for metabolism, it is important to consider the additional free fructose from sucrose when determining the overall effect of fructose on health-related outcomes.

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[3] Supplemental Table 1 and Supplemental Figure 1 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 jn.nutrition.org.
[6] N. K. Pollock and V. Bundy contributed equally to this work.
[7] Abbreviations used: FFST, fat-free soft tissue; HFCS, high-fructose corn syrup; NDS-R, Nutrition Data System for Research; PA, physical activity; SAAT, s.c. abdominal adipose tissue; VAT, visceral adipose tissue.
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Given that adolescents have been found to consume more fructose than any other age group over the last few decades (2,21) combined with recent findings in adolescents of increasing rates of insulin resistance, hypertension, and dyslipidemia (22,23), it is vital to understand the role of greater fructose consumption on factors known to increase risk for cardiovascular disease and type 2 diabetes in this population. Currently, two pediatric studies have linked high fructose intake to cardiometabolic risk factors (17,24). In an investigation of 74 Swiss children aged 6–14 y, Aeberili et al. (17) reported no associations between fructose consumption and weight status, total cholesterol, HDL-cholesterol, or LDL-cholesterol. However, negative associations were observed between fructose intake and LDL particle size, a marker of cardiovascular disease risk. In the other pediatric investigation, Davis et al. (24) reported inverse relationships between total fructose intake (free fructose + 50% of free sucrose) and insulin sensitivity in 120 overweight Latino youth aged 10–17 y. Although these two studies provide important insight into the relationship between fructose consumption and cardiometabolic risk factors, additional work is warranted. The primary objective of this study was to determine relations between total fructose intake (free fructose + 50% of free sucrose) and measures known to increase risk for cardiovascular disease and type 2 diabetes in a cohort of white and black adolescents living in the southern US. A secondary objective was to determine whether the type of fat (s.c. vs. visceral) modified relations between total fructose intake and the markers of cardiometabolic risk.

Materials and Methods

Participants. The participants in this study were 559 adolescents who were recruited from local high schools in the Augusta, Georgia area. With approval from superintendents and school principals, flyers were distributed to all students in the high schools. Inclusion criteria for the study were white or black/African American race and age 14–18 y. Adolescents were excluded if they were taking medications or had any medical conditions that could affect growth, maturation, PA, nutritional status, or metabolism. Informed consent and assent were obtained from all parents and adolescents, respectively. The protocol was approved by the Human Assurance Committee at Georgia Health Sciences University (institutional review board). All measurements were performed at the Georgia Prevention Institute at Georgia Health Sciences University between 2001 and 2005.

Anthropometry, blood pressure, pubertal stage, and socioeconomic status. A trained laboratory technician collected height and weight measurements for calculating sex- and age-specific BMI percentiles for which we used body weight classification: not overweight (<85th percentile), overweight, (85–94.99th percentile), or obese (≥95th percentile) (25). Seated blood pressure was measured five times at 1-min intervals after a 10-min rest using the Dinamap Pro 100 (Critikon) and the last three measures were averaged. Pubertal maturation stage (or Tanner stage) was measured with a five-stage scale ranging from I (prepubertal) to V (fully mature) as described by Tanner (26). Using this gender-specific questionnaire, participants reported their pubertal stage by comparing their own physical development to the five stages in standard sets of diagrams. A parent or research coordinator then reviewed the results with the children to make sure they understood the questionnaire. When an individual reported discordant stages of pubic hair and breast or genital development, the higher of the two stages was used. The socioeconomic status was assessed using the Hollingshead 4-factor index of social class (27), which combines the educational attainment and occupational prestige for the number of working parents in the child's family. Scores ranged from 11 to 51, with higher scores indicating higher theoretical socioeconomic status.

Biochemical variables. Blood samples were collected from fasting participants for assessment of serum glucose, serum insulin, plasma TG, plasma total cholesterol, plasma HDL-cholesterol, plasma LDL-cholesterol, serum leptin, plasma adiponectin, plasma resistin, and plasma C-reactive protein. Serum glucose concentrations were measured using an Ektachem DT system (Johnson and Johnson Clinical Diagnostics) and run in duplicate, with intra- and interassay CV of 0.6 and 1.5%, respectively. Specific insulin was measured in serum and assayed in duplicate using RIA (Linco Research), with intra- and interassay CV of 5 and 5.6%, respectively. HOMA-IR[7] was calculated by using the formula: fasting insulin (pmol/L) × fasting glucose (mmol/L)/22.5 (28).

Plasma TG and HDL-cholesterol concentrations were measured using the Ektachem DT II system. Plasma HDL-cholesterol was analyzed using a two-reagent system (Equal Diagnostics) involving stabilization of LDL-cholesterol, VLDL-cholesterol, and chylomicrons using cyclodextrin and dextrin sulfate and subsequent enzymatic-colorimetric detection of HDL-cholesterol (29). Plasma LDL-cholesterol concentrations were calculated using the Friedewald formula (30).

Serum leptin concentrations were assayed using ELISA (R & D Systems) and run in duplicate, with intra- and interassay CV of 2.2 and 5.3%, respectively. Adiponectin and resistin were measured in plasma that was assayed in duplicate by ELISA (Linco Research). Intra- and interassay CV were 7.4 and 8.4%, respectively, for plasma adiponectin and 3.2 and 7.1%, respectively, for plasma resistin. Plasma C-reactive protein concentrations were assayed using high-sensitivity ELISA (ALPCO Diagnostics) and run in duplicate, with intra- and interassay CV of 10 and 10.2%, respectively.

Body composition and type of adiposity. FFST mass and fat mass were assessed using DXA (QDR-4500W; Hologic). For determination of measurement reproducibility, one-way random effects model, single measure intraclass correlation coefficients were calculated in participants 15–18 y of age (n = 219). Each participant was scanned twice within a 7-d period for FFST mass, fat mass, and percentage body fat (all $r \geq 0.97$). SAAT and VAT were measured using MRI (1.5-T; GE Medical Systems). Assessments of SAAT and VAT are described in detail elsewhere (31). Briefly, a series of five transverse images was acquired from the lumbar region beginning at the inferior border of the fifth lumbar vertebra and proceeding toward the head; a 2-mm gap between images was used to prevent crosstalk. To calculate volumes for SAAT and VAT, the cross-sectional area from each slice was multiplied by the slice width (1 cm) and then the individual volumes were summed. The intraclass correlation coefficients for repeat analyses of the same scans on separate days within a 7-d period were $r \geq 0.98$ for both SAAT and VAT.

PA. The mean daily minutes spent in moderate and vigorous PA was assessed using MTI Actigraph monitors (model 7164; MTI Health Services), uniaxial accelerometers that measure vertical acceleration and deceleration. With epoch length set at 1 min and expressed as counts/min, the accelerometers were to begin recording when the participant left our laboratory after the first day of testing. The participants were instructed to: *1*) wear the monitor for a period of 7 d; *2*) remove it for sleep, bathing, and any activity that may cause harm to either the monitor or another person (e.g. during contact sports); and *3*) bring the monitor back to us 1 wk later. Data from d 1 and 7 were discarded, because a full day of information was not available for those days. Movement counts were converted to min/d spent in moderate (3–6 metabolic equivalents) and vigorous (>6 metabolic equivalents) PA by the software accompanying the device.

Dietary intake. To assess mean daily intakes of energy, protein, fat, carbohydrate, free fructose, free sucrose, and fiber, a trained registered dietitian conducted four to seven 24-h diet recalls (1 weekend day) using NDS-R software (version 2006). Four, 5, 6, and 7 d of dietary information were collected in 10, 21, 22, and 47% of the participants, respectively, within 4 wk of the blood collection. The first two recalls were performed in person at our institute with the use of food models, portion booklets, or serving containers to assist in estimating serving size and the remaining interviews were conducted by telephone. To minimize the potential for undereating during the time frame for 24-h recalls,

participants were unaware of the telephone recall schedule. A trained research assistant coded and analyzed dietary intake data using the NDS-R software. Because NDS-R software computes the intake of sugar type and servings of food and beverage groups based on the Dietary Guidelines for Americans 2005 (32) or the FDA (33), we provided information on mean daily intakes of total sugars, added sugars, free fructose subgroups (vegetables, fruit, and 100% fruit juice), and HFCS subgroups (sugar-sweetened foods and sugar-sweetened beverages).

Statistical analysis. In our analyses, the primary independent/predictor variable of interest was total fructose intake, which takes into account the fructose found in foods (free fructose) and the fructose released from sucrose during digestion (bound fructose) (1,24).

$$\text{Total fructose (g/d)} = \text{free fructose (g/d)} + \tfrac{1}{2}\,\text{free sucrose (g/d)}.$$

Separate multivariate linear regression analyses were conducted to examine associations of total fructose intake with measures known to increase cardiovascular disease and type 2 diabetes (blood pressure, serum glucose, HOMA-IR, plasma TG, plasma total cholesterol, plasma HDL-cholesterol, plasma LDL-cholesterol, serum leptin, plasma adiponectin, plasma resistin, plasma C-reactive protein, SAAT, and VAT). Potential confounding variables that were included in the analyses were age, sex, race, Tanner stage, body composition (FFST mass and fat mass), PA, energy intake, fiber intake, and socioeconomic status (24,34). Because there were no interactions with age, sex, or race, we ran the analyses in all participants, adjusting for age, sex, and race rather than conducting analyses for separate groups.

We further explored the fructose-cardiometabolic risk factor relationship by comparing the cardiometabolic risk factor variables across tertile groups of the percentage of energy intake from total fructose. Total fructose intake values reported within each group are medians (range) (**Tables 1** and **2**). Group differences for anthropometric, body composition, PA, socioeconomic status, and dietary intake variables were determined by using ANOVA. Descriptive statistics for raw variables are presented as mean ± SD if not stated otherwise. The proportions of males and females and of blacks and whites were compared between groups by using chi-square test of goodness of fit. For comparison of the primary dependent variables (i.e., blood pressure, serum glucose, HOMA-IR, plasma TG, plasma total cholesterol, plasma HDL-cholesterol, plasma LDL-cholesterol, serum leptin, plasma adiponectin, plasma resistin, plasma C-reactive protein), an *F* test was performed to test the assumption of homogeneity of regression slopes for the interactions between the independent variable (i.e., total fructose tertile groups) and the covariates (age, sex, race, Tanner stage, FFST mass, fat mass, PA, energy intake, fiber intake, and socioeconomic status). Because there were no interactions, ANCOVA was used to compare the primary dependent variables across total fructose tertile groups after adjusting for age, sex, race, Tanner stage, FFST mass, fat mass, PA, energy intake, fiber intake, and socioeconomic status. We subsequently tested whether the association between total fructose intake and cardiometabolic risk factor variable was dependent on type of fat (SAAT vs. VAT). By using this approach, if an observed association with total fructose intake was dependent on type of fat, there would be no association between total fructose intake and the dependent variable of interest when controlled for the type of fat (35). If the trend for difference in the dependent variable of interest across a tertile of total fructose was significant ($P < 0.05$), differences among individual tertiles, adjusted for multiple comparisons, were tested by using Tukey's honestly significant difference adjustment. Adjusted means are reported as mean ± SE. Because HOMA-IR, plasma TG, serum leptin, plasma adiponectin, plasma resistin, plasma C-reactive protein, SAAT, and VAT had skewed distributions, they were transformed to their natural logarithm for analyses but back-transformed when we present the results for ease of interpretation. Data were analyzed using SAS software (version 9.1, SAS Institute) and statistical significance was set at $P < 0.05$.

Results

The sample was composed of 559 white and black adolescents aged 14–18 y (49% female, 45% black). The majority of adolescents (86%) reported to be in pubertal stages IV and V; however, 55 were in pubertal stage III and 8 in stage II. The majority of females (97.8%) reported having started menstruation. The percentages of overweight and obese participants were 11.4 and 14%, respectively. For context, total sample characteristics on anthropometry, blood pressure, body composition, blood pressure, biochemistries, PA, socioeconomic status, and dietary variables are provided in **Supplemental Table 1**.

Pearson's bivariate analyses revealed that total fructose intake was associated with intakes of the following carbohydrate-related variables: free fructose ($r = 0.87$), free sucrose ($r = 0.78$), fiber ($r = 0.45$), total sugars ($r = 0.38$), added sugars ($r = 0.44$), vegetables ($r = 0.14$), fruits ($r = 0.19$), 100% fruit juices ($r = 0.11$), sugar-sweetened foods ($r = 0.69$), and sugar-sweetened beverages ($r = 0.57$) (all $P < 0.05$). Multiple linear regression, adjusting for age, sex, race, Tanner stage, FFST mass, fat mass, PA, energy intake, fiber intake, and socioeconomic status, revealed that total fructose intake was associated with systolic blood pressure ($\beta = 0.14$), fasting serum glucose ($\beta = 0.13$), HOMA-IR ($\beta = 0.11$), plasma TG ($\beta = 0.11$), plasma HDL-cholesterol ($\beta = -0.17$), plasma LDL-cholesterol ($\beta = 0.10$), plasma adiponectin ($\beta = -0.17$), and plasma C-reactive protein ($\beta = 0.11$) and VAT ($\beta = 0.13$) (all $P < 0.05$). When determining relations between total fructose intake and type of adiposity (**Supplemental Fig. 1**), only VAT was associated with total fructose intake after controlling for the same covariates ($P = 0.03$). No relations were found between total fructose intake and diastolic blood pressure, plasma total cholesterol, serum leptin, plasma resistin, or SAAT (all $P > 0.05$).

Age, sex, race, Tanner stage, BMI percentile, FFST mass, fat mass, SAAT, moderate/vigorous PA, socioeconomic status, energy intake, and macronutrient intakes did not differ across tertiles of total fructose intake (Table 1). However, significant linear upward trends in levels of VAT and intakes of free fructose, free sucrose, total sugars, added sugars, 100% fruit juices, sugar-sweetened foods, and sugar-sweetened beverages were found across tertiles of total fructose intake (all P-trend < 0.05). Significant linear downward trends across tertiles of total fructose intake were observed with intakes of fiber and free fructose subgroups vegetables and fruit (all P-trend < 0.04).

When cardiometabolic risk factor variables were compared across tertiles of total fructose intake adjusting for age, sex, race, Tanner stage, FFST mass, fat mass, moderate/vigorous PA, socioeconomic status, energy intake, and fiber intake (Table 2), there were significant linear upward trends for systolic blood pressure, fasting serum glucose, HOMA-IR, and plasma C-reactive protein across tertiles of total fructose intake (all P-trend < 0.04; model 1). Conversely, significant linear downward trends across tertiles of total fructose intake were observed for plasma HDL-cholesterol and plasma adiponectin (both P-trend < 0.03). When SAAT was added as a covariate, these significant trends persisted (all P-trend < 0.05; model 2). However, when VAT was included as a covariate, it attenuated these significant trends (all P-trend > 0.05; model 3). There were no differences in diastolic blood pressure, plasma total cholesterol, plasma LDL-cholesterol, serum leptin, or plasma resistin across tertiles of total fructose intake (all P-trend > 0.05).

Discussion

In this study of white and black adolescents living in the southern US, we found that total fructose consumption, which included both free fructose plus one-half the intake of free sucrose, was positively associated with systolic blood pressure, fasting serum glucose, HOMA-IR, plasma TG, plasma LDL-cholesterol, plasma

TABLE 1 Characteristics by tertile categories of total fructose intake in adolescents aged 14–18 y[1]

Characteristics	Total fructose, *% energy*			*P*-trend
	Tertile 1 8.6% (2.1−10.9%)	Tertile 2 12.4% (11.0−13.8%)	Tertile 3 16.4% (13.9−28.4%)	
n	186	186	187	
Age, *y*	16.1 ± 1.2	16.0 ± 1.1	16.1 ± 1.1	0.30
Females, *%*	46.8	46.8	56.6	0.11
Blacks, *%*	41.0	45.1	48.6	0.38
Tanner stage (1–5)	4.6 ± 0.7	4.5 ± 0.6	4.6 ± 0.6	0.29
BMI percentile	64.5 ± 26.9	58.3 ± 27.4	62.2 ± 28.8	0.44
BMI percentile category, *%*				0.36
Not overweight	73.4	81.5	68.8	
Overweight	12.1	9.3	14.5	
Obese	14.5	9.2	16.7	
FFST mass, *kg*	46.5 ± 10.8	47.3 ± 9.5	46.5 ± 10.6	0.81
Fat mass, *kg*	15.1 ± 8.6	14.3 ± 8.6	17.7 ± 11.5	0.06
SAAT, cm^3	787 ± 656	770 ± 579	973 ± 793	0.06
VAT, cm^3	86 ± 50[b]	91 ± 51	103 ± 59[a]	0.025
Moderate/vigorous PA, *min/d*	43 ± 26	47 ± 31	38 ± 27	0.16
Socioeconomic status	35 ± 9	33 ± 8	33 ± 9	0.24
Dietary intake				
Energy, *kJ/d*	7990 ± 2720	8500 ± 2490	7820 ± 2500	0.34
Protein, % energy	14.8 ± 3.1	14.6 ± 3.2	13.8 ± 2.5	0.15
Fat, *% energy*	33.2 ± 5.7	33.1 ± 4.4	34.3 ± 4.3	0.58
Carbohydrate, *% energy*	52.9 ± 6.5	53.2 ± 6.9	52.8 ± 6.5	0.73
Total fructose, *g/d*	41.7 ± 17.7[c]	62.6 ± 18.4[b]	73.4 ± 20.9[a]	<0.001
Free fructose				
g/d	21.2 ± 10.9[c]	34.2 ± 13.0[b]	43.1 ± 14.6[a]	<0.001
% energy	4.4 ± 1.6[c]	6.8 ± 1.6[b]	9.6 ± 2.8[a]	<0.001
Free sucrose				
g/d	41.2 ± 19.4[c]	56.8 ± 22.9[b]	62.5 ± 28.0[a]	<0.001
% energy	8.5 ± 2.6[c]	11.3 ± 3.2[b]	13.7 ± 4.4[a]	<0.001
Fiber				
g/d	11.0 ± 4.5[a]	11.1 ± 4.4[a]	9.3 ± 4.2[b]	0.020
g/4186 kJ	5.9 ± 1.6[a]	5.5 ± 1.3[b]	5.2 ± 1.6[c]	<0.001
Total sugars				
g/d	102 ± 44[c]	138 ± 43[b]	157 ± 45[a]	<0.001
% energy	21.2 ± 4.0[c]	27.7 ± 2.8[b]	34.6 ± 3.9[a]	<0.001
Added sugars				
g/d	77 ± 70[c]	89 ± 76[b]	100 ± 81[a]	0.007
% energy	15.5 ± 11.8[c]	17.3 ± 12.9[b]	20.9 ± 15.6[a]	0.001
Free fructose subgroups				
Vegetables, *g/d*	7.1 ± 5.6[a]	6.1 ± 4.1	5.1 ± 3.6[b]	0.010
Fruit, *g/d*	9.0 ± 7.5[a]	7.5 ± 7.5	6.0 ± 7.5[b]	0.011
100% fruit juices, *mL/d*	24 ± 72[b]	48 ± 72	72 ± 96[a]	0.038
HFCS subgroups				
Sugar-sweetened foods, *g/d*	46.8 ± 25.7[b]	60.4 ± 24.2	69.5 ± 28.7[a]	0.013
Sugar-sweetened beverages, *mL/d*	384 ± 312[c]	552 ± 240[b]	840 ± 336[a]	<0.001

[1] Values are means ± SD or percent. Values in a row with superscripts without a common letter differ, $P < 0.05$. FFST, fat-free soft tissue; HFCS, high-fructose corn syrup; PA, physical activity; SAAT, s.c. abdominal adipose tissue; VAT, visceral adipose tissue.

C-reactive protein, and visceral adiposity but negatively associated with HDL-cholesterol and plasma adiponectin. These relationships were independent of potentially confounding factors such as age, sex, race, pubertal stage, body composition, PA, socioeconomic status, energy intake, and fiber consumption. When we compared differences in cardiometabolic risk factors across tertiles of total fructose intake adjusting for the same covariates, our findings were quite similar to the correlational data. Collectively, our data reflect interventional studies in animals and adults (5–10), suggesting that greater fructose consumption is associated with multiple factors known to increase risk for cardiovascular disease and type 2 diabetes.

In further analyses, we revealed that associations between fructose consumption and markers of cardiometabolic risk may be dependent on the type of fat accumulation, because visceral, not s.c., fat attenuated the significant findings between total fructose intake and cardiometabolic risk factors. This dietary fructose-visceral fat relationship that we observed is supported by a recent adult intervention by Stanhope et al. (9). When the investigators gave overweight adults either glucose-sweetened or fructose-sweetened beverages for 10 wk, they observed significant increases in total body fat in both groups, but only significant increases in visceral fat in the group consuming fructose. These interventional findings combined with our data

TABLE 2 Markers known to increase risk for cardiovascular disease and type 2 diabetes across tertiles of total fructose intake in adolescents aged 14–18 y[1,2]

	Total fructose, *% energy*			
	Tertile 1 18.6% (2.1−10.9%)	Tertile 2 12.4% (11.0−13.8%)	Tertile 3 16.4% (13.9−28.4%)	*P*-trend
n	186	186	187	
Systolic blood pressure, *mm Hg*				
Model 1	109 ± 1[b]	111 ± 1	113 ± 1[a]	0.007
Model 2	109 ± 1[b]	111 ± 1	113 ± 1[a]	0.013
Model 3	110 ± 1	111 ± 1	113 ± 1	0.28
Diastolic blood pressure, *mm Hg*				
Model 1	59 ± 0.4	60 ± 0.4	60 ± 0.4	0.41
Model 2	59 ± 0.4	60 ± 0.4	60 ± 0.4	0.40
Model 3	60 ± 1	59 ± 1	60 ± 1	0.52
Fasting serum glucose, *mmol/L*				
Model 1	4.93 ± 0.03[b]	5.01 ± 0.03[a]	5.05 ± 0.03[a]	0.024
Model 2	4.93 ± 0.03[b]	5.01 ± 0.03[a]	5.04 ± 0.03[a]	0.033
Model 3	4.91 ± 0.04	4.95 ± 0.04	4.99 ± 0.04	0.10
HOMA-IR				
Model 1	3.39 ± 0.13[b]	3.65 ± 0.13	3.79 ± 0.13[a]	0.038
Model 2	3.40 ± 0.11[b]	3.71 ± 0.12	3.73 ± 0.12[a]	0.046
Model 3	3.36 ± 0.15	3.63 ± 0.15	3.50 ± 0.16	0.53
Plasma TG, *mmol/L*				
Model 1	0.69 ± 0.03[b]	0.75 ± 0.03	0.79 ± 0.03[a]	0.027
Model 2	0.69 ± 0.03[b]	0.76 ± 0.03	0.79 ± 0.03[a]	0.038
Model 3	0.71 ± 0.03	0.78 ± 0.03	0.77 ± 0.04	0.27
Plasma total cholesterol, *mmol/L*				
Model 1	3.88 ± 0.08	3.80 ± 0.08	3.86 ± 0.08	0.84
Model 2	3.88 ± 0.08	3.81 ± 0.08	3.86 ± 0.08	0.86
Model 3	3.87 ± 0.08	3.81 ± 0.08	3.86 ± 0.08	0.91
Plasma HDL-cholesterol, *mmol/L*				
Model 1	1.24 ± 0.03[a]	1.23 ± 0.03[a]	1.17 ± 0.03[b]	0.029
Model 2	1.25 ± 0.02[a]	1.23 ± 0.02	1.17 ± 0.02[b]	0.026
Model 3	1.26 ± 0.03	1.25 ± 0.03	1.21 ± 0.03	0.07
Plasma LDL-cholesterol, *mmol/L*				
Model 1	2.36 ± 0.06	2.30 ± 0.06	2.41 ± 0.06	0.61
Model 2	2.35 ± 0.06	2.32 ± 0.06	2.40 ± 0.06	0.61
Model 3	2.38 ± 0.08	2.29 ± 0.08	2.44 ± 0.09	0.61
Serum leptin, *μg/L*				
Model 1	10.6 ± 0.4[b]	11.3 ± 0.4	11.3 ± 0.4	0.21
Model 2	10.5 ± 0.4	10.5 ± 0.5	10.8 ± 0.4	0.64
Model 3	10.5 ± 0.5	10.5 ± 0.5	10.8 ± 0.5	0.71
Plasma adiponectin, *mg/L*				
Model 1	9.1 ± 0.4[a]	8.7 ± 0.4	8.4 ± 0.4[b]	0.033
Model 2	9.2 ± 0.4[a]	8.6 ± 0.4	8.4 ± 0.4[b]	0.021
Model 3	9.5 ± 0.5	9.2 ± 0.5	9.1 ± 0.5	0.21
Plasma resistin, *μg/L*				
Model 1	11.8 ± 0.6	12.2 ± 0.5	12.0 ± 0.5	0.81
Model 2	11.8 ± 0.6	12.3 ± 0.5	12.0 ± 0.5	0.80
Model 3	12.5 ± 0.7	13.1 ± 0.7	13.4 ± 0.7	0.36
Plasma C-reactive protein, *mg/L*				
Model 1	0.67 ± 0.16[b]	0.84 ± 0.15	1.21 ± 0.15[a]	0.012
Model 2	0.67 ± 0.15[b]	0.92 ± 0.15	1.14 ± 0.14[a]	0.025
Model 3	0.81 ± 0.15	0.71 ± 0.15	1.04 ± 0.16	0.31

[1] Values are mean ± SEM. Means in a row with superscripts without a common letter differ, $P < 0.05$. FFST, fat-free soft tissue mass; PA, physical activity; SAAT, s.c. abdominal adipose tissue; VAT, visceral adipose tissue.

[2] Model 1 was adjusted for age, sex, race, Tanner stage, FFST mass, fat mass, moderate/vigorous PA, socioeconomic status, energy intake, and fiber intake; model 2 was adjusted for the same covariates in model 1 and further adjusted for SAAT; model 3 was adjusted for the same covariates in model 1 and further adjusted for VAT.

suggest that fructose consumption might specifically promote visceral fat accumulation. The mechanism by which high fructose intake may increase visceral adiposity is unclear; however, it has been postulated that a diet chronically high in fructose may lead to greater visceral fat accumulation due to the increased exposure to TG and remnant lipoproteins (36,37).

Our finding that fructose consumption was positively correlated with measures of insulin resistance may indicate decreased

removal from the blood, increased fasting glycogenolysis, or the beginnings of insulin resistance in our otherwise healthy adolescent sample. One potential impact of the fructose-related increase in TG production is the downstream consequence of a decrease in glycogen synthesis and increases in glycogenolysis and glucogenesis (38). Other reports show a rise in intestinal glucose production after fructose administration, secondary to the conversion of triose-phosphates to glucose within enterocytes (39). Moreover, our findings may be due to decreased glucose tolerance resulting from the increased hepatic lipid supply to stimulate the protein kinase C, tyrosine/serine phosphorylation cascade, leading to a decrease in insulin receptor sensitivity (36,40,41). Although, to the best of our knowledge, there are no known direct mechanisms to explain the ability of fructose to decrease circulating adiponectin or increase C-reactive protein, greater fructose consumption is thought to induce inflammation through activation of cytokines, endothelial cells, reactive oxygen species, and the renin-angiotensin-aldosterone system (6,42).

Strengths of the study include the assessment of visceral adiposity using MRI and the consideration of potential confounding variables in our analyses with fructose consumption. However, we acknowledge study limitations. Given that our study used cross-sectional data, we cannot be certain that fructose consumption has a direct effect on the measures associated with cardiometabolic risk. Second, although dietary recalls have been shown to more accurately detail types and amounts of food intake than FFQ, it is possible that the recalls may not accurately represent usual dietary intake (43). Lastly, our study findings are limited to adolescents living in the southern U.S. and thus differences in socioeconomic status, geographic location, social environment, lifestyle, or food habits of the study population may preclude generalizability of the study findings. However, given that the mean fructose consumption (60.2 g/d) in our study sample is comparable to the most recent national average in 12–18 y olds (72.8 g/d) (21), our findings are likely generalizable to many other settings.

In conclusion, our adolescent data suggest that greater fructose consumption is associated with multiple markers known to increase risk for cardiovascular disease and type 2 diabetes, and it appears that these relationships are dependent on visceral obesity. With increasing use of HFCS in processed foods and soft drinks, additional research is needed to assess the long-term implications of increasing fructose consumption on cardiometabolic disease risk in youth.

Acknowledgments

N.K.P., W.K., C.L.D., P.J.B., and Y.D. designed the research; B.G., H.Z., and Y.D. conducted the research; N.K.P. and V.B. wrote the paper; N.K.P. analyzed the data and had primary responsibility for the final content. All authors read and approved the final manuscript.

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