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Sweetened Beverage Consumption, Incident Coronary Heart Disease and Biomarkers of Risk in Men

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Abstract

Background—Sugar-sweetened beverage consumption is associated with weight gain and risk of type 2 diabetes. Few studies have tested for a relationship with coronary heart disease (CHD), or intermediate biomarkers. The role of artificially sweetened beverages is also unclear.

Methods and Results—We performed an analysis of the Health Professionals Follow-up study, a prospective cohort study including 42 883 men. Associations of cumulatively averaged sugar-sweetened (e.g. sodas) and artificially sweetened (e.g. diet sodas) beverage intake with incident fatal and non-fatal CHD (myocardial infarction) were examined using proportional hazard models. There were 3683 CHD cases over 22 years of follow-up. Participants in the top quartile of sugar-sweetened beverage intake had a 20% higher relative risk of CHD than those in the bottom quartile (RR=1.20, 95% CI: 1.09, 1.33, p for trend < 0.01) after adjusting for age, smoking, physical activity, alcohol, multivitamins, family history, diet quality, energy intake, BMI, pre-enrollment weight change and dieting. Artificially sweetened beverage consumption was not significantly associated with CHD (multivariate RR=1.02, 95% CI: 0.93, 1.12, p for trend = 0.28). Adjustment for self-reported high cholesterol, high triglycerides, high blood pressure and diagnosed type 2 diabetes slightly attenuated these associations. Intake of sugar-sweetened but not artificially sweetened beverages was significantly associated with increased triglycerides, CRP, IL6, TNFr1, TNFr2, decreased HDL, Lp(a), and leptin (p values < 0.02).

Conclusions—Consumption of sugar-sweetened beverages was associated with increased risk of CHD and some adverse changes in lipids, inflammatory factors, and leptin. Artificially sweetened beverage intake was not associated with CHD risk or biomarkers.

Keywords

nutrition; myocardial infarction; inflammation; lipids; epidemiology

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Introduction

Consumption of sugar-sweetened beverages has been repeatedly associated with weight gain and type 2 diabetes (T2D).[1-3] However few studies have investigated the relationship between sugar-sweetened beverage intake and incident cardiovascular disease (CVD). Such a relationship might be expected given their association with adiposity and T2D. In an analysis of the Nurses' Health Study, sugar-sweetened beverage intake was associated with incident coronary heart disease (CHD) even after adjustment for these factors [4], which suggests that other mechanisms are involved.

While artificially sweetened beverages such as diet soda have been suggested as alternatives, some prospective cohort studies have linked the consumption of these beverages with cardiometabolic dysfunction.[5-7] In an analysis of the Health Professionals Follow-up Study, we found strong evidence that such relationships are due to confounding and reverse causality.[8] The primary objective of this study was to further define the association between sugar- and artificially sweetened beverage intake and CHD in the Health Professionals Follow-up Study - a large prospective cohort study of men. The secondary objective was to identify a possible mechanism by adjusting for potential mediators of this relationship, and measuring cross-sectional associations between beverage intake and blood lipids, HbA1c, inflammatory factors, and adipokines.

Subjects and Methods

Subjects

The Health Professionals Follow-up Study is prospective cohort study that began in 1986 with the recruitment of 51,529 middle aged (40-75 y) male dentists, pharmacists, optometrists, osteopath physicians, podiatrists, and veterinarians. Approximately 97% of participants were of white European descent. Questionnaires were mailed to participants at baseline and biennially to assess health and lifestyle traits (94% response rate). The HPFS was approved by the Harvard School of Public Health Institutional Review board, and all participants gave written consent.

Beverage intake

A semi-quantitative food frequency questionnaire (FFQ) was sent to participants every 4 years. The FFQ asked participants to report their usual intake (never to ≥6 times per day) of a standard 355 mL (12 oz) serving (1 glass, can or bottle) of sugar-sweetened (caffeinated colas, caffeine-free colas, other carbonated sugar-sweetened beverages, non-carbonated sugar-sweetened beverages [fruit punches, lemonades or other fruit drinks]) and artificially-sweetened (caffeinated low-calorie beverages and non-carbonated low-calorie beverages) beverages. Frequency of intake was multiplied by the nutrient content for each food item and summed to produce daily intakes of nutrients and energy.

In a validation study, intake of cola was highly correlated (de-attenuated for measurement error) with mean intake from two 7-day diet records (0.84 for sugar-sweetened, 0.74 for artificially sweetened). Intake of non-colas had poorer correlations with intake from 7-day diet records (0.55 for carbonated non-colas and 0.40 for fruit punches/lemonades/other fruit drinks). [9]

Blood samples

Between 1993 and 1995, 18,225 participants provided a blood sample. Blood was collected in tubes containing liquid EDTA and returned to the laboratory on ice via an overnight courier, where they were frozen in liquid nitrogen. Participants were subjects in nested case-

control studies (e.g. T2D, CVD, Parkinson's disease, prostate cancer, pancreatic cancer, colon cancer) or healthy men who were randomly selected on the basis of their alcohol-consumption patterns for a study on alcohol intake and biomarkers of ischemic heart disease. Nearly 60% of participants fasted for more than 9 hours.

Ascertainment of endpoints

Incident CHD was defined as non-fatal or fatal myocardial infarction. Participants were asked in a biennial follow-up questionnaire whether they had experienced a myocardial infarction between January 1986 and December 2008. When an event was reported, we asked permission from the participant to obtain medical records for confirmation. Non-fatal myocardial infarction was defined using WHO criteria, which required clinical symptoms and diagnostic changes on electrocardiogram or elevated cardiac enzymes. Death ascertainment was performed by searching the National Death Index[10], by family members' response to follow-up questionnaires, or by reports from participants' professional organizations. We requested access to medical records, autopsy reports and death certificates to confirm all suspected deaths due to myocardial infarction. Fatal myocardial infarction was confirmed by medical records or autopsy reports. Death certificates alone were not considered sufficient to confirm myocardial infarction as the cause of death unless family members or medical records indicated that the participant was diagnosed with coronary artery disease before death but after admission into the study.

Measurement of biomarkers

Plasma concentrations of total, HDL, and direct LDL cholesterol and triglycerides were measured by standard methods with reagents from Roche Diagnostics (Indianapolis, IN) and Genzyme (Cambridge, MA). [11, 12] Lp(a) was measured using a turbidimetric assay on the Hitachi 911 analyzer (Roche Diagnostics, Indianapolis, IN), using reagents and calibrators from Denka Seiken (Niigata, Japan). This is the only commercial assay not affected by Kringle type 2 repeats.[13] Red blood cell glycated hemoglobin (HbA1c) was measured by a temperature-controlled HPLC method.[14] C-reactive protein (CRP) was measured on the Hitaci 911 analyzer (Roche Diagnostics, Indianapolis, IN) using an immunoturbidimetric assay (Denka Seiken, Niigata, Japan). Interleukin-6 (IL-6), tumor necrosis factor receptors 1 and 2 (TNFr1 & 2), ICAM-1, and VCAM-1, were measured by enzyme-linked immunosorbent assays (R&D Systems, Minneapolis, MN). Plasma adiponectin and leptin concentrations were measured by competitive RIA (Linco Research, St. Charles, MO). Coefficients of variation for most assays were below 10%.

Statistical analysis

Participants with a history of T2D, CVD (heart attack, stroke, angina, coronary artery bypass graft), cancer (except non-melanoma skin cancer) at baseline were excluded. Participants with an implausible energy intake (<335 or > 1758 MJ / day) were also excluded, leaving 42 883 participants for analysis. (See Supplemental Material for a flow-chart showing all exclusions) Person-time was calculated from the return of the baseline questionnaire until December 31 2008, death, loss to follow-up, diagnosis of CHD (fatal or non-fatal), or whichever occurred first. Cox proportional hazard models with time-varying covariates using age as the time-scale were used for all analysis. Cumulative averages of beverage intake and dietary variables were calculated at each time point, and were not updated after a diagnosis of cancer or CVD to limit recall bias. Other covariates were updated at each time point. This was compared to a secondary analysis which used only baseline dietary information. For missing data, the last value was carried forward for BMI, smoking and physical activity.

Beverage intake was grouped into fourths (quartiles), and the Wald test (1 df) of the median value in quartiles was used to evaluate linear trends. Models were adjusted for smoking (never, past, current 1-15 cigarettes/day, current >15 cigarettes/day, missing), physical activity (quintiles of METs/wk, missing), alcohol intake (abstainers, 0-9.9 grams / day, 10-20 grams / day, > 20 grams / day, missing), multivitamin use, family history of CHD, pre-enrollment (1981-1986) weight gain (0, 0.9–1.8, 2.3–4.1, 4.5–6.4, 6.8–8.6, 9.1–13.2, or ≥13.6 kg); weight loss (0, 0.9–1.8, 2.3–4.1, 4.5–6.4, or ≥6.8 kg), adherence to a low-calorie diet (1992), total energy intake (quintiles), and body mass index ([BMI] < 23, 23-23.9, 24-24.9, 25-26.9, 27-28.9, 29-30.9, 31-32.9, 33-34.9, >35 kg/m^2, missing). Smoking status was missing in 3.9% of participants, whereas physical activity was missing in 0.5% and BMI in 2.2% of participants.

We also adjusted for the alternative Healthy Eating Index (aHEI, quintiles)[15] to help rule out confounding by other dietary factors. The aHEI ranks participants according to their adherence to a healthy dietary pattern, awarding points for higher intakes of fruit, vegetables, nuts/soy, cereal fiber (fiber from cereals e.g. wheat) polyunsaturated:saturated fat, white:red meat; moderate alcohol intake, daily multivitamin use, and low intakes of trans fat. Potential mediators (updated values for self-reported high cholesterol, high triglycerides, high blood pressure and a past confirmed diagnosis of T2D) were adjusted for in a separate model. We tested for non-linear associations using cubic splines (5 knot), and in a sensitivity analysis excluded CHD cases occurring during the first 4 years of follow-up. This was done to evaluate the influence of subclinical disease on associations. We also performed an 8-year latency analysis where diet was updated only after 8 years to determine the role of elapsed time between the assessment of beverage intake and CHD.

Analyses were stratified by age (≥ vs < 65 years), smoking (ever vs never), alcohol consumption (drinker vs abstainer), physical activity (low [quintile 1 and quintile 2], medium [quintile 3 and quintile 4], high [quintile 5]), family history of CHD (yes vs no), BMI (<25, 25-29.9, ≥30 kg/m^2), past diagnosis of CHD (yes vs no), self-reported high triglycerides (yes vs no), high cholesterol (yes vs no), and high blood pressure (yes vs no). We also stratified for all combinations of mediators (e.g. high triglycerides + T2D vs neither). Interaction tests were performed using the Wald test of cross-product terms (e.g. median beverage intake * median BMI in categories).

Cross-sectional associations between cumulatively averaged sugar- and artificially sweetened beverage intake with blood total cholesterol, triglycerides, LDL, HDL, Lp(a), HbA1c, CRP, IL6, TNFr 1, TNFr 2, ICAM-1, VCAM-1, adiponectin and leptin were examined in 1994 using linear regression with a robust variance estimator. Due to skewed distributions for CRP and IL6, these variables were log-transformed. All analyses were adjusted for the case control study from which blood samples were drawn, and associations were evaluated for differences by fasting state using cross-product terms (fasting*sugar-sweetened beverages).

SAS version 9.1 was used for all analyses, and a two-tailed p value < 0.05 was considered statistically significant.

Results

Baseline characteristics

At baseline, participants reported consuming less sugar-sweetened beverages (2.5 / week; 0.36 / day, sd=0.61) than artificially sweetened beverages (3.4 / week; 0.49 / day, sd=0.94). Consumption of sugar-sweetened beverages was associated with several unhealthy lifestyle traits at baseline, including a higher prevalence of current smoking, lower physical activity,

but a decreased family history of CHD. (Table 1) It was also associated with a lower overall diet quality (aHEI), intake of cereal fiber, protein, alcohol and multivitamins but a higher intake of carbohydrate, glycemic load (product of glycemic index [white bread as reference food] and carbohydrate) , total fat, trans fat and energy. (Table 1) Sugar-sweetened beverages consumption was associated with higher pre-enrollment weight gain, decreased pre-enrollment weight loss, and a lower adherence to a low-calorie diet. (Table 1) Conversely, artificially sweetened beverage consumption was associated with some healthy lifestyle traits, including a lower prevalence of current smoking, higher physical activity, but a greater family history of CHD. (Table 1) It was also associated with a higher prevalence of high triglycerides, high cholesterol and high blood pressure. (Table 1) Artificially sweetened beverage consumption was associated with higher overall diet quality (aHEI), a lower intake of carbohydrate, cereal fiber and glycemic load, but a higher intake of protein, total fat, saturated fat, trans fat and multivitamins. Artificially sweetened beverage intake was also associated with higher pre-enrollment weight gain, pre-enrollment weight loss, adherence to a low-calorie diet, and BMI. (Table 1)

Cox regression

There were 3683 incident cases of CHD over 22 years of follow-up (790 852 person years). Sugar-sweetened beverages intake was associated with an increased risk of CHD (top vs bottom quartile, RR = 1.21, 95% CI: 1.10, 1.33; p for trend < 0.01; Table 2), however artificially sweetened beverages were not (RR = 1.04, 95% CI: 0.96, 1.15; p for trend = 0.05; Table 2). Adjustment for smoking, physical activity, alcohol intake, multivitamin use, and family history attenuated the association for sugar-sweetened beverages, but strengthened the association for artificially sweetened beverages. (Table 2) Further adjustment for pre-enrollment weight change and adherence to a low-calorie diet in 1992 strengthened the association for sugar-sweetened beverages, but weakened it for artificially sweetened beverages. (Table 2) Adjustment for dietary factors had the opposite effect, but after adjusting for BMI the association for artificially sweetened beverages was no longer significant. (Table 2) Further adjustment for a past diagnosis of T2D, high blood lipids, and high blood pressure only slightly attenuated these associations. (Table 2) Cubic splines revealed no evidence of non-linearity in these associations (p for curvature > 0.21).

Using continuous intake yielded similar results. (Table 3) For each additional serving per day, sugar-sweetened beverage consumption was associated with a 19-25% increased risk of CHD (p < 0.02; Table 3). Overall, artificially sweetened beverages were not associated with risk of CHD (p = 0.05). Artificially sweetened carbonated non-colas were associated with increased risk, however these made a small contribution to intake.

Repeating this analysis using continuous covariates did not substantially alter the results. (data not shown) Associations were similar when using baseline beverage intake, after eliminating CHD cases in the first 4 years (n=272), and in a latency analysis where diet was updated after 8 years. (data not shown) No significant interactions with age, smoking, alcohol, physical activity, family history, BMI, or any mediators or their combinations were observed. (data not shown)

Blood biomarkers

Intake of sugar-sweetened beverages was associated with significantly higher triglycerides, CRP, IL6, TNFr1, TNFr2, and lower HDL, Lp (a) and leptin. (Table 4) Associations did not significantly differ according to fasting status (data not shown).

Discussion

In this analysis, consumption of sugar-sweetened but not artificially sweetened beverages was associated with an increased risk of CHD. Sugar-sweetened beverage consumption was associated with some adverse changes in blood lipids, inflammatory factors, and leptin.

Sugar-sweetened beverages provide approximately 63 MJ per serving[16] and are less satiating then solid foods[17-19], which make them important determinants of BMI. In a pooled analysis of the Health Professionals Follow-up Study and the Nurses Study I and II, an increase in sugar-sweetened beverage intake was associated with a 0.45 kg greater 4-year weight gain in men and women. [3] Conversely, in the PREMIER lifestyle intervention and weight loss trial, a reduced intake of sugar-sweetened beverages was associated with significant weight loss.[20] In trials among overweight children and adolescents, those randomized to consume less sugar-sweetened beverages lost significantly more weight than participants in control groups.[21, 22] Sugar-sweetened beverages also have a high carbohydrate content and glycemic load, which may elevate the risk of T2D[23] and lead to unfavorable changes in blood lipids independent of BMI. In a meta-analysis of 60 trials, replacing dietary fat with carbohydrate increased triglycerides and lowered HDL.[24] A similar effect is attributed to fructose from sugar-sweetened beverages, which increases de-novo lipogenesis[25] but also the synthesis of uric acid which may elevate blood pressure[26]. In the PREMIER trial, a reduction in sugar-sweetened beverage intake was associated with a significant decrease in systolic and diastolic blood pressure.[27] Finally, advanced glycation end products present in the caramel coloring of colas may play a role as they decrease insulin sensitivity in rodents. [28] In light of this evidence, and that in 2004 sugar-sweetened beverages made up approximately 7% of the total daily energy intake of Americans,[29] sugar-sweetened beverages are important risk factors for CVD.

In this study, consumption of sugar-sweetened beverages was significantly associated with an increased risk of CHD. This was after adjusting for multiple lifestyle-related factors including overall diet quality and BMI, which were strong risk factors for CHD. We also adjusted for prior weight change and dieting, which could motivate participants to switch from sugar- to artificially sweetened beverages. [30] For a one serving per day increase in sugar-sweetened beverage intake, the risk of CHD increased by 19% (RR = 1.19, 95% CI: 1.11, 1.28, $p < 0.01$). Similar results were observed in the Nurses' Health Study (n = 88 520, cases = 3105, follow-up = 24 y), where a 1 serving per day increase in sugar-sweetened beverage intake was associated with a 15% increase in risk (RR = 1.15, 95% CI: 1.07, 1.20, $p < 0.01$).[4] The average baseline intake of sugar-sweetened beverages was slightly higher in the Nurses' Health Study (0.41 servings / day) than in the Health Professionals Follow-up study. (0.36 servings / day)[4] Our results were stable after a number of sensitivity analyses. Using baseline dietary intake did not change the results, and associations were still significant after excluding early cases of CHD, which could be a marker of pre-existing disease and a more recent change in beverage intake. Results were essentially the same in an 8-year latency analyses. We found no differences in associations among different strata, including past diagnosis of T2D, self-reported high triglycerides, high cholesterol, high blood pressure, or their combinations.

Like in the Nurses' Health Study [4], we found that the relationship between sugar-sweetened beverage consumption and CHD was not explained by conventional mediators. After adjusting for a past diagnosis of T2D, self-reported high triglycerides, self-reported high cholesterol, and self-reported high blood pressure, the relationship was only slightly attenuated. This suggests that sugar-sweetened beverages may impact on CHD risk above and beyond traditional risk factors.

We looked for possible biochemical mediators in our study, and found that sugar-sweetened beverage consumption was associated with higher triglycerides and lower HDL. This is consistent with results from a meta-analysis of intervention studies evaluating the replacement of fat with carbohydrate on blood lipids[24], as well as other trials of fructose intake.[31] We found a slight decrease in Lp (a) for increased consumption of sugar-sweetened beverages, however the reason for this is unclear. Importantly, sugar-sweetened beverages consumption was associated with increased levels of several circulating inflammatory factors, including CRP, IL-6, TNFr1 and TNFr2. In the Nurses' Health Study, a dietary pattern rich in sugar-sweetened beverages was associated with higher levels of TNFr2, CRP and IL6. [32] These findings have been validated in a recent trial, where low to moderate intake of sugar-sweetened beverages increased inflammatory factors such as CRP.[33] In this study, fructose-enriched beverages produced the greatest increases in inflammatory factors. [33] Inflammation is a key factor in the pathogenesis of CVD and cardiometabolic disease [34], and could represent an additional pathway by which sugar-sweetened beverages influence risk. Intake of sugar-sweetened beverages could stimulate an inflammatory response through hyperglycemia which can activate the electron transport chain to produce superoxide radicals.[35] Fructose also stimulates transcription of inflammatory factors by activating NF-kappa B in mice.[36] Finally, we observed an inverse relationship between sugar-sweetened beverage intake and leptin. Small trials indicate that fructose supplemented meals lead to poor stimulation of leptin, lower satiety, higher energy intake and weight gain. [37]

We found no evidence to suggest that overall consumption of artificially sweetened beverages was associated with CHD risk or changes in biomarkers, however non-carbonated artificially sweetened beverages were associated with increased risk in an analysis of continuous intake. The reason for this is unclear, especially since we found no significant associations between artificially sweetened beverages and biomarkers. Previous studies have found significant associations between artificially sweetened beverage consumption, cardiometabolic dysfunction and T2D, [5-7] however these findings are probably due to confounding and reverse causality. In the Health Professionals Follow-up Study, participants appear to be consuming artificially sweetened beverages as part of a weight loss strategy or in response to the diagnosis of a chronic condition. In a previous analysis of this study, sugar-sweetened beverage consumption was associated with an increased risk of T2D, but this was not significant after adjusting for BMI, pre-enrollment weight change and dieting.[8] We saw a similar pattern of attenuation in the present analysis, however the magnitude of confounding was smaller. Our results highlight the need for cautious interpretation of studies reporting positive associations between diet drinks and cardiometabolic and cardiovascular outcomes.

Our study has some limitations. First, dietary intakes were measured with some error. Second, participants in our study may be dissimilar to those living in the general population. For example, intake of sugar-sweetened beverages was much lower in our study (mean = 0.36 servings / day) than in US adults (mean > 1 serving / day).[38] However, the similarity of the SSBCHD relationship across various strata suggests it is likely to be the same in different populations. Third, we cannot exclude the possibility of unmeasured and residual confounding. To address this issue, we adjusted for a wide range of potential confounders and used continuous covariates in an attempt to control residual confounding. We could not account for residual confounding due to missing smoking, physical activity and BMI data. Fourth, we tested for a large number of cross-sectional associations. However, our results are supported by other studies, which suggests they are not due to chance.

In conclusion, consumption of **s**ugar-sweetened but not artificially sweetened beverages was associated with a significantly increased risk of CHD. Sugar-sweetened beverage intake was

also associated with adverse changes in some blood lipids, inflammatory factors, and leptin. These results, as well as those from other observational studies and trials, support recommendations to reduce the consumption of sugar-sweetened beverages in order to prevent CVD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical perspective

Consuming sugar-sweetened beverages such as cola puts individuals at an increased risk for weight gain and type 2 diabetes, both of which are risk factors for coronary heart disease (CHD). However few studies have studied the relationship between sugar sweetened beverage consumption and CHD events. In our analysis of the Health Professionals Follow-up Study, a prospective cohort study which includes a well characterized population of over 40 000 men, we found that sugar sweetened beverage consumption was associated with a higher risk of CHD independent of BMI, type 2 diabetes and other established cardiovascular risk factors. For each additional serving per day, sugar-sweetened beverages were associated with a 19% increased risk of CHD. We also found that sugar sweetened beverage consumption was associated with adverse changes in blood lipids, higher circulating inflammatory factors and lower leptin. These biomarker changes may help to explain why sugar sweetened beverage consumption is a risk factor for CHD and, in the case of leptin, obesity. Conversely, consumption of artificially sweetened beverages such as diet soda was not associated with CHD risk or biomarkers in our study, but was associated with baseline co-morbidities, higher BMI, pre-enrollment weight change and dieting which could lead to confounding,

Table 1

Baseline age-adjusted characteristics of participants by quartiles of sugar-sweetened and artificially sweetened beverage intake

	Sugar-sweetened Beverages				Artificially sweetened Beverages			
	Q1	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
Quartile range	Never	2 / month	1 – 3 / week	3.7 week – 9 / day	Never	2 / month	1 – 4 / week	4.8 / week – 18 / day
Median	Never	2 / month	1.6 / week	6.5 / week	Never	2 / month	2 / week	1.1 / day
N	14 599	5 348	12 405	10 531	19 558	2 844	10 064	10 416
Current smoking (%)	9	9	9	12	12	8	8	7
Physical activity (METs/wk)	23.7 (32.2)	21.3 (26.0)	20.6 (30.2)	19.6 (27.9)	19.9 (27.0)	20.4 (28.0)	22.2 (31.4)	23.4 (33.5)
Family history of CHD (%)	34	31	31	31	30	32	32	34
Take multivitamins (%)	45	43	41	39	40	42	43	44
High triglycerides (%)	9	9	8	9*(*)*	7	8	9	11
High Blood Pressure	20	19	19	19*(*)*	17	19	21	24
High Cholesterol (%)	11	11	10	10*(*)*	9	10	11	13
Alternative healthy eating index (aHEI)	45.9 (11.7)	44.7 (11.1)	43.8 (10.7)	42.3 (10.5)	43.4 (11.4)	44.9 (11.2)	45.1 (10.8)	44.7 (11.0)
Carbohydrate (% energy)	45.5 (9.5)	45.9 (8.2)	46.6 (7.6)	49.6 (7.3)	47.5 (8.6)	47.4 (8.5)	46.8 (8.1)	45.5 (8.4)
Glycemic load	106 (43)	113 (41)	124 (42)	154 (49)	130 (49)	123 (47)	120 (46)	118 (47)
Cereal fiber intake (g / day)	6.5 (4.7)	6.2 (3.8)	5.7 (3.6)	5.0 (2.8)	5.7 (3.7)	6.2 (4.9)	6.0 (3.8)	5.9 (4.1)
Protein (% energy)	19.6 (3.6)	19.0 (3.1)	18.4 (3.0)	16.8 (2.9)	17.9 (3.3)	18.5 (3.3)	18.8 (3.2)	19.2 (3.5)
Total fat (% energy)	31.7 (7.0)	32.5 (6.2)	32.7 (5.8)	31.9 (5.5)	31.9 (6.3)	31.7 (6.1)	31.8 (6.0)	32.8 (6.3)
Saturated fat intake (g / day)	24.2 (6.9)	24.9 (6.2)	25.1 (5.8)	24.5 (5.4)*(*)*	24.6 (6.3)	24.0 (6.0)	24.2 (5.8)	25.1 (6.2)
Trans fat (g / day)	1.2 (0.5)	1.3 (0.5)	1.3 (0.5)	1.4 (0.5)	1.3 (0.5)	1.3 (0.5)	1.2 (0.5)	1.3 (0.5)
Alcohol (g / day)	12.6 (16.4)	11.5 (15.1)	11.1 (14.9)	10.1 (14.6)	11.6 (15.9)	10.9 (15.0)	11.4 (14.6)	11.4 (15.4)*(*)*
Total energy intake (MJ / day)	751 (233)	789 (236)	845 (246)	963 (271)	857 (265)	819 (254)	814 (256)	823 (260)*(*)*
Pre-enrollment weight gain (kg)†	2.0 (4.1)	2.0 (3.9)	2.1 (3.8)	2.2 (3.8)	1.8 (3.4)	2.0 (3.8)	2.1 (3.7)	2.6 (4.7)
Pre-enrollment weight loss (kg)†	0.9 (2.0)	0.7 (1.8)	0.6 (1.6)	0.5 (1.5)	0.5 (1.5)	0.6 (1.7)	0.7 (1.7)	0.9 (2.0)
Low-calorie diet in 1992 (%)	26	23	21	18	15	22	24	33
BMI (kg/m2)	25.5 (3.3)	25.3 (3.2)	25.5 (3.3)	25.5 (3.3)*(*)*	24.8 (3.1)	25.3 (3.1)	25.7 (3.2)	26.5 (3.5)

* Means are shown for continuous variables (standard deviation), and row percentage for dichotomous variables. Linear and logistic regression were used to assess linear trends across quartiles, and are significant unless noted.

† Pre-enrollment (1981-1986) weight gain and loss are mutually exclusive. One serving is equivalent to a standard 355 mL (12 oz) can, glass or bottle.

Table 2

Risk of coronary heart disease according to consumption of sugar-sweetened and artificially sweetened beverages

	Q1	Q2	Q3	Q4	p for trend
Sugar-sweetened beverages					
Quartile range (servings)	Never	2 / month	1 – 4 / week	4.5 week – 7.5 / day	
Median	Never	2 / month	2 / week	6.5 / week	
Person-years	184 040	185 951	211 438	209 424	
Cases of CHD	902	906	929	946	
Age adjusted	1.00	0.99 (0.90, 1.09)	1.02 (0.93, 1.12)	1.21 (1.10, 1.33)	< 0.01
Multivariate	1.00	1.00 (0.91, 1.10)	1.03 (0.94, 1.13)	1.18 (1.08, 1.31)	< 0.01
+ pre-enrollment weight change, low-calorie diet	1.00	1.03 (0.94, 1.13)	1.07 (0.97, 1.18)	1.27 (1.15, 1.39)	< 0.01
+ diet quality (aHEI) and total energy intake	1.00	1.02 (0.91, 1.11)	1.04 (0.94, 1.15)	1.20 (1.08, 1.32)	< 0.01
+ BMI	1.00	1.02 (0.93, 1.12)	1.04 (0.95, 1.15)	1.20 (1.09, 1.33)	< 0.01
+ previous T2D, high triglycerides, high cholesterol, high blood pressure	1.00	1.03 (0.94, 1.13)	1.05 (0.95, 1.15)	1.18 (1.06, 1.31)	< 0.01
Artificially sweetened beverages					
Quartile range (servings)	Never	2 / month	1 – 4 / week	4.5 / week – 18 / day	
Median	Never	2 / month	2 / week	1.1 / day	
Person-years	273 802	116 417	199 519	201 114	
Cases of CHD	1386	579	889	829	
Age adjusted	1.00	0.87 (0.79, 0.96)	0.92 (0.84, 1.00)	1.04 (0.96, 1.15)	0.05
Multivariate	1.00	0.90 (0.82, 1.00)	0.96 (0.88, 1.05)	1.10 (1.00, 1.20)	0.01
+ pre-enrollment weight change, low-calorie diet	1.00	0.90 (0.81, 0.99)	0.94 (0.86, 1.03)	1.06 (0.96, 1.16)	0.06
+ diet quality (aHEI) and total energy intake	1.00	0.92 (0.83, 1.01)	0.96 (0.88, 1.05)	1.07 (0.98, 1.18)	0.03
+ BMI	1.00	0.90 (0.82, 1.00)	0.93 (0.85, 1.01)	1.02 (0.93, 1.12)	0.28
+ previous T2D, high triglycerides, high cholesterol, high blood pressure	1.00	0.90 (0.82, 1.00)	0.92 (0.84, 1.00)	0.98 (0.90, 1.09)	0.72

Relative risks and their 95% confidence intervals (in parenthesis) are shown. Multivariate models are adjusted for age, smoking (categories, missing) physical activity (quintiles of METs/wk, missing), alcohol intake (categories), multivitamin use, and family history of CHD. Pre-enrollment weight change includes variables for weight gain (categories) and weight loss (categories). The variable for low-calorie diet is for adherence to a low-calorie diet in 1992. Previous T2D refers to any past diagnosis of type 2 diabetes, whereas high triglycerides, high cholesterol and high blood pressure are self-reported.

Table 3

Risk of coronary heart disease per serving of sugar-sweetened and artificially sweetened beverages

Beverage	Mean servings per day (SD)	Relative risk for 1 serving per day (95% C.I.)	P value
Total sugar-sweetened beverages	0.36 (0.61)	1.19 (1.11, 1.28)	< 0.01
Colas	0.21 (0.46)	1.19 (1.09, 1.31)	< 0.01
Carbonated non-colas	0.07 (0.20)	1.25 (1.04, 1.51)	0.02
Fruit punches, lemonades, other non-carbonated fruit drinks	0.08 (0.27)	1.25 (1.08, 1.46)	< 0.01
Artificially sweetened beverages	0.49 (0.94)	1.05 (1.00, 1.10)	0.05
Colas	0.37 (0.80)	1.03 (0.97, 1.09)	0.30
Carbonated non-colas	0.11 (0.33)	1.20 (1.07, 1.35)	<0.01

Models are adjusted for the same covariates as in Table 2, except for mediators (high cholesterol, high blood pressured, type 2 diabetes). SD = standard deviation.

Table 4

Cross-sectional associations between the cumulative average (1986-1994) intake of sugar and artificially sweetened beverages and biomarkers

	N	Mean	Change per 1 sugar-sweetened beverage / day	P	Change per 1 artificially sweetened beverage / day	P
Total cholesterol, mg/dL	3746	207 (43)	0.51 (−2.24, 3.27)	0.72	−0.43 (−2.21, 1.35)	0.63
Triglycerides, mg/dL	2064	164 (107)	12.7 (4.2, 21.2)	0.01	0.01 (−5.59, 5.62)	1.00
LDL, mg/dL	3025	130 (34)	−0.84 (−3.3, 1.59)	0.50	−0.82 (−2.49, 0.85)	0.34
HDL, mg/dL	3025	46 (16)	−1.87 (−2.70, −1.03)	<0.01	0.04 (−0.48, 0.56)	0.88
Lp (a), mg/dL	1594	20 (28)	−2.81 (−4.90, −0.72)	0.01	0.11 (−1.59, 1.81)	0.90
HbA1c (%)	2339	5.85 (1.10)	0.05 (−0.06, 0.16)	0.41	0.03 (−0.03, 0.09)	0.43
C-Reactive Protein (CRP), mg/L*	3217	1.20 (2.94)	0.12 (0.02, 0.23)	0.02	−0.05 (−0.10, 0.01)	0.11
IL-6, pg/mL*	1314	1.52 (2.41)	0.16 (0.03, 1.65)	0.02	−0.05 (−0.13, 1.60)	0.22
TNF-α receptor 1 (TNFR1), pg/mL	729	1493 (511)	78.5 (23.5, 133.5)	0.01	45.3 (−4.1, 94.7)	0.07
TNF-α receptor 2 (TNFR2), pg/mL	1613	2889 (872)	99.3 (11.4, 187.2)	0.03	−16.0 (−69.3, 37.3)	0.56
VCAM, ng/mL	1407	1283 (381)	5.61 (−26.3, 37.5)	0.73	2.44 (−20.5, 25.4)	0.83
ICAM, ng/mL	1407	352 (95)	3.70 (−4.19, 11.59)	0.36	−1.88 (−7.84, 4.07)	0.54
Adiponectin, ng/mL	1849	12761 (7936)	−458 (−1235, 319)	0.25	−304 (−694, 87)	0.13
Leptin, pg/mL	608	7526 (5797)	−796 (−1442,−149)	0.02	132 (−356, 620)	0.60

Models are adjusted for the same covariates as in Table 2, except for mediators (high cholesterol, high blood pressured, type 2 diabetes).

*CRP and IL6 were log-transformed because of highly skewed distributions. Changes in CRP and IL6 are calculated from parameter estimates representing % change in the geometric mean (shown). Blood samples were provided in 1994.