Sugar-sweetened and artificially sweetened beverage consumption and risk of type 2 diabetes in men[1–3]

Lawrence de Koning, Vasanti S Malik, Eric B Rimm, Walter C Willett, and Frank B Hu

ABSTRACT

Background: Sugar-sweetened beverages are risk factors for type 2 diabetes; however, the role of artificially sweetened beverages is unclear.

Objective: The objective was to examine the associations of sugar- and artificially sweetened beverages with incident type 2 diabetes.

Design: An analysis of healthy men (n = 40,389) from the Health Professionals Follow-Up Study, a prospective cohort study, was performed. Cumulatively averaged intakes of sugar-sweetened (sodas, fruit punches, lemonades, fruit drinks) and artificially sweetened (diet sodas, diet drinks) beverages from food-frequency questionnaires were tested for associations with type 2 diabetes by using Cox regression.

Results: There were 2680 cases over 20 y of follow-up. After age adjustment, the hazard ratio (HR) for the comparison of the top with the bottom quartile of sugar-sweetened beverage intake was 1.25 (95% CI: 1.11, 1.39; P for trend < 0.01). After adjustment for confounders, including multivitamins, family history, high triglycerides at baseline, high blood pressure, diuretics, pre-enrollment weight change, dieting, total energy, and body mass index, the HR was 1.24 (95% CI: 1.09, 1.40; P for trend < 0.01). Intake of artificially sweetened beverages was significantly associated with type 2 diabetes in the age-adjusted analysis (HR: 1.91; 95% CI: 1.72, 2.11; P for trend < 0.01) but not in the multivariate-adjusted analysis (HR: 1.09; 95% CI: 0.98, 1.21; P for trend = 0.13). The replacement of one serving of sugar-sweetened beverage with 1 cup ($\approx$237 mL) of coffee was associated with a risk reduction of 17%.

Conclusion: Sugar-sweetened beverage consumption is associated with a significantly elevated risk of type 2 diabetes, whereas the association between artificially sweetened beverages and type 2 diabetes was largely explained by health status, pre-enrollment weight change, dieting, and body mass index. *Am J Clin Nutr* 2011;93:1321–7.

INTRODUCTION

Consumption of sugar-sweetened beverages (eg, sodas, sweetened fruit drinks) in the United States rose 135% between 1977 and 2001, and in 2004 soda represented 7% of per-capita energy intake (1, 2). In parallel with these changes, the prevalence of obesity and type 2 diabetes in the United States has risen dramatically (3). In prospective cohort studies, sugar-sweetened beverages are major risk factors for weight gain and type 2 diabetes (4, 5).

Taxing of sugar-sweetened beverages has been proposed to encourage the consumption of other potentially healthier beverages, such as water, low-fat milk, 100% fruit juice, coffee, and tea (6). It is unclear whether artificially sweetened beverages should be recommended because they have been shown to be associated with an increased risk of type 2 diabetes and cardiometabolic dysfunction in some studies (7–9).

The purposes of this study were to examine the associations of sugar and artificially sweetened beverages with type 2 diabetes in a well-characterized cohort of men and to determine what other beverages should be considered as alternatives.

SUBJECTS AND METHODS

Subjects

In 1986, 51,529 men aged 40–75 y were recruited to form the Health Professionals Follow-Up Study (HPFS). As part of the study, questionnaires were mailed every other year to participants to assess health status and lifestyle factors (94% response rate). The HPFS was approved by the Harvard Institutional Review Board (Dietary Etiologies of Heart Disease and Cancer Protocol no. 10446). The procedures followed were in accordance with the ethical standards of Harvard University and with the Helsinki Declaration of 1975, as revised in 1983.

Assessment of beverage intake

Intake of sugar-sweetened and artificially sweetened beverages was assessed by using a 131-item semiquantitative food-frequency questionnaire (FFQ) that was sent to participants every 4 y. Participants were asked to report their usual intake (never to $\geq$6 times/d) of a standard portion of foods and beverages (one

[1] From the Departments of Nutrition (LdK, VSM, EBR, WCW, and FBH) and Epidemiology (EBR, WCW, and FBH), Harvard School of Public Health, Boston, MA; the Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA (EBR, WCW, and FBH); and the Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA (EBR, WCW, and FBH).

[2] Supported by postdoctoral fellowships from the Canadian Institutes of Health Research and the Canadian Diabetes Association (to LdK). The Health Professionals Follow-Up Study is supported by grants CA55075, HL35464, and DK58845 from the National Institutes of Health.

[3] Address correspondence to FB Hu, Harvard School of Public Health, 665 Huntington Avenue, Boston, MA, 02115. E-mail: frank.hu@channing.harvard.edu.

Received November 8, 2010. Accepted for publication March 4, 2011.

First published online March 23, 2011; doi: 10.3945/ajcn.110.007922.

standard glass, can, or bottle). Nutrient and energy intakes were calculated by multiplying intakes by nutrient and energy contents and summing across all items. Total sugar-sweetened beverages were defined as caffeinated colas, caffeine-free colas, other carbonated sugar-sweetened beverages, and noncarbonated sugar-sweetened beverages (fruit punches, lemonades, or other fruit drinks). Artificially sweetened beverages were defined as caffeinated, caffeine-free, and noncarbonated low-calorie beverages.

The FFQ was validated against two 7-d diet records administered 6 mo apart in a validation study ($n = 127$) (10). Correlations between these measures after correction for within-person variation were 0.84 for colas, 0.74 for low-calorie colas, and 0.55 for other carbonated sugar-sweetened beverages (10) For noncarbonated sugar-sweetened beverages (fruit punches, lemonades, and fruit drinks), the correlation was 0.40, which was not corrected for within-person variation because of the high ratio of within- to between-person variance (7.26) (10). Correlations were 0.53 for water, 0.88 for low-fat milk, 0.75–0.89 for fruit juices, 0.93 for coffee, and 0.77 for tea (10).

Ascertainment of endpoints

To verify self-reported diagnoses of type 2 diabetes, a supplementary questionnaire was mailed to the participants (11). Cases before 1998 were defined by using National Diabetes Data Group criteria, and American Diabetes Association criteria were used for those after 1998. Participants with type 1 diabetes were excluded. In a validation study, 97% of type 2 diabetes cases were confirmed by medical record review (11).

Statistical analysis

Participants with type 2 diabetes, cardiovascular disease (heart attack, stroke, angina, or coronary artery bypass graft), cancer (except nonmelanoma skin cancer) or an implausible energy intake ($<$800 or $>$4200 kcal/d) at baseline were excluded, which left 40,389 participants.

Person-time was calculated from the return of the baseline questionnaire until 31 January 2006, death, loss to follow-up, development of type 2 diabetes, or whichever occurred first. Hazard ratios (HRs) for type 2 diabetes were modeled by using age-stratified Cox proportional hazard models with time-varying covariates. Beverage intake was grouped into quartiles, and linear trends were evaluated by using the Wald test (1 df) on a term representing the median intake in each quartile.

Cumulative averages of dietary variables were calculated at each time point to account for previous dietary information and to reflect long-term patterns of intake. To control for recall bias, averages were not updated after the diagnosis of cancer or cardiovascular disease. Other covariates were updated at each time point. Analyses were repeated by using baseline dietary data to assess the association between a single measure of beverage intake and type 2 diabetes.

We adjusted for smoking (never; past; current, 1–15 cigarettes/d; current, $>$15 cigarettes/d; or missing), physical activity (quintiles of metabolic equivalents/wk, or missing), and alcohol intake (abstainers, 0–9.9 g/d, 10–20 g/d, $>$20 g/d, or missing). We also adjusted for family history of type 2 diabetes, high triglycerides in 1986, and high blood pressure to control for known diabetes and cardiovascular disease risk, which might motivate participants to change their beverage consumption. We did not adjust for high triglycerides during the follow-up because it could be an early marker for type 2 diabetes. Diuretic use was adjusted for as a marker of overall health and because diuretics affect thirst. Multivitamin intake from 1988 onward was adjusted to control for self-interest in maintaining good health, which could be a marker of diabetes risk as well as beverage intake. Diet quality was controlled for by using the alternative Healthy Eating Index (aHEI; in quintiles) (12). Recalled weight change between 1981 and 1986 (weight gain: 0, 0.9–1.8, 2.3–4.1, 4.5–6.4, 6.8–8.6, 9.1–13.2, or $\geq$13.6 kg; weight loss: 0, 0.9–1.8, 2.3–4.1, 4.5–6.4, or $\geq$6.8 kg) and adherence to a low-calorie diet in 1994 were adjusted to control for changes in overall health and diabetes risk associated with dieting and also possible changes in beverage intake. Finally, total energy intake (quintiles) and body mass index [BMI (in kg/m^2) $<$23, 23–23.9, 24–24.9, 25–26.9, 27–28.9, 29–30.9, 31–32.9, 33–34.9, $\geq$35, or missing] were adjusted to study potential mediators of the relation between beverage intake and type 2 diabetes. If BMI, smoking, or physical activity was missing during the follow-up, the last value was carried forward. Cubic splines with 3, 4, and 5 knots were used to test for nonlinear associations.

In a sensitivity analysis, cases of type 2 diabetes occurring during the first 2 y of follow-up were excluded to assess the extent that pre-existing insulin resistance may bias associations. Also, to explore the role of elapsed time between the assessment of beverage intake and a diagnosis of type 2 diabetes, 4- and 8-y lagged analyses were performed. For these analyses, beverage intake was used to predict disease occurring 4 or 8 y later.

Analyses were repeated after stratification by age ($>$ compared with $<$65 y), alcohol consumption (drinker compared with abstainer), family history of type 2 diabetes (yes or no), physical activity [low (quintile 1 and quintile 2), medium (quintile 3 and quintile 4), or high (quintile 5)], and BMI ($<$25, 25–29.9, or $\geq$30). The Wald test (1 df) was used for interaction testing of cross-product terms (eg, median beverage intake $\times$ median BMI).

Risk of type 2 diabetes was also determined according to the per-serving (continuous) intake of sugar-sweetened (total, colas, carbonated noncolas, fruit punches, and lemonades) and artificially sweetened beverages after adjustment for continuous covariates. A similar analysis was performed for water, low-fat milk (skim, 1% fat, and 2% fat), fruit juice (orange, apple, grapefruit, and other fruit juice), coffee (caffeinated and decaffeinated), and tea (caffeinated) as a comparison. Beverages with significant associations with type 2 diabetes were included in a mutually adjusted model to assess the effect of substituting one beverage for another. Cross-product terms were included in the regression models to test for synergistic effects. Because the aHEI includes a measure of low-fat milk and fruit juice, red and processed meat and cereal fiber were adjusted for in these analyses. SAS version 9.1 (SAS, Cary, NC) was used for all analyses, and a P value $\leq$0.05 was considered statistically significant.

RESULTS

Baseline characteristics

The mean intake of sugar-sweetened beverages was 2.5 servings/wk or 0.36 servings/d (SD: 0.61/d) and was mostly cola

(mean ± SD: 0.21 ± 0.46/d). The mean consumption of artificially sweetened beverages was 3.4 servings/wk (mean ± SD: 0.49 ± 0.94/d). The intakes of sugar and artificially sweetened beverages were weakly but inversely correlated (Pearson's $R = -0.10$, $P < 0.01$)

Consumption of sugar-sweetened beverages was significantly associated with lower overall diet quality as measured by the aHEI (**Table 1**). Sugar-sweetened beverages were also associated with higher intakes of red and processed meat, carbohydrate, total fat, glycemic load, and energy, but with lower intakes of protein, vegetable fat, cereal fiber, and alcohol. Compared with nonconsumers, high consumers of sugar-sweetened beverages either lost less weight or gained more weight between 1981 and 1986 and were less likely to have followed a low-calorie diet in 1994. They were also more likely to be current smokers and were less likely to be physically active, to have a family history of type 2 diabetes, or take multivitamins.

Consumption of artificially sweetened beverages was significantly associated with higher overall diet quality. This corresponded to a lower intake of red and processed meat, carbohydrate, glycemic load, and energy but with a higher intake of protein, total fat, animal fat, vegetable fat, and cereal fiber. Compared with nonconsumers, high consumers either lost more weight or gained more weight between 1981 and 1986 and were more likely to have followed a low-calorie diet in 1994. They also had a higher BMI, were less likely to be current smokers, and were more likely to be physically active, to have a family history of type 2 diabetes, to take multivitamins, to have high triglycerides, to have high blood pressure, or to use diuretics.

Regression analysis

There were 2680 incident cases of type 2 diabetes over 20 y of follow-up (370,331 observations, 710,537 person-years). After adjustment for age, both beverage types were significantly associated with an increased risk of type 2 diabetes: top compared with bottom quartile of sugar-sweetened beverages (HR: 1.25; 95% CI: 1.11, 1.39; P for trend < 0.01) and top compared with

TABLE 1
Age-adjusted characteristics of participants at baseline by quartile (Q) of sugar-sweetened and artificially sweetened beverage consumption[1]

	Sugar-sweetened beverages				Artificially sweetened beverages			
	Q1 (never)	Q2 (2/mo)	Q3 (1–4/wk)	Q4 (4.5/wk to 7.5/d)	Q1 (never)	Q2 (2/mo)	Q3 (1–4/wk)	Q4 (4.5/wk to 18/d)
Median consumption	Never	2/mo	2/wk	6.5/wk	Never	2/mo	2/wk	1.1/d
n	13,675	5022	11,729	9963	18,442	2681	9448	9818
Alternative Healthy Eating Index	46.0 ± 11.7[2]	44.7 ± 11.1	43.8 ± 10.7	42.2 ± 10.6	43.4 ± 11.4	44.8 ± 11.2	45.1 ± 10.8	44.7 ± 11.0
Red and processed meat (servings/d)	0.8 ± 0.7	0.9 ± 0.7	1.0 ± 0.7	1.2 ± 0.8	1.0 ± 0.8	0.9 ± 0.7	0.9 ± 0.7	1.0 ± 0.7
Carbohydrate (% of energy)	45.5 ± 9.5	45.9 ± 8.2	46.6 ± 7.6	49.6 ± 7.3	47.7 ± 8.6	47.4 ± 8.5	46.8 ± 8.1	45.5 ± 8.4
Protein (% of energy)	19.6 ± 3.6	19.0 ± 3.1	18.4 ± 3.0	16.8 ± 2.9	17.9 ± 3.2	18.5 ± 3.3	18.8 ± 3.2	19.2 ± 3.5
Total fat (% of energy)	31.7 ± 7.0	32.4 ± 6.2	32.7 ± 5.8	31.9 ± 5.5	31.9 ± 6.3	31.7 ± 6.1	31.8 ± 5.9	32.7 ± 6.3
Animal fat (% energy)	18.3 ± 6.2	18.7 ± 5.7	18.9 ± 5.3	18.6 ± 5.0[3]	18.6 ± 5.8	18.1 ± 5.5	18.3 ± 5.3	18.9 ± 5.5
Vegetable fat (% of energy)	13.4 ± 4.9	13.7 ± 4.5	13.8 ± 4.3	13.3 ± 4.1	13.3 ± 4.5	13.6 ± 4.5	13.5 ± 4.3	13.9 ± 4.6
Cereal fiber (g/d)	6.5 ± 4.7	6.2 ± 3.8	5.7 ± 3.5	5.0 ± 2.8	5.7 ± 3.7	6.2 ± 4.9	6.0 ± 3.8	5.9 ± 4.1
Glycemic load	106 ± 43	113 ± 41	124 ± 42	154 ± 49	130 ± 49	123 ± 48	120 ± 46	118 ± 47
Alcohol (g/d)	12.5 ± 16.2	11.6 ± 15.1	11.0 ± 14.7	10.1 ± 14.6	11.5 ± 15.8	10.8 ± 15.0	11.3 ± 14.3	11.5 ± 15.4[3]
Total energy intake (kcal/d)	1793 ± 554	1886 ± 567	2019 ± 588	2298 ± 647	2049 ± 632	1956 ± 610	1945 ± 602	1965 ± 619
Weight loss between 1981 and 1986 (kg)	0.9 ± 2.0	0.7 ± 1.7	0.6 ± 1.6	0.5 ± 1.5	0.5 ± 1.5	0.6 ± 1.6	0.7 ± 1.7	0.9 ± 2.0
Weight gain between 1981 and 1986 (kg)	2.0 ± 4.0	2.0 ± 3.8	2.0 ± 3.8	2.2 ± 3.8	1.8 ± 3.4	1.9 ± 3.7	2.0 ± 3.6	2.6 ± 4.6
Low-calorie diet in 1994 (%)	26	23	21	17	15	22	24	33
BMI (kg/m^2)	25.5 ± 3.3	25.4 ± 3.2	25.4 ± 3.2	25.5 ± 3.3[3]	24.8 ± 3.1	25.3 ± 3.0	25.6 ± 3.1	26.5 ± 3.5
Current smoking (%)	8	8	9	12	12	8	8	7
Physical activity (METs/wk)	23.9 ± 32.3	21.5 ± 26.2	20.7 ± 29.3	19.6 ± 28.0	20.1 ± 27.2	20.5 ± 28.4	22.2 ± 30.4	23.6 ± 33.5
Family history of type 2 diabetes (%)	13	11	11	11	10	12	12	13
Multivitamin use in 1988 (%)	33	33	31	30	31	31	32	32
High triglycerides (%)	8	9	8	8[3]	7	8	9	11
High blood pressure (%)	20	18	18	19[3]	16	18	20	23
Diuretic use (%)	9	9	9	9[3]	7	8	10	11

[1] All values were adjusted to a mean age of 51 y. Linear and logistic regression analyses were used to assess linear trends of participant characteristics across quartiles and are significant ($P \leq 0.05$) unless noted otherwise. Sugar-sweetened beverages include caffeinated and caffeine-free colas, other carbonated sugar-sweetened beverages, fruit punches, lemonades, and other fruit-flavored beverages. Artificially sweetened beverages include caffeinated and caffeine-free low-calorie colas and other low-calorie carbonated beverages. Reported weight loss and weight gain between 1981 and 1986 are mutually exclusive. METs, metabolic equivalents.

[2] Mean ± SD (all such values).

[3] NS.

bottom quartile of artificially sweetened beverages (HR: 1.91; 95% CI: 1.72, 2.11; P for trend < 0.01) (**Table 2**).

After adjustment for smoking, physical activity, alcohol intake, and multivitamin use, associations were partly attenuated for sugar-sweetened beverages but with <1% for artificially sweetened beverages. Progressive adjustment for family history, high triglycerides, high blood pressure, diuretic use, previous weight change, and a low-calorie diet strengthened the association for sugar-sweetened beverages but weakened the association for artificially sweetened beverages. Further adjustment for the aHEI and total energy weakened the association for sugar-sweetened beverages but strengthened the association for artificially sweetened beverages. Adjustment for BMI strengthened the association for sugar-sweetened beverages, but attenuated the association for artificially sweetened beverages. In the fully adjusted models, intake of sugar-sweetened beverages was significantly associated with the risk of type 2 diabetes (HR: 1.24; 95% CI: 1.09, 1.40; P for trend < 0.01); however, intake of artificially sweetened beverages was not (HR: 1.09; 95% CI: 0.98, 1.21; P for trend = 0.13). Associations were tested for nonlinearity, but no significant evidence of nonlinearity was found (P for curvature >0.13). Use of baseline beverage intake yielded similar results for sugar-sweetened beverages (HR: 1.19; 95% CI: 1.07, 1.33; P for trend < 0.01) and artificially sweetened beverages (HR: 1.08; 95% CI: 0.98, 1.19; P for trend = 0.12), as did the exclusion of the first 2 y of type 2 diabetes cases or performing lagged analyses (data not shown). No significant interactions were observed between beverage intake and age, alcohol, physical activity, or family history (data not shown).

The use of continuous variables and covariates did not change the results (**Table 3**). One serving of sugar-sweetened beverages per day was significantly associated with a 16% increased risk of type 2 diabetes (HR: 1.16; 95% CI: 1.08, 1.25; $P < 0.01$), which was primarily due to colas and carbonated noncolas. Fruit punches, lemonades, and other fruit drinks were not significantly associated with type 2 diabetes. However the intake was low, the

TABLE 2
Risk of type 2 diabetes according to quartile (Q) of cumulatively averaged sugar-sweetened and artificially sweetened beverage consumption[1]

	Q1	Q2	Q3	Q4	P for trend
Sugar-sweetened beverages					
Quartile range (servings)	Never	2/mo	1–4/wk	4.5/wk to 7.5/d	
Median consumption (servings)	Never	2/mo	2/wk	6.5/wk	
Person-years	167,462	165,515	189,851	187,709	
Type 2 diabetes cases	586	629	685	780	
Age adjusted[2]	1.00	1.00 (0.89, 1.13)	1.03 (0.92, 1.15)	1.25 (1.11, 1.39)	<0.01
Multivariate adjusted[2]	1.00	1.01 (0.90, 1.13)	1.03 (0.92, 1.15)	1.21 (1.08, 1.36)	<0.01
Family history	1.00	1.02 (0.91, 1.14)	1.05 (0.94, 1.17)	1.22 (1.09, 1.36)	<0.01
High triglycerides in 1986, high blood pressure, diuretics	1.00	1.04 (0.93, 1.17)	1.05 (0.94, 1.18)	1.20 (1.08, 1.35)	<0.01
Previous weight change and low-calorie diet	1.00	1.07 (0.95, 1.20)	1.07 (0.95, 1.20)	1.25 (1.12, 1.40)	<0.01
aHEI	1.00	1.06 (0.94, 1.19)	1.06 (0.94, 1.18)	1.22 (1.09, 1.37)	<0.01
Total energy intake	1.00	1.04 (0.92, 1.16)	1.01 (0.90, 1.13)	1.12 (0.99, 1.26)	0.04
BMI	1.00	1.09 (0.97, 1.22)	1.07 (0.95, 1.20)	1.24 (1.09, 1.40)	<0.01
Artificially sweetened beverages					
Quartile range (servings)	Never	2/mo	1–4/wk	4.5/wk to 18/d	
Median consumption (servings)	Never	2/mo	2/wk	1.1/d	
Person-years	252,323	101,307	178,125	178,782	
Type 2 diabetes cases	723	377	660	920	
Age adjusted[2]	1.00	1.18 (1.04, 1.33)	1.25 (1.13, 1.40)	1.91 (1.72, 2.11)	<0.01
Multivariate adjusted[2]	1.00	1.21 (1.06, 1.37)	1.29 (1.16, 1.44)	1.94 (1.75, 2.14)	<0.01
Family history	1.00	1.18 (1.04, 1.34)	1.26 (1.13, 1.41)	1.84 (1.66, 2.03)	<0.01
High triglycerides in 1986, high blood pressure, diuretics	1.00	1.16 (1.02, 1.32)	1.18 (1.06, 1.31)	1.60 (1.45, 1.78)	<0.01
Previous weight change and low-calorie diet	1.00	1.13 (1.00, 1.29)	1.10 (0.99, 1.23)	1.35 (1.22, 1.50)	<0.01
aHEI	1.00	1.15 (1.01, 1.31)	1.11 (1.00, 1.24)	1.38 (1.24, 1.53)	<0.01
Total energy intake	1.00	1.17 (1.03, 1.33)	1.14 (1.02, 1.27)	1.40 (1.26, 1.56)	<0.01
BMI	1.00	1.09 (0.96, 1.24)	0.98 (0.88, 1.09)	1.09 (0.98, 1.21)	0.13

[1] Multivariate models were adjusted for age, smoking (never; past; current, 1–15 cigarettes/d; current, >15 cigarettes/d; or missing), physical activity (quintiles of metabolic equivalents/wk or missing), alcohol intake (abstainers, 0–9.9 g/d, 10–20 g/d, >20 g/d, or missing), multivitamin use, family history of type 2 diabetes, high triglycerides (in 1986), high blood pressure, and use of diuretics. Previous weight change represents separate variables for weight gain (0, 0.9–1.8, 2.3–4.1, 4.5–6.4, 6.8–8.6, 9.1–13.2, or ≥13.6 kg) and weight loss (0, 0.9–1.8, 2.3–4.1, 4.5–6.4, or ≥6.8 kg) between 1981 and 1986. Low-calorie diet refers to adherence to a low-calorie diet in 1994 (yes, no, or missing). The alternative Healthy Eating Index (aHEI) and total energy were classified as quintiles, and BMI was classified as 9 categories (in kg/m^2; < 23, 23–23.9, 24–24.9, 25–26.9, 27–28.9, 29–30.9, 31–32.9, 33–34.9, ≥35, or missing). One serving is equivalent to a standard glass, can, or bottle.

[2] Values are hazard ratios; 95% CIs in parentheses.

TABLE 3
Risk of type 2 diabetes associated with one serving per day of sugar-sweetened beverages and other beverages[1]

Beverage	Mean ± SD servings/d	Hazard ratio for one serving/d (95% CI)	*P* value
Total sugar-sweetened beverages	0.36 ± 0.61	1.16 (1.08, 1.25)	<0.01
Colas	0.21 ± 0.46	1.20 (1.09, 1.32)	<0.01
Carbonated noncolas	0.07 ± 0.20	1.35 (1.08, 1.69)	<0.01
Fruit punches, lemonades, other noncarbonated fruit drinks	0.08 ± 0.27	1.05 (0.89, 1.25)	0.65
Artificially sweetened beverages	0.49 ± 0.94	1.03 (0.99, 1.08)	0.12
Water	2.59 ± 1.82	1.03 (1.01, 1.06)	0.01
Low-fat milk	0.73 ± 0.97	0.98 (0.93, 1.03)	0.50
Fruit juice	0.78 ± 0.84	1.02 (0.96, 1.09)	0.51
Total coffee	1.92 ± 1.79	0.94 (0.91, 0.96)	<0.01
Caffeinated coffee	1.33 ± 1.59	0.96 (0.93, 0.99)	<0.01
Decaffeinated coffee	0.59 ± 1.10	0.94 (0.90, 0.98)	0.01
Tea	0.43 ± 0.84	0.97 (0.92, 1.03)	0.35

[1] Models were multivariate adjusted as in Table 2 by using continuous covariates (except for smoking and alcohol). In this analysis, red and processed meat and cereal fiber (both continuous variables) replace the alternative Healthy Eating Index. For sugar-sweetened and artificially sweetened beverages, one serving is equivalent to a standard glass, can, or bottle. For other beverages, one serving is equivalent to 1 cup (≈237 mL). Low-fat milk includes skim, 1% fat, and 2% fat milk. Coffee includes both caffeinated and decaffeinated coffee. Tea includes only caffeinated tea. Fruit juice includes apple, orange, grapefruit, and other fruit juices. Because of missing data, there were 368,293 observations and 2670 events in this analysis.

CIs included those for colas, and there was a great deal of within-person variation in intake.

Low-fat milk, tea, and fruit juice were not significantly associated with type 2 diabetes, but water was associated with a 3% greater risk of type 2 diabetes per serving per day (HR: 1.03; 95% CI: 1.01, 1.06; $P = 0.01$; Table 3). One serving of coffee per day was significantly associated with a 6% lower risk of type 2 diabetes (HR: 0.94; 95% CI: 0.91, 0.96; $P < 0.01$). In a mutually adjusted model, nearly 3.5 cups (≈830 mL) coffee were required to negate the risk associated with 1 serving of sugar-sweetened beverages, and replacement of one sugar-sweetened beverage with 1 cup coffee was associated with a risk reduction of 17%. The risk of type 2 diabetes according to the intake of coffee and sugar-sweetened beverages is shown in **Table 4**. No significant interaction was observed between coffee and sugar-sweetened beverages. ($P = 0.72$).

DISCUSSION

In the current study, we showed that consumption of sugar-sweetened beverages was associated with an increased risk of type 2 diabetes in a large cohort of men. Artificially sweetened beverages were not associated with type 2 diabetes after multivariate adjustment, whereas coffee was inversely associated with type 2 diabetes as reported previously (13).

Sugar-sweetened beverages may increase the risk of type 2 diabetes through several mechanisms. The first is adiposity, which is the most important risk factor for type 2 diabetes. Sugar-sweetened beverages contain ≈150 kcal per serving, which if consumed in excess of daily energy balance may promote a 6.8-kg annual weight gain (14). In small feeding studies, consumption of sugar-sweetened beverages before meals leads to greater energy consumption than does consumption of water and other beverages (15). This is attributed to the lower satiating effect of liquids (16) and possibly to the high fructose content of sugar-sweetened beverages (2). However, the mechanism underlying these observations is unknown, and in recent trials sucrose-sweetened beverages had the same effect on satiety as did fructose-sweetened beverages or milk (17). Second, sugar-sweetened beverages provide large quantities of easily absorbable sugars, which increase glycemic load and the insulin response and may elevate type 2 diabetes risk above that predicted by total energy intake and adiposity alone (18). Third, sugar-sweetened beverages contain additives that may increase diabetes risk. For example, caramel coloring in cola contains advanced glycation end products, which induces insulin resistance in animal models (19).

In this study, and in a recent meta analysis by members of our research group (4), sugar-sweetened beverages were significantly associated with an increased risk of type 2 diabetes after adjustment for confounders, including markers of diet quality. This decreases the chance that sugar-sweetened beverages are markers of a poor diet. Adjustment for total energy intake and BMI had little effect, which suggests that they are not major mediators.

TABLE 4
Risk of type 2 diabetes according to intake of sugar-sweetened beverages and coffee[1]

	Sugar-sweetened beverages		
Coffee	<1/wk	1/wk to 1/d	>1/d
<1/d	1.32 (1.11, 1.56)	1.35 (1.13, 1.60)	1.67 (1.31, 2.13)
1–3/d	1.31 (1.11, 1.54)	1.30 (1.10, 1.53)	1.44 (1.12, 1.85)
>3/d	1.00 (reference)	1.19 (0.98, 1.44)	1.36 (0.94, 1.95)

[1] The model was multivariate adjusted as in Table 3. Sugar-sweetened beverages (total) were positively associated with type 2 diabetes risk ($P < 0.01$), whereas coffee (decaffeinated and caffeinated) was inversely associated with type 2 diabetes risk ($P < 0.01$). There was no significant interaction between coffee and sugar-sweetened beverages ($P = 0.72$).

Artificially sweetened beverages are marketed as healthier than sugar-sweetened beverages because they contain no sugar and negligible calories. However in the Multi-Ethnic Study of Atherosclerosis, Atherosclerosis Risk in Communities, and Framingham offspring prospective cohort studies, consumption of artificially sweetened beverages was significantly associated with an increased risk of type 2 diabetes and the metabolic syndrome (7–9). One explanation for these findings is that artificially sweetened beverages stimulate appetite for sweet foods at subsequent meals (20). However, reverse causation and confounding are more plausible explanations. Individuals consuming artificially sweetened beverages may be doing so in an attempt to lose weight, or may have switched to artificially sweetened beverages after gaining weight (21). They may also have switched in response to a diagnosis of a chronic condition such as high triglycerides, impaired fasting glucose, or high blood pressure (21). The underlying health of these participants may therefore be compromised, and their risk of type 2 diabetes increased.

In our study, participants consuming artificially sweetened beverages were more likely to have reported either weight gain or weight loss before the start of the study, to have tried a low-calorie diet, and to have an elevated BMI at baseline. They were also more likely to have a family history of type 2 diabetes, have high triglycerides, have high blood pressure, use diuretics, and take multivitamins—each of which was associated with an increased risk of type 2 diabetes except for multivitamin use, which was protective (data not shown). After adjusting for these factors as well as for total energy intake and BMI, artificially sweetened beverages were no longer significantly associated with type 2 diabetes. This supports our hypothesis that participants use artificially sweetened beverages as dieting aids or because of poor health. A lack of adjustment for these factors may therefore have contributed to illusory associations in other studies.

Our results support the replacement of sugar-sweetened beverages with others such as artificially sweetened beverages, low-fat milk, fruit juice, coffee, and tea. Water had a weak association with type 2 diabetes, which could have been due to residual confounding by unmeasured health conditions or medications related to diabetes risk and water consumption. The small effect size of this association also suggests that it could be an artifact. Low-fat milk was not associated with type 2 diabetes in our study; however, an earlier analysis indicated that total low-fat dairy is protective (22). This is consistent with other studies; however, the mechanism is unknown (23).

Our results for fruit juice were surprising given that juices made a similar contribution to glycemic load as sugar-sweetened beverages (mean: 7.4% compared with 6.9% in 1986). In the Nurses' Health Study I (24), but not in the Nurse Health Study II (25), fruit juice intake was positively associated with type 2 diabetes risk. Other prospective studies have similarly found both positive (26) and null (27) associations. The reason for these discrepancies is unknown, but may involve methodologic differences. For example, the Nurses' Health Study I has more assessments of fruit juice intake than does the Nurses' Health Study II (5 compared with 2) and more cases of type 2 diabetes (4521 compared with 749) (24, 25). On the other hand, misclassification of fruit juice with fruit-flavored sugar-sweetened beverages, which have a higher glycemic index, could create a false association. In the Nurses' Health Study I and II, consumption of these beverages was associated with an increased risk of type 2 diabetes (24, 25). Evidence also indicates that consumption of a moderate amount of fruit juice may provide some benefits. For example, sugar-sweetened beverage consumption is associated with a greater risk of inadequate intake of vitamins E, A, and C and magnesium (28), which could be provided in part by fruit juice (29). Fruit juice also contains antioxidants, such as flavonoids, which may improve long-term insulin sensitivity by reducing inflammation (30). In a trial by Ghanim et al (31), fresh orange juice prevented the rise in several proinflammatory cytokines and reactive oxygen species after a high-carbohydrate, high-fat meal. However, antioxidant content and antiinflammatory properties vary enormously by fruit juice (32) and are likely affected by freshness and processing (33). As such, further research is needed to clarify the role of fruit juice in diabetes risk.

While substituting sugar-sweetened for artificially sweetened beverages was not associated with excess risk, controversy still surrounds their use. Aspartame is hypothesized to increase the risk of neurologic deficits or cancer because of its conversion to methanol and formaldehyde (34). However, no convincing data have been published to validate this hypothesis, and, in a recent position statement, the American Dietetic Association has supported the use of artificial sweeteners in the US diet (35). Interestingly, in a recent analysis of a large Danish birth cohort study, intake of artificially sweetened beverages was associated with preterm birth, which is consistent with the effects of low-dose methanol in animal models (36). Further research on the safety of artificially sweetened beverages may therefore be warranted.

We found that substituting coffee for sugar-sweetened beverages was associated with a substantial benefit because of its inverse association with type 2 diabetes risk. This relation is consistent across many prospective cohort studies (37) and is attributed to magnesium and flavonoids, such as chlorogenic acid (37). Two randomized trials over 8 wk (N Wedick, personal communication, 2010) and 3 mo (38) suggest that coffee may decrease inflammatory factors and increase adiponectin. Tea was not associated with type 2 diabetes in our study, although its intake was low compared with coffee. Others studies suggest that tea might be similarly protective through an antioxidant mechanism (39).

Our study had several strengths. The first is that beverage intake was measured before the development of type 2 diabetes. This minimizes reverse causality and recall bias. Second, participants were similar in socioeconomic status, which reduces the possibility of residual confounding as in studies of diverse populations. Third, beverage intakes were calculated as cumulative averages, which captures long-term intake and reduces measurement error. Fourth, we controlled for several health and lifestyle-related confounders throughout the follow-up and explored residual confounding by early weight change and dieting. Fifth, the large sample size allowed for the detection of small but potentially important changes in risk.

Our study had 2 major limitations. The first was generalizability, because most of the participants were white men. However, the consistency of our results in different strata suggests that they may be reproducible in other studies. The second major limitation was unmeasured and residual confounding, which is a problem with all observational studies. However, we adjusted for a wide range of potential confounders and used continuous covariates to control residual confounding. We also eliminated early cases of type 2 diabetes and performed lagged analyses, which did not change the results.

In conclusion, sugar-sweetened beverage consumption was associated with a significantly elevated risk of type 2 diabetes, independent of lifestyle factors, whereas the association between artificially sweetened beverages and diabetes risk was largely explained by health status, pre-enrollment weight change, dieting, and BMI. Substituting sugar-sweetened beverages with coffee was associated with the greatest benefit.

The authors' responsibilities were as follows—LdK: designed and conducted the analysis, interpreted the data, and wrote the manuscript; VSM: assisted in interpreting the data and edited the manuscript; EBR and WCW: obtained funding, managed and conducted the Health Professionals Follow-Up Study, and edited the manuscript; and FBH: provided conceptual support for this analysis, helped interpret the data, and edited the manuscript. None of the authors had a conflict of interest.

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