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Surrogate Markers of Insulin Resistance Are Associated with Consumption of Sugar-Sweetened Drinks and Fruit Juice in Middle and Older-Aged Adults[1,2]

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Abstract

In this study, we examined the association between sugar-sweetened drink, diet soda, and fruit juice consumption and surrogate measures of insulin resistance. Sugar-sweetened drink, diet soda, and fruit juice consumption was estimated using a semiquantitative FFQ in 2500 subjects at the fifth examination (1991–1995) of the Framingham Offspring Study. Surrogate markers of insulin resistance measured in this study included fasting insulin, fasting glucose, homeostatic model assessment of insulin resistance, and the insulin sensitivity index ($ISI_{0,120}$). Sugar-sweetened drink consumption was positively associated with fasting insulin (none vs. ≥2 servings/d, 188 vs. 206 pmol/L, *P*-trend <0.001) after adjusting for potential confounders. Sugar-sweetened drink consumption was not associated with fasting glucose or $ISI_{0,120}$. Fruit juice consumption was inversely associated with fasting glucose (none vs. ≥2 servings/d, 5.28 vs. 5.18 mmol/L, *P*-trend = 0.006), but not with fasting insulin (none vs. ≥2 servings/d, 200 vs. 188 pmol/L, *P*-trend = 0.37) or $ISI_{0,120}$ (none vs. ≥2 servings/d, 26.0 vs. 27.0, *P*-trend = 0.19) in multivariate models. Diet soda consumption was not associated with any surrogate measures of insulin resistance after adjustment for potential confounders (insulin: none vs. ≥2 servings/d, 195 vs. 193 pmol/L, *P*-trend = 0.59; glucose: 5.26 vs. 5.24 mmol/L, *P*-trend = 0.84; and $ISI_{0,120}$: 26.2 vs. 26.7, *P*-trend = 0.37). In these healthy adults, sugar-sweetened drink consumption appears to be unfavorably associated with surrogate measures reflecting hepatic more than peripheral insulin sensitivity. Studies of long-term beverage consumption using more direct measures of insulin sensitivity are clearly warranted. J. Nutr. 137: 2121–2127, 2007.

Introduction

Obesity has been linked to insulin resistance in both normoglycemic and type 2 diabetic individuals (1–3), and it is an underlying risk factor for the metabolic syndrome (4). In the past 2 decades, sugar-sweetened drink and fruit juice consumption has increased among adults by 61 and 42%, respectively (5), and thus, both are major contributors to total sugar intake in the diet of U.S. Americans (6,7). In adults, observational studies have linked sugar-sweetened drink consumption to increased body weight (8,9) and increased risk of type 2 diabetes mellitus (DM)[6] (9,10). Obesity is an important determinant of insulin resistance (11), a key clinical feature in the pathogenesis of type 2 DM (4,11). To date, however, little is known about the role of sugar-sweetened beverages in the progression of insulin resistance in healthy adults.

The metabolic effects of fruit juice may differ from those of sugar-sweetened drinks because these beverages provide vitamins, minerals, soluble fiber, and various phenolic compounds, in addition to sugars. In the Nurses Health Study, higher fruit juice consumption was not associated with type 2 DM risk (9), in contrast to sugar-sweetened drink consumption. Thus, we hypothesized that higher consumption of sugar-sweetened drinks, but not fruit juice consumption, is unfavorably associated with insulin sensitivity, independent of body weight. To test this hypothesis, we examined the cross-sectional relationship between sugar-sweetened drink, diet soft drink, and fruit juice

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[6] Abbreviations used: DM, diabetes mellitus; HOMA-IR, homeostatic model assessment of insulin resistance; $ISI_{0,120}$, insulin sensitivity index; OGTT, oral glucose tolerance test.

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consumption and glucose and insulin homeostasis measures in adult men and women.

Study Design and Methods

Ethical and human research considerations. The Institutional Review Board for Human Research at Boston University and the Human Investigation Research Committee of New England Medical Center approved the procedures and protocols for this study.

Participants. The Framingham Offspring Study is a longitudinal community-based study of cardiovascular disease in the offspring of the original participants of the Framingham Heart Study Cohort and their spouses (12). In 1971, 5135 participants were enrolled into the study (13). During the fifth examination cycle of the Framingham Offspring Study (1991–1995), 3799 participants underwent a standardized medical history and physical examination. Valid FFQ data were available for 3418 patients. Dietary information was considered valid if reported energy intakes were ≥2,512 kJ/d (600 kcal/d) for men and women or <17,585 kJ/d (4200 kcal/d) for men and 16,747 kJ/d (4,000 kcal/d) for women, respectively, or if fewer than 13 food items were left blank. Participants were excluded from analyses if they had DM (n = 396), based on the use of insulin, oral hypoglycemic medication, fasting plasma glucose ≥7.0 mmol/L (126 mg/dL), or 2-h post 75-g oral glucose tolerance test (OGTT) plasma glucose concentrations ≥11.1 mmol/L (200 mg/dL). We also excluded participants with missing information for major covariates, exposure, or outcome data, including intake of sweetened beverages, levels of fasting insulin, fasting glucose, or 2-h post-OGTT plasma glucose concentrations (n = 522). The final sample size was 2500 (1154 men and 1346 women).

Dietary data. Usual dietary intake for the previous year was assessed at the fifth study examination using a semiquantitative 126-item FFQ (14). The questionnaire was mailed to participants before the examination, and the participants were asked to bring the completed questionnaire with them to their appointment. The FFQ consisted of a list of foods with a standard serving size and a selection of 9 frequency categories, ranging from never or <1 serving/mo to >6 servings/d. Nutrient intake was calculated by multiplying the frequency of consumption of each unit of food from the FFQ by the nutrient contents of the specific portion. Participants were asked to report their frequency of beverage consumption during the previous year, of *1*) sugar-sweetened drinks (including Coke, Pepsi, or other cola with sugar, caffeine-free Coke, Pepsi, or other cola with sugar, and other carbonated beverage with sugar); 2) diet soda (including low-calorie cola with caffeine, low-calorie caffeine-free cola, and other low-calorie carbonated beverages); and *3*) fruit juice (including apple juice or apple cider, orange juice, grapefruit juice, and other juice). One serving of sugar-sweetened drink and diet soda was equivalent to 360 mL (12 fl oz.). One serving of fruit juice was equivalent to 180 mL (6 fl oz.). Separate questions about vitamin and mineral supplement use were also included in the FFQ. The relative validity of this FFQ has been examined in several populations for both nutrients and foods (14–18). The correlation coefficients between FFQ and multiple diet records are 0.51 for both sugar-sweetened drinks and fruit drinks, 0.66 for diet soda, and 0.76 for fruit juice (18).

Laboratory procedures. Blood samples were obtained from participants who had fasted for at least 8 h, and samples were stored at −70°C. Fasting plasma insulin concentrations were determined using the Coat-A-Count ^{125}I-radioimmunoassay (Diagnostic Products). This is assay has cross-reactivity with proinsulin at the midcurve of 40%, intra- and inter-assay CV of 5–10%, and a lower limit of sensitivity of 7.9 pmol/L (1.1 μU/mL). Fasting plasma glucose concentrations were measured in fresh specimens with a hexokinase reagent kit. The intra-assay CV was <3%. The 75-g OGTT was administered according to the WHO standards (19), and 2-h post-OGTT plasma glucose and insulin concentrations were measured. Homeostatic model assessment of insulin resistance (HOMA-IR) is the surrogate measure of insulin resistance at fasting state, and it tends to represent hepatic insulin resistance (20). HOMA-IR was calculated using the following formula (21):

$$[\text{fasting plasma insulin } (\mu\text{U/mL}) \times \text{fasting plasma glucose (mmol/L)}]/22.5.$$

A more recently proposed index for insulin sensitivity is the insulin sensitivity index ($ISI_{0,120}$) (22). This measure reflects peripheral insulin resistance and glucose disposal and is a direct measurement of the β-cell response to energy stress (20). $ISI_{0,120}$ was calculated using the following formula (22):

$$ISI_{0,120} = (m/MPG)/\log MSI,$$

where

$$m = [75,000 \text{ mg} + (\text{fasting glucose} - \text{2-h post-OGTT glucose}) \times 0.19 \times \text{body wt (kg)}]/120 \text{ min}.$$

MPG is the mean of fasting and 2-h post-OGTT glucose concentrations (mg/dL), and MSI is the mean of fasting and 2-h post-OGTT insulin concentrations (μU/L).

Potential confounding factors. Potential confounding factors for the associations between beverage consumption and insulin resistance included sex, age (y), BMI [weight (kg)/height (m^2)], waist circumference (cm), smoking dose (none, 1–15, 16–25, or ≥25 cigarettes/d), total energy intake (kJ/d), alcohol intake (g/d), saturated fatty acid intake (g/d), current multivitamin use (yes/no), cholesterol-lowering medication (yes/no), hypertension medication use (yes/no), and physical activity score (23). Additional potential dietary confounding factors included dietary glycemic index, dietary fiber, whole grain, fruit, and vegetable intakes.

Statistical analyses. Statistical analyses were conducted using SAS statistical software (version 8; SAS Institute). The α-level <0.05 was considered as significant. We tested the surrogate measures of insulin resistance for normality and, because fasting insulin concentrations and HOMA-IR were positively skewed, analyses of these measures were performed on the natural logarithm transformations. Inverse transformations were performed to provide geometric mean and 95% CI for fasting insulin concentrations and HOMA-IR. In this study population, HOMA-IR and fasting insulin are highly correlated (Spearman $r = 0.96$). The tables include both fasting insulin and HOMA-IR data; however because they have the same interpretation, the results are not discussed in the text.

We compared characteristics (means ± SD or %) of nonconsumers (0 servings/d) with those of consumers of sugar-sweetened drinks, diet soft drinks, and fruit juice (≥0.5 serving/d) using Student's t tests and χ^2 tests. We also compared intakes of selected nutrients between consumers and nonconsumers using ANCOVA. All dietary variables except total energy intake were adjusted for age, sex, and total energy intake, and least squares adjusted means ± SD are presented.

To examine the relation between beverage consumption and surrogate measures of insulin resistance, we categorized beverage consumption into 4 groups: nonconsumers, <1 serving/d, 1–2 servings/d, and ≥2 servings/d. We compared least squares means of insulin, glucose, HOMA-IR, and $ISI_{0,120}$ across consumption frequency categories for each beverage type (sugar-sweetened drink, diet soft drink, and fruit juice). In addition to age- and sex-adjusted models, we also considered multivariate models, in which we controlled for sex, age, BMI, waist circumference, physical activity, smoking status, hypertension, cholesterol-lowering medication use, multivitamin use, and intakes of alcohol, total energy, and saturated fat. Additional models further adjusted the relations between beverage consumption and measures of insulin resistance for additional dietary factors, including dietary glycemic index and dietary fiber, whole grain, and fruit and vegetable intake. In all models, tests for linear trend across 4 categories of beverage consumption were measured by assigning the median beverage intake as the value for the respective beverage categories and treating this variable in the analyses as a continuous variable. The P-value for the regression coefficient for beverage intake was reported as P for trend. We tested each association for interactions with age, sex, BMI, and waist circumference, but none of these interactions were statistically significant.

Results

The 2500 participants (1154 men and 1346 women) in this study ranged in age from 26 to 82 y; their mean age was 53.8 ± 9.8 y. Sugar-sweetened drinks were consumed by 1330 (53%) of the participants, diet soft drinks by 1396 (55%) of participants, and fruit juice by 2201 (88%) of participants. Among consumers, the median intakes of sugar-sweetened drinks, diet soda, and fruit juice were 2.0, 4.0, and 6.0 servings/wk, respectively. Participants who consumed sugar-sweetened drinks were younger and more likely to be male, to smoke, and to take multivitamins than nonconsumers (**Table 1**). Sugar-sweetened drink consumers also had lower BMI, and were more physically active than nonconsumers. In consumers of sugar-sweetened drinks, intakes of total energy, carbohydrate, saturated fat, and dietary glycemic index were higher, whereas protein, fiber, magnesium, and alcohol intakes were lower than in those who did not consume sugar-sweetened drinks.

Diet soda drinkers were younger, had a higher BMI, were less physically active, and were less likely to smoke than those who did not consume diet soda (Table 1). Intakes of protein, fiber, and magnesium were higher, and intake of carbohydrate and dietary glycemic index were lower in diet soft drink consumers than in those who did not consume diet soft drinks.

Fruit juice consumers were less likely to be female and current smokers, and had a higher prevalence of hypertension than those who did not consume fruit juice (Table 1). Fruit juice drinkers had higher total energy, carbohydrate, fiber, magnesium, and dietary glycemic index, and lower saturated fat and alcohol intakes than those who did not consume fruit juice.

After adjustment for potential confounding variables, the frequency of sugar-sweetened drink intake was positively associated with fasting insulin (none vs. ≥2 servings/d, 188 vs. 206 pmol/L, P-trend < 0.001) (**Table 2**). The associations between the frequency of sugar-sweetened drink consumption and fasting plasma insulin and HOMA-IR remained statistically significant after further adjustment for dietary glycemic index, fruit intake, or vegetable intake. No significant associations were found between sugar-sweetened drink intake and fasting glucose or $ISI_{0,120}$. There were positive associations between diet soda and fasting insulin and glucose, HOMA-IR, and $ISI_{0,120}$ in the age- and sex-adjusted model. However, these associations were confounded by mainly BMI and waist circumference, and were no longer significant after adjusting potential confounders (Table 2). Both BMI and waist circumference were included in the multivariate models because they were significant predictors in the models. However, we performed the analysis with adjustment for either BMI or waist circumference and the associations remained unchanged.

After adjustment for potential confounding variables, fruit juice consumption was inversely associated with fasting glucose

TABLE 1 Characteristics of subjects in Framingham Offspring Cohort[1]

	Sugar-sweetened drink[2]			Diet soda[2]			Fruit juice[2]		
	Nonconsumer	Consumer	P-value[3]	Nonconsumer	Consumer	P-value[3]	Nonconsumer	Consumer	P-value[3]
Participants, *n (%)*	1170 (46.8)	1330 (53.2)		1104 (44.2)	1396 (55.8)		299 (12.0)	2201 (88.0)	
Characteristics									
Age, *y*	54.7 ± 9.8	53.1 ± 9.8	<0.001	54.4 ± 10.1	53.4 ± 9.5	0.007	54.5 ± 9.3	53.8 ± 9.9	0.25
Female, *n (%)*	766 (65.5)	580 (43.6)	<0.001	575 (52.1)	771 (55.2)	0.12	180 (60.2)	1166 (53.0)	0.02
Current smoker, *n (%)*	196 (16.8)	291 (21.9)	0.001	275 (24.9)	212 (15.2)	<0.001	75 (25.1)	412 (18.7)	0.01
Multivitamin use, *n (%)*	374 (32.0)	351 (26.4)	0.002	308 (27.9)	417 (29.9)	0.28	87 (29.1)	638 (28.8)	0.97
BMI, kg/m^2	27.2 ± 4.9	26.8 ± 4.4	0.03	26.2 ± 4.3	27.7 ± 4.8	<0.001	27.2 ± 4.9	27.0 ± 4.6	0.51
Physical activity score	34.8 ± 5.7	35.2 ± 6.4	<0.001	35.1 ± 6.4	34.6 ± 5.8	0.03	34.5 ± 5.9	34.8 ± 4.6	0.34
Estrogen use, *n (%) of women*	146 (19.1)	93 (16.0)	0.15	90 (15.7)	149 (19.3)	0.08	27 (15.0)	212 (18.2)	0.30
Hypertension, *n (%)*	259 (22.1)	301 (22.6)	0.77	241 (22.0)	319 (22.9)	0.54	52 (17.4)	508 (23.1)	0.03
Cholesterol-lowering medication use, *n (%)*	74 (6.3)	81 (6.1)	0.81	61 (5.5)	94 (6.7)	0.21	16 (5.4)	139 (6.3)	0.52
Dietary characteristics [4]									
Total energy, *kJ/d*	7266.5 ± 2556.6	8281.0 ± 2508.9	<0.001	7868.6 ± 2544.0	7771.9 ± 2550.3	0.34	6903.1 ± 2526.0	7937.3 ± 2523.1	<0.001
Protein, *g/d*	79.8 ± 15.5	74.2 ± 15.3	<0.001	74.6 ± 15.1	78.5 ± 15.2	<0.001	76.3 ± 15.4	76.9 ± 15.3	0.54
Carbohydrate, *g/d*	233.7 ± 42.2	241.3 ± 41.4	<0.001	241.5 ± 40.8	234.9 ± 40.9	<0.001	225.4 ± 41.0	239.5 ± 40.8	<0.001
Saturated fat, *g/d*	21.4 ± 6.5	22.2 ± 6.4	0.005	22.0 ± 6.3	21.7 ± 6.3	0.25	23.7 ± 6.3	21.6 ± 6.3	<0.001
Fiber, *g/d*	19.1 ± 5.9	16.5 ± 5.8	<0.001	17.1 ± 5.8	18.2 ± 5.8	<0.001	17.0 ± 5.9	17.8 ± 5.8	0.02
Magnesium, *mg/d*	318.0 ± 74.8	284.9 ± 73.5	<0.001	293.3 ± 73.8	305.7 ± 74.0	<0.001	287.0 ± 74.5	302.0 ± 74.1	0.001
Dietary glycemic index[5]	76.9 ± 5.0	78.8 ± 4.9	<0.001	78.3 ± 4.9	77.6 ± 4.9	<0.001	76.8 ± 4.9	78.1 ± 4.9	<0.001
Alcohol, *g/d*	12.6 ± 16.2	9.9 ± 15.9	<0.001	10.9 ± 15.8	11.3 ± 15.8	0.57	13.3 ± 15.9	10.8 ± 15.8	0.01

[1] Values are means ± SD or *n* (%), $n = 2500$.

[2] Sugar-sweetened drink includes Coke, Pepsi, and other colas with sugar, caffeine-free Coke, Pepsi, and other colas with sugar, and other carbonated beverages with sugar. Diet soda includes low-calorie cola, low-calorie caffeine-free cola, and other low-calorie carbonated beverages. Fruit juice includes apple juice or cider, orange juice, grapefruit juice, and other fruit juices. Nonconsumers are individuals with 0 servings/d intake. Consumers are individuals with ≥0.5 servings/wk intake. The median intakes of sugar-sweetened drink, diet soda, and fruit juice in consumers were 2.0, 4.0, and 6.0 servings/wk, respectively. For sugar-sweetened drink and diet soda, 0.5 serving was equivalent to 180 mL (6 fl oz.). For fruit juice, 0.5 serving was equivalent to 90 mL (3 fl oz.).

[3] P-values for Student's t test for continuous variables, linear regression model for dietary variables, or $\chi 2$ test for categorical variables between beverage consumers and nonconsumers.

[4] Total energy intake is adjusted for age and sex. Other dietary variables are adjusted for age, sex, and total energy intake.

[5] White bread was used as reference for dietary glycemic index.

TABLE 2 Multivariate adjusted mean plasma insulin and glucose concentrations, HOMA-IR, and $ISI_{0,120}$ across beverage intake groups[1]

	Intake[2]				
	None	0 < servings/d < 1	1 ≤ servings/d < 2	≥2 servings/d	*P*-trend
Sugar-sweetened drink					
n	1170	1109	125	96	
Fasting insulin, *pmol/L*					
Model 1[3]	190.8 (187.4, 194.2)	192.8 (189.4, 196.3)	204.5 (194.0, 215.8)	205.6 (193.5, 218.6)	0.003
Model 2[4]	188.1 (185.2, 191.1)	193.8 (190.8, 196.8)	204.6 (195.4, 214.3)	206.1 (195.2, 217.4)	<0.001
Fasting glucose, *mmol/L*					
Model 1	5.27 (5.24, 5.30)	5.26 (5.23, 5.29)	5.27 (5.18, 5.36)	5.16 (5.06, 5.26)	0.07
Model 2	5.25 (5.22, 5.28)	5.27 (5.24, 5.30)	5.26 (5.18, 5.35)	5.18 (5.08, 5.27)	0.17
HOMA-IR Unit					
Model 1	6.43 (6.30, 6.55)	6.45 (6.32, 6.58)	6.79 (6.40, 7.21)	6.71 (6.26, 7.19)	0.10
Model 2	6.29 (6.18, 6.40)	6.50 (6.39, 6.62)	6.86 (6.51, 7.23)	6.79 (6.39, 7.21)	0.004
$ISI_{0,120}$[5]					
Model 1	26.5 (26.1, 26.9)	26.3 (25.9, 26.7)	25.5 (24.3, 26.7)	26.5 (25.2, 27.9)	0.68
Model 2	26.7 (26.3, 27.1)	26.2 (25.8, 26.6)	25.5 (24.3, 26.6)	26.4 (25.1, 27.6)	0.37
Diet soda					
n	1104	894	245	257	
Fasting insulin, *pmol/L*					
Model 1	190.6 (187.3, 194.1)	191.5 (187.7, 195.3)	194.8 (187.6, 202.3)	207.0 (199.5, 214.9)	<0.001
Model 2	195.3 (192.2, 198.4)	188.8 (185.6, 192.2)	189.2 (183.1, 195.5)	192.9 (186.6, 199.3)	0.59
Fasting glucose, *mmol/L*					
Model 1	5.24 (5.21, 5.27)	5.26 (5.23, 5.29)	5.32 (5.26, 5.38)	5.32 (5.26, 5.38)	0.009
Model 2	5.26 (5.23, 5.29)	5.25 (5.22, 5.28)	5.29 (5.23, 5.35)	5.24 (5.19, 5.30)	0.84
HOMA-IR					
Model 1	6.38 (6.25, 6.51)	6.42 (6.28, 6.56)	6.59 (6.32, 6.87)	6.91 (6.63, 7.20)	<0.001
Model 2	6.55 (6.43, 6.66)	6.31 (6.19, 6.44)	6.37 (6.14, 6.61)	6.44 (6.21, 6.68)	0.56
$ISI_{0,120}$					
Model 1	26.6 (26.2, 27.0)	26.3 (25.9, 26.8)	25.9 (25.0, 26.7)	25.6 (24.8, 26.4)	0.02
Model 2	26.2 (25.8, 26.5)	26.6 (26.2, 27.0)	26.4 (25.6, 27.2)	26.7 (25.9, 27.4)	0.37
Fruit juice					
n	299	1209	775	217	
Fasting insulin, *pmol/L*					
Model 1	201.5 (194.7, 208.5)	192.3 (189.0, 195.6)	193.2 (189.1, 197.4)	184.6 (177.3, 192.2)	0.02
Model 2	199.9 (194.0, 206.1)	189.9 (187.1, 192.8)	193.8 (190.2, 197.4)	188.4 (181.8, 195.3)	0.37
Fasting glucose, *mmol/L*					
Model 1	5.29 (5.23, 5.34)	5.28 (5.26, 5.31)	5.25 (5.22, 5.29)	5.16 (5.10, 5.23)	<0.001
Model 2	5.28 (5.23, 5.33)	5.27 (5.25, 5.30)	5.25 (5.22, 5.28)	5.18 (5.11, 5.24)	0.006
HOMA-IR					
Model 1	6.85 (6.59, 7.11)	6.45 (6.33, 6.58)	6.45 (6.29, 6.60)	6.11 (5.84, 6.40)	0.004
Model 2	6.72 (6.50, 6.95)	6.38 (6.27, 6.49)	6.48 (6.34, 6.61)	6.21 (5.97, 6.47)	0.10
$ISI_{0,120}$					
Model 1	26.1 (25.4, 26.9)	26.3 (25.9, 26.7)	26.3 (25.8, 26.7)	27.1 (26.2, 28.0)	0.14
Model 2	26.0 (25.3, 26.7)	26.4 (26.1, 26.8)	26.4 (25.9, 26.8)	27.0 (26.1, 27.8)	0.19

[1] $n = 2500$. Values of fasting insulin and HOMA-IR are adjusted geometric means (95% CI). Values of fasting glucose and $ISI_{0,120}$ and ISI are adjusted means (95% CI); $P < 0.05$.
[2] Intake categories are based on beverage consumption. One serving of sugar-sweetened drink and diet soda was equivalent to 360 mL (12 fl oz.). One serving of fruit juice was equivalent to 180 mL (6 fl oz.).
[3] Adjusted for age and sex.
[4] Adjusted for sex, age, BMI, waist circumference, physical activity, cigarette smoking, hypertension, cholesterol-lowering medication use, total energy intake, alcohol intake, saturated fat intake, and multivitamin use.
[5] Due to the availability of 2-h post-OGTT insulin measures, 2492 subjects were included in analysis with $ISI_{0,120}$.

levels (none vs. ≥2 servings/d, 5.28 vs. 5.18 mmol/L, *P*-trend = 0.006) (Table 2). The association between fruit juice and fasting glucose remained significant after adjustment for dietary glycemic index, fiber intake, whole grain, fruit intake, or vegetable intake. We found no significant associations between fruit juice intake and fasting insulin, HOMA-IR, or $ISI_{0,120}$ after adjustment for potential confounders. Mutual adjustment for other beverages did not alter the findings; for instance, adjustment for diet soda and fruit juice intakes did not change the association between sugar-sweetened drink consumption and surrogate measures of insulin resistance.

Discussion

In this study, consumption of sugar-sweetened drinks was positively associated with levels of fasting insulin and HOMA-IR.

These surrogate measures of insulin resistance are based on fasting glucose regulation, and elevated levels primarily reflect hepatic insulin resistance and compensatory hyperinsulinemia. In this study, the HOMA-IR largely reflected fasting insulin concentrations ($r = 0.96$) and therefore our interpretations concerning these 2 variables are the same. We did not find consumption of sugar-sweetened drinks to be associated with the $ISI_{0,120}$. This measure incorporates fasting and 2-h glucose and insulin levels after an OGTT, as well as body weight, and it is a surrogate measure of peripheral insulin resistance.

Both insulin resistance and β-cell dysfunction precede type 2 DM, and thus increased consumption of calorically sweetened beverages containing rapidly absorbable simple sugars may contribute to an increased risk of type 2 DM. In the Nurses' Health Study, the risk of type 2 DM doubled in women who consumed at least 1 sugar-sweetened beverage a day (RR = 1.87, 95% CI: 1.42–2.36), compared with women with the lowest intake (<1/mo) (9). In contrast, sweetened beverage consumption, which included fruit punch, nondiet soda, and orange and grapefruit juice, was not related to type 2 DM risk in middle-aged adults in the Atherosclerosis Risk in Communities Study. (24). The discrepancies between studies may be in part due to the inclusion of fruit juices with sugar-added beverages in the Atherosclerosis Risk in Communities study.

Sugar-sweetened drinks contain large amounts of high fructose corn syrup (25), which consists of ~55% fructose and 45% glucose (26). The composition of high fructose corn syrup is similar to sucrose (27), and, therefore, these added caloric sweeteners should in theory be considered equivalent with respect to their effects on metabolic risk factors. Evidence from animal studies suggests that long-term sucrose consumption can lead to glucose intolerance and decreased insulin sensitivity, although this may be attributed to weight gain (28). In observational studies, dietary sucrose has been associated with higher fasting insulin in young adults (29), and positively associated with 2-h insulin concentrations after a glucose load in a small sample of Asian and European men (30). In contrast, no relationship was found between sucrose intake and HOMA-IR in middle-aged adults (31). Our findings contribute to the sparse data in the literature examining the relationship between sugar-sweetened drink consumption and surrogate markers of insulin sensitivity in adults. One cross-sectional study in overweight Latino children found that greater consumption of calorically sweetened beverages was related to insulin resistance and poor β-cell function, as measured by a frequently sampled intravenous glucose-tolerance test and minimal model (32). This study differed from ours with respect to the age group, to the classification of calorically sweetened beverages that included any beverage containing added sugar (such as sweetened tea or coffee), and to the fact that beverage consumption was estimated from 3-d diet records (32).

Sugar-sweetened sodas and fruit drinks are the leading source of added sugar in the U.S. diet (7) and contribute to the overall glycemic index of the diet (9). Dietary glycemic index, a measure of a carbohydrate food's ability to affect postprandial glycemia, has been linked to an increased risk of type 2 DM (33–35). In the Framingham Offspring Cohort, a higher dietary glycemic index was associated with a higher HOMA-IR, and greater prevalence of the metabolic syndrome (36). In this study, the positive associations between the consumption of sugar-sweetened drinks and fasting insulin and the HOMA-IR remained statistically significant after further adjustment for dietary glycemic index, indicating that this relationship was not fully explained by the effect of the high glycemic index of sugar-sweetened drinks.

Although higher fruit juice consumption was inversely associated with lower fasting plasma glucose, no significant relationship was observed with the fasting insulin, HOMA-IR, and $ISI_{0,120}$. In our cohort, the lifestyle and dietary characteristics of fruit juice consumers were more favorable for the prevention of insulin resistance. For instance, fruit juice consumers were less likely to smoke and they consumed diets lower in saturated fat and higher in total fiber intakes than nonconsumers. It is possible, therefore, that the observed inverse association between fruit juice intake and fasting glucose is potentially due to residual confounding. In middle-aged Japanese Brazilians, no relationship was observed between the consumption of fruit and fruit juice combined and risk of impaired glucose tolerance (37). Further studies on fruit juice and measures of insulin sensitivity among different populations with varying degrees of glucose tolerance are needed. To date, there is little evidence that the sugar present in fruits or fruit juices is associated with adverse metabolic effects, with the possible exception of weight gain in some populations (9,38). However, it is important to recognize that excess energy intake from fruit juice may contribute to increased body weight.

The evidence linking diet soda to adverse health consequences is scarce. Clinical studies have demonstrated that an increased consumption of caloric soda increased energy intake and body weight in healthy individuals, whereas increased consumption of diet soda significantly reduced energy intake and body weight (39). Similarly, a clinical study in overweight individuals found that daily supplementation with 152 g of sucrose caused an increase in energy intake, body weight, fat mass, and blood pressure, whereas reductions in body weight and fat mass were observed after supplementation with an equivalent amount of an artificial sweetener (40). In this study, there was no relationship between diet soda consumption and measures of glucose homeostasis. Although it is recognized that diet beverages are preferable to calorically sweetened beverages (41), little is known is about the health consequences of diet sodas. The effects of long-term consumption of sodas on metabolic risk factors have not been studied in longitudinal studies to date, and further research is clearly warranted.

Interpretation of our findings is subject to some caveats. Although the results from this study support the hypothesis that sugar-sweetened drink consumption may be an important determinant of insulin resistance, the cross-sectional design precludes assigning cause and effect. The FFQ has many limitations with respect to the assessment of beverage consumption, such as misreporting frequency of consumption and the lack of individual information on portion size. To date, the majority of observational studies on sugar-sweetened/caloric beverages and body weight have been conducted in children or adolescents, and not middle-aged or older adults (42,43). Excessive consumption of caloric beverages contributes to energy intake and may lead to a positive energy balance and subsequent weight gain. A recent systematic review of the topic suggests that sugar-sweetened beverage intake is related to weight gain (43). In this cross-sectional study, sugar-sweetened drink consumers had a lower BMI and were more physical active, whereas paradoxically, diet soda drinkers had higher BMI and were less physically active. A common practice in weight control is the consumption of noncaloric sweeteners and/or beverages (44). Our multivariate models included both BMI and waist circumference, as these measures reflect different distributions in body fat. However, because of the cross-sectional design, we cannot determine the associations between caloric and noncaloric beverages and weight gain, and thus more prospective studies of this topic are needed.

Sugar-sweetened drink consumption is high in the U.S. (45), with an estimated 76% of the population consuming sugared beverages daily (46). The 2005 Dietary Guidelines for America recommends that the public choose beverages with less caloric sweetener (47). A new proposed guidance system for beverage consumption (41) urges individuals to increase their consumption of water while limiting their intake of calorically sweetened, nutrient-poor beverages. Long-term sugar-sweetened drink consumption may lead to deterioration in insulin sensitivity, which increases an individual's risk of developing type 2 DM. However, more detailed physiological studies of the metabolic effects of sugar-sweetened drinks are needed to determine whether their consumption preferentially affects fasting vs. postprandial energy regulation. In the meantime, in accordance with current dietary recommendations (41,47), individuals are advised to limit consumption of calorically sweetened beverages.

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Literature Cited

1. Bonadonna RC, Groop L, Kraemer N, Ferrannini E, Del Prato S, DeFronzo RA. Obesity and insulin resistance in humans: a dose-response study. Metabolism. 1990;39:452–9.
2. Lillioja S, Mott DM, Spraul M, Ferraro R, Foley JE, Ravussin E, Knowler WC, Bennett PH, Bogardus C. Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus. Prospective studies of Pima Indians. N Engl J Med. 1993;329: 1988–92.
3. Weyer C, Tataranni PA, Bogardus C, Pratley RE. Insulin resistance and insulin secretory dysfunction are independent predictors of worsening of glucose tolerance during each stage of type 2 diabetes development. Diabetes Care. 2001;24:89–94.
4. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes. 1988;37:1595–607.
5. Putnum JJAJ. Food Consumption, Prices, and Expenditures, 1970–97. Washington, DC: US Dept of Agriculture; 1999.
6. Bray GA, Nielsen SJ, Popkin BM. Consumption of high-fructose corn syrup in beverages may play a role in the epidemic of obesity. Am J Clin Nutr. 2004;79:537–43.
7. Guthrie JF, Morton JF. Food sources of added sweeteners in the diets of Americans. J Am Diet Assoc 2000;100:43–51, quiz 49–50.
8. Ludwig DS, Peterson KE, Gortmaker SL. Relation between consumption of sugar-sweetened drinks and childhood obesity: a prospective, observational analysis. Lancet. 2001;357:505–8.
9. Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willett WC, Hu FB. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. JAMA. 2004;292: 927–34.
10. Willett W, Manson J, Liu S. Glycemic index, glycemic load, and risk of type 2 diabetes. Am J Clin Nutr. 2002;76:274S–80S.
11. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature. 2006;444:840–6.
12. Dawber TR, Meadors GF, Moore FE, Jr. Epidemiological approaches to heart disease: the Framingham Study. Am J Public Health. 1951;41:279–81.
13. Feinleib M, Kannel WB, Garrison RJ, McNamara PM, Castelli WP. The Framingham Offspring Study. Design and preliminary data. Prev Med. 1975;4:518–25.
14. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. Am J Epidemiol. 1992;135:1114–26.
15. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH, Speizer FE. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol. 1985;122:51–65.
16. Salvini S, Hunter DJ, Sampson L, Stampfer MJ, Colditz GA, Rosner B, Willett WC. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. Int J Epidemiol. 1989;18: 858–67.
17. Feskanich D, Rimm EB, Giovannucci EL, Colditz GA, Stampfer MJ, Litin LB, Willett WC. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. J Am Diet Assoc. 1993;93:790–6.
18. Hu FB, Rimm E, Smith-Warner SA, Feskanich D, Stampfer MJ, Ascherio A, Sampson L, Willett WC. Reproducibility and validity of dietary patterns assessed with a food-frequency questionnaire. [see comment] Am J Clin Nutr. 1999;69:243–9.
19. World Health Organization (1980). WHO Expert Committee on Diabetes mellitus: Second Report, Geneva, World Health Organization.
20. Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB, Sr., Wilson PW. Insulin resistance, the metabolic syndrome, and incident cardiovascular events in the Framingham Offspring Study. Diabetes. 2005;54: 3252–7.
21. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28:412–9.
22. Gutt M, Davis CL, Spitzer SB, Llabre MM, Kumar M, Czarnecki EM, Schneiderman N, Skyler JS, Marks JB. Validation of the insulin sensitivity index (ISI(0,120)): comparison with other measures. Diabetes Res Clin Pract. 2000;47:177–84.
23. Kannel WB, Sorlie P. Some health benefits of physical activity. The Framingham Study. Arch Intern Med. 1979;139:857–61.
24. Paynter NP, Yeh HC, Voutilainen S, Schmidt MI, Heiss G, Folsom AR, Brancati FL, Kao WH. Coffee and sweetened beverage consumption and the risk of type 2 diabetes mellitus: the atherosclerosis risk in communities study. Am J Epidemiol. 2006;164:1075–84.
25. Park YK, Yetley EA. Intakes and food sources of fructose in the United States. Am J Clin Nutr. 1993;58(suppl):737S–47S.
26. Elliott SS, Keim NL, Stern JS, Teff K, Havel PJ. Fructose, weight gain, and the insulin resistance syndrome. Am J Clin Nutr. 2002;76:911–22.
27. Hanover LM, White JS. Manufacturing, composition, and applications of fructose. Am J Clin Nutr. 1993;58(suppl):724S–32S.
28. Kawasaki T, Kashiwabara A, Sakai T, Igarashi K, Ogata N, Watanabe H, Ichiyanagi K, Yamanouchi T. Long-term sucrose-drinking causes increased body weight and glucose intolerance in normal male rats. Br J Nutr. 2005;93:613–8.
29. Manolio TA, Savage PJ, Burke GL, Hilner JE, Liu K, Orchard TJ, Sidney S, Oberman A. Correlates of fasting insulin levels in young adults: the CARDIA study. J Clin Epidemiol. 1991;44:571–8.
30. Sevak L, McKeigue PM, Marmot MG. Relationship of hyperinsulinemia to dietary intake in south Asian and European men. Am J Clin Nutr. 1994;59:1069–74.
31. Lau C, Faerch K, Glumer C, Tetens I, Pedersen O, Carstensen B, Jorgensen T, Borch-Johnsen K; Inter99 Study. Dietary glycemic index, glycemic load, fiber, simple sugars, and insulin resistance: the Inter99 study. Diabetes Care. 2005;28:1397–403.
32. Davis JN, Ventura EE, Weigensberg MJ, Ball GD, Cruz ML, Shaibi GQ, Goran MI. The relation of sugar intake to beta cell function in overweight Latino children. Am J Clin Nutr. 2005;82:1004–10.
33. Salmeron J, Ascherio A, Rimm EB, Colditz GA, Spiegelman D, Jenkins DJ, Stampfer MJ, Wing AL, Willett WC. Dietary fiber, glycemic load, and risk of NIDDM in men. Diabetes Care. 1997;20:545–50.
34. Schulze MB, Liu S, Rimm EB, Manson JE, Willett WC, Hu FB. Glycemic index, glycemic load, and dietary fiber intake and incidence of type 2 diabetes in younger and middle-aged women. Am J Clin Nutr. 2004;80:348–56.
35. Hodge AM, English DR, O'Dea K, Giles GG. Glycemic index and dietary fiber and the risk of type 2 diabetes. Diabetes Care. 2004;27: 2701–6.
36. McKeown NM, Meigs JB, Liu S, Saltzman E, Wilson PW, Jacques PF. Carbohydrate nutrition, insulin resistance, and the prevalence of the metabolic syndrome in the Framingham Offspring Cohort. Diabetes Care. 2004;27:538–46.
37. Sartorelli DS, Freire RD, Ferreira SR, Cardoso MA. Dietary fiber and glucose tolerance in Japanese Brazilians. Diabetes Care. 2005;28: 2240–2.
38. Dennison BA, Rockwell HL, Baker SL. Excess fruit juice consumption by preschool-aged children is associated with short stature and obesity. Pediatrics. 1997;99:15–22.

39. Tordoff MG, Alleva AM. Effect of drinking soda sweetened with aspartame or high-fructose corn syrup on food intake and body weight. Am J Clin Nutr. 1990;51:963–9.
40. Raben A, Vasilaras TH, Moller AC, Astrup A. Sucrose compared with artificial sweeteners: different effects on ad libitum food intake and body weight after 10 wk of supplementation in overweight subjects. Am J Clin Nutr. 2002;76:721–9.
41. Popkin BM, Armstrong LE, Bray GM, Caballero B, Frei B, Willett WC. A new proposed guidance system for beverage consumption in the United States. Am J Clin Nutr. 2006;83:529–42.
42. Drewnowski A, Bellisle F. Liquid calories, sugar, and body weight. Am J Clin Nutr. 2007;85:651–61.
43. Malik VS, Schulze MB, Hu FB. Intake of sugar-sweetened beverages and weight gain: a systematic review. Am J Clin Nutr. 2006;84:274–88.
44. Malinauskas BM, Raedeke TD, Aeby VG, Smith JL, Dallas MB. Dieting practices, weight perceptions, and body composition: a comparison of normal weight, overweight, and obese college females. Nutr J. 2006;5:11.
45. Storey ML, Forshee RA, Anderson PA. Beverage Consumption in the US Population. J Am Diet Assoc. 2006;106:1992–2000.
46. Nielsen SJ, Popkin BM. Changes in beverage intake between 1977 and 2001. Am J Prev Med. 2004;27:205–10.
47. Department of Health and Human Service and Department of AgricultureWashington DC: The 2005 Dietary guideline for America. [cited 2007 Jun 6] Available from http://www.health.gov/DietaryGuidelines/.