Sugar- and Artificially Sweetened Beverages and the Risks of Incident Stroke and Dementia

A Prospective Cohort Study

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Background and Purpose—Sugar- and artificially-sweetened beverage intake have been linked to cardiometabolic risk factors, which increase the risk of cerebrovascular disease and dementia. We examined whether sugar- or artificially sweetened beverage consumption was associated with the prospective risks of incident stroke or dementia in the community-based Framingham Heart Study Offspring cohort.

Methods—We studied 2888 participants aged >45 years for incident stroke (mean age 62 [SD, 9] years; 45% men) and 1484 participants aged >60 years for incident dementia (mean age 69 [SD, 6] years; 46% men). Beverage intake was quantified using a food-frequency questionnaire at cohort examinations 5 (1991–1995), 6 (1995–1998), and 7 (1998–2001). We quantified recent consumption at examination 7 and cumulative consumption by averaging across examinations. Surveillance for incident events commenced at examination 7 and continued for 10 years. We observed 97 cases of incident stroke (82 ischemic) and 81 cases of incident dementia (63 consistent with Alzheimer's disease).

Results—After adjustments for age, sex, education (for analysis of dementia), caloric intake, diet quality, physical activity, and smoking, higher recent and higher cumulative intake of artificially sweetened soft drinks were associated with an increased risk of ischemic stroke, all-cause dementia, and Alzheimer's disease dementia. When comparing daily cumulative intake to 0 per week (reference), the hazard ratios were 2.96 (95% confidence interval, 1.26–6.97) for ischemic stroke and 2.89 (95% confidence interval, 1.18–7.07) for Alzheimer's disease. Sugar-sweetened beverages were not associated with stroke or dementia.

Conclusions—Artificially sweetened soft drink consumption was associated with a higher risk of stroke and dementia. **(*Stroke*. 2017;48:1139-1146. DOI: 10.1161/STROKEAHA.116.016027.)**

Key Words: dementia ■ Framingham Heart Study ■ soft drinks ■ stroke ■ sugar

See related article, p 1129.

Sugar-sweetened beverages are associated with cardiometabolic diseases,[1,2] which may increase the risk of stroke and dementia.[3,4] Limited prior findings suggest that sugar- and artificially sweetened beverages are both associated with an increased risk of incident stroke,[5] although conflicting findings have been reported.[6] To our knowledge, studies are yet to examine the associations between sugary beverage consumption and the risk of incident dementia. Accordingly, we examined whether sugar- or artificially sweetened soft drinks were associated with the 10-year risks of incident stroke and dementia in the community-based Framingham Heart Study. We also examined total sugary beverages, which combined sugar-sweetened soft drinks with noncarbonated high sugar beverages, such as fruit juices and fruit drinks.

Methods

The Framingham Heart Study comprises a series of community-based prospective cohorts originating from the town of Framingham, Massachusetts. We studied the Framingham Heart Study Offspring cohort, which commenced in 1971 with the enrollment of 5124 volunteers. Participants have been studied across 9 examination cycles approximately every 4 years, with the latest cycle concluding in 2014.

We estimated the 10-year risk of both incident stroke and dementia beginning from the 7th examination cycle (1998–2001). For the study of stroke in relation to beverage intake, we excluded people with prevalent stroke or other significant neurological disease at baseline

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and those <45 years. For investigating the incidence of dementia, we excluded people with prevalent dementia, mild cognitive impairment, or other significant neurological disease at baseline and those <60 years. These age cutoffs are consistent with our prior work in this area.[3] There were 2888 and 1484 participants available for analysis of incident stroke and new-onset dementia, respectively (Figure 1). All participants provided written informed consent, and the study procedures were approved by the Institutional Review Board at Boston University School of Medicine.

Assessment of Sugary Beverage Intake

Participants completed the Harvard semiquantitative food-frequency questionnaire (FFQ) at examination cycles 5 (1991–1995), 6 (1995–1998), and 7 (1998–2001). The FFQ provides a validated measure of dietary intake over the past 12 months.[7] Participants responded according to how frequently they consumed 1 glass, bottle, or can of each sugary beverage item, on average, across the previous year. The FFQ included 3 items on sugar-sweetened soft drink, 4 items on fruit juice, 1 item on noncarbonated sugar-sweetened fruit drinks, and 3 items on artificially sweetened soft drinks. Each item was scored according to 9 responses spanning from never or <1 per month to 6+ per day. Intake of soft drinks using the FFQ has been validated against dietary records (correlation coefficients of 0.81 for Coke/Pepsi)[8,9] and is reliable when readministered after 12 months (correlation coefficients of 0.85 for Coke/Pepsi).[8,9]

We combined FFQ items to create variables reflecting intake of (1) total sugary beverages (combining sugar-sweetened soft drinks, fruit juice, and fruit drinks), (2) sugar-sweetened soft drinks (high-sugar carbonated beverages, such as cola), and (3) artificially sweetened soft drinks (sugar-free carbonated beverages, such as diet cola). We created new intake categories to ensure that an adequate number of participants were retained in each intake group across each variable. Cut points were determined before conducting the main analyses based on the relative distribution of intake for each variable. Total sugary beverage consumption was examined as <1 per day (reference), 1 to 2 per day, and >2 per day; sugar-sweetened soft drink intake was examined as 0 per week (reference), ≤3 per week, and >3 per week; and artificially sweetened soft drink intake was examined as 0 per week (reference), ≤6 per week, and ≥1/d. We used FFQ data obtained from examination cycle 7 as a measure of recent intake. In an additional analysis, we also averaged responses across examination cycles 5, 6, and 7 to calculate cumulative intake over a maximum of 7 years. For this later variable, we averaged FFQ data from examination cycle 7, with FFQ data from at least 1 other examination (5 or 6). However, we averaged across all 3 examination cycles where possible (72% of participants completed all 3 FFQs; n=935 for stroke analysis sample and n=755 for dementia analysis sample).

Incident Stroke and Dementia

We related beverage consumption to the 10-year risk of stroke and dementia. Surveillance commenced from examination cycle 7 to the time of incident event over a maximum of 10 years or until last known contact with the participant. We defined stroke as the rapid onset of focal neurological symptoms of presumed vascular origin, lasting >24 hours or resulting in death. A diagnosis of dementia was made in line with the Diagnostic and Statistical Manual of Mental Disorders, 4th edition.[10] A diagnosis of Alzheimer's disease (AD) dementia was based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association for definite, probable, or possible AD.[11] Please see the online-only Data Supplement for complete details on our methods of surveillance, diagnosis, and case ascertainment.

Statistical Analysis

We used SAS software (SAS Institute, Cary, NC) to estimate Cox proportional hazards regression models (after confirming the assumption of proportionality of hazards). Recent intake and cumulative intake of total sugary beverages, sugar-sweetened soft drinks, and artificially sweetened soft drinks were related separately to the risk of all stroke, ischemic stroke, all-cause dementia, and AD dementia. Hazard ratios (HR) are presented accompanied by 95% confidence intervals (CIs).

We first performed minimally adjusted statistical models, which included adjustments for age, sex, education (for analysis of dementia only), and total caloric intake (Model 1). Next, we stepped in adjustments for lifestyle factors, including the Dietary Guidelines Adherence Index (a variable quantifying adherence to the 2005 Dietary Guidelines for Americans), as a measure of overall diet quality,[12] self-reported physical activity,[13] and smoking status (Model 2). A third statistical model included the adjustments outlined in Model

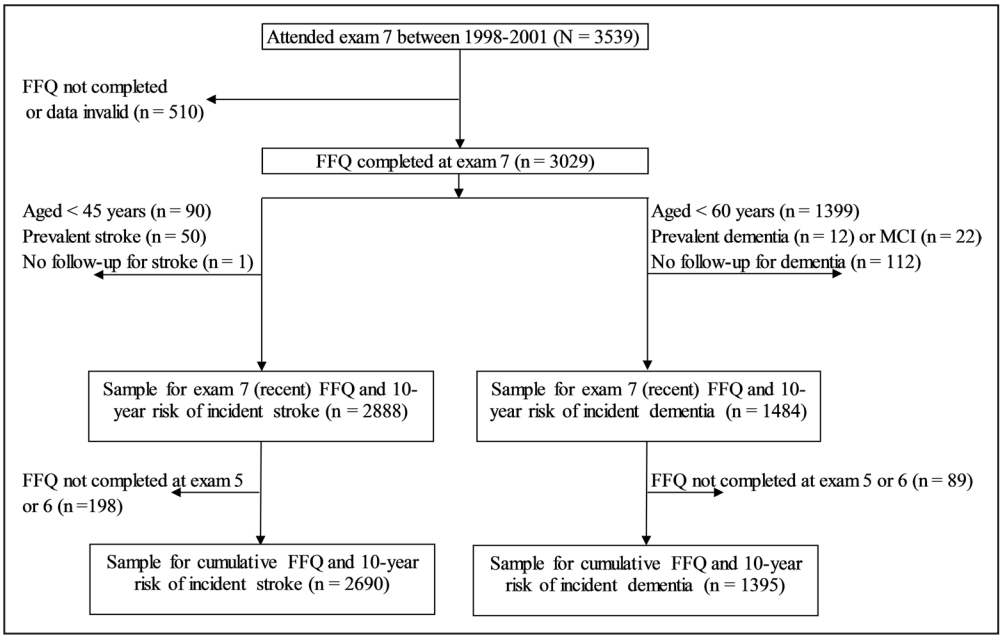

Figure 1. Selection of study participants. The risk of incident stroke and dementia were calculated as the 10-year risk, starting from examination cycle 7. Cumulative intake was calculated by averaging responses across the FFQ completed at examination cycles 5, 6, and 7 (to be included, a participant must have had examination cycle 7 data and at least one of examination cycles 5 or 6). FFQ indicates food frequency questionnaire; and MCI, mild cognitive impairment.

1, as well as additional cardiometabolic variables that may be influenced by sugary beverage intake[1,2,14,15] or associated with an increased risk of stroke or dementia.[3,4,16] These variables included systolic blood pressure, treatment of hypertension, prevalent cardiovascular disease, atrial fibrillation, left ventricular hypertrophy, total cholesterol, high-density lipoprotein cholesterol, prevalent diabetes mellitus, positivity for at least 1 apolipoprotein E ε4 allele (for analysis of dementia only) and waist-to-hip ratio (Model 3). All covariates were obtained from examination cycle 7. We report Models 2 and 3 as our primary analyses (please see Tables I and II in the online-only Data Supplement for Model 1 results).

We explored for interactions between beverage consumption and important confounders, including waist-to-hip ratio, apolipoprotein E ε4 allele status, and prevalent diabetes mellitus. We considered results statistically significant if a 2-sided $P<0.05$, except for tests of interaction which were considered statistically significant if a 2-sided $P<0.1$.

Sensitivity Analysis

We performed mediation analyses to examine if any of the following covariates mediated the observed associations between cumulative intake of artificially sweetened soft drink and the outcomes: prevalent hypertension, prevalent cardiovascular disease, prevalent diabetes mellitus, waist-to-hip ratio, total cholesterol, and high-density lipoprotein cholesterol.

Results

Table 1 displays cohort characteristics classified by total sugary beverage and artificially sweetened soft drink intake for the larger stroke study sample (see Table III in the online-only Data Supplement for a summary of the dementia study sample). Total caloric intake increased across categories of total sugary beverage but not artificially sweetened soft drink intake categories. The prevalence of cardiovascular disease and diabetes mellitus decreased with more frequent consumption of total sugary beverages but increased with greater consumption of artificially sweetened soft drink.

Sweetened Beverage Consumption and the Risk of Stroke

Greater recent consumption of artificially sweetened soft drink was associated with an increased risk of stroke, with the

Table 1. Cohort Demographics at Examination Cycle 7 for the Stroke Study Sample (N=2888)

	Total Sugary Beverages			Artificially Sweetened Soft Drinks		
	<1/d	1–2/d	>2/d	0/wk	1–6/wk	≥1/d
N (%)	1317 (46)	1103 (38)	468 (16)	1343 (47)	1024 (35)	519 (18)
Age, y	61 (9)	63 (9)	62 (10)	63 (9)	63 (8)	60 (8)
Male, n (%)	533 (40)	521 (47)	248 (53)	573 (43)	458 (45)	270 (52)
No HS degree	54 (4)	40 (4)	14 (3)	61 (5)	28 (3)	19 (4)
Waist/hip, ratio, median (Q1, Q3)	0.95 (0.90, 1.00)	0.96 (0.90, 1.01)	0.96 (0.91, 1.00)	0.95 (0.89, 0.99)	0.96 (0.90, 1.01)	0.97 (0.92, 1.02)
BMI, ratio, median (Q1, Q3)	28 (25, 31)	27 (24, 30)	27 (24, 31)	27 (24, 30)	28 (25, 31)	29 (26, 33)
SBP, mm Hg	127 (19)	128 (19)	127 (18)	127 (19)	128 (19)	127 (18)
Rx Hyp, n (%)	453 (34)	382 (35)	148 (32)	407 (30)	372 (36)	204 (39)
TC, mg/dL	203 (37)	200 (37)	199 (37)	203 (37)	200 (37)	197 (36)
HDL-C, mg/dL	55 (18)	54 (17)	51 (15)	55 (17)	54 (17)	52 (16)
DM, n (%)	187 (15)	128 (12)	36 (8)	94 (7)	145 (15)	112 (22)
AF, n (%)	40 (3)	57 (5)	17 (4)	44 (3)	42 (4)	28 (5)
CVD, n (%)	157 (12)	126 (11)	45 (10)	135 (10)	125 (12)	68 (13)
Smoker, n (%)*	182 (14)	114 (10)	56 (12)	204 (15)	91 (9)	57 (11)
APOE ε4, n (%)†	287 (22)	242 (22)	107 (23)	286 (22)	225 (22)	123 (24)
PAI, units, median (Q1, Q3)	36 (33, 41)	37 (33, 41)	37 (34, 42)	37 (34, 42)	37 (33, 41)	36 (33, 40)
Total caloric intake, Cal/d	1647 (539)	1839 (548)	2257 (612)	1840 (608)	1767 (573)	1869 (590)
DGAI, units	9 (3)	10 (3)	9 (3)	9 (3)	10 (3)	9 (3)
Saturated fat, g/d	21 (10)	22 (9)	25 (11)	22 (10)	21 (10)	23 (10)
Trans fat, g/d	2 (1)	3 (1)	3 (2)	3 (1)	3 (1)	3 (2)
Omega-3, g/d	11 (5)	12 (5)	13 (6)	12 (6)	11 (5)	13 (5)
Dietary fiber, g/d	17 (8)	19 (7)	21 (8)	18 (8)	18 (8)	18 (7)
Alcohol, g/d	11 (17)	10 (14)	9 (13)	10 (16)	10 (15)	10 (15)

Mean (SD) reported unless specified otherwise. AF indicates atrial fibrillation; APOE, apolipoprotein E; BMI, body mass index; cal, calories; CVD, prevalent cardiovascular disease; DGAI, dietary guidelines adherence index; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HS, high school; PAI, physical activity index; Rx Hyp, treatment for hypertension; SBP, systolic blood pressure; and TC, total cholesterol.

*Defined as current smoker.

†Presence of at least one APOE ε4 allele. Sugar-sweetened soft drink consumption was as follows: never, 1539 (53%); ≤3 times/week, 936 (32%); ≥3 times/week, 412 (14%).

strongest associations observed for ischemic stroke (Table 2). Higher cumulative intake of artificially sweetened soft drink was also associated with an increased risk of ischemic stroke (Table 2 and Figure 2). Neither intake of total sugary beverages nor intake of sugar-sweetened soft drink was associated with the risks of stroke.

Sweetened Beverage Consumption and the Risk of Dementia

When examining cumulative beverage consumption, daily intake of artificially sweetened soft drink was associated with an increased risk of both all-cause dementia and AD dementia in Models 1 and 2 (Table 3; Table II in the online-only Data Supplement). However, such associations were no longer significant after adjustment for the covariates outlined in Model 3. With respect to recent beverage intake, daily intake of artificially sweetened beverages was associated with an increased risk of dementia in Model 2 only. Neither total sugary beverages nor sugar-sweetened soft drink was associated with the risks of dementia.

Interactions

We did not observe any interactions with waist-to-hip ratio, diabetes mellitus status, or the presence of the apolipoprotein E ε4 allele with intake of any beverage examined.

Mediation Analysis

Prevalent diabetes mellitus status was identified as a potential mediator of the association between artificially sweetened beverage intake and the risk of both incident all-cause dementia and AD dementia (see Results in the online-only Data Supplement). When repeating the primary analysis excluding those with prevalent diabetes mellitus and adjusting for Model 1 covariates, daily intake of artificially sweetened beverages (versus no intake) remained a significant predictor of both incident all-cause dementia (HR, 2.45; 95% CI, 1.07–5.59; N/events, 53/1148) and AD dementia (HR, 3.23; 95% CI, 1.22–8.52; N/events, 40/1148). Thus, diabetes mellitus was a partial but not full mediator of the association between artificially sweetened beverage intake and incident dementia. Prevalent hypertension was a potential mediator of the association between artificially

Table 2. Beverage Intake and the Risk of Stroke

		Recent Intake				Cumulative Intake			
		All Stroke		Ischemic Stroke		All Stroke		Ischemic Stroke	
	Model	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Total sugary beverages									
<1/d (ref)	2								
1–2/d		1.12 (0.67–1.88)	0.65	1.06 (0.61–1.82)	0.84	1.09 (0.65–1.81)	0.75	0.90 (0.51–1.58)	0.71
>2/d		1.29 (0.65–2.55)	0.47	0.86 (0.38–1.91)	0.70	0.75 (0.33–1.69)	0.49	0.60 (0.24–1.49)	0.27
<1/d (ref)	3								
1–2/d		1.15 (0.73–1.81)	0.55	1.14 (0.70–1.85)	0.61	1.22 (0.77–1.94)	0.40	1.16 (0.70–1.92)	0.58
>2/d		1.22 (0.65–2.29)	0.54	0.92 (0.44–1.93)	0.83	0.88 (0.42–1.83)	0.73	0.70 (0.30–1.65)	0.41
Sugar-sweetened soft drinks									
0/wk (ref)	2								
>0–3/wk		1.15 (0.71–1.88)	0.57	1.11 (0.65–1.89)	0.72	1.17 (0.70–1.97)	0.55	1.12 (0.63–1.99)	0.69
>3/wk		0.69 (0.29–1.62)	0.40	0.69 (0.27–1.73)	0.43	0.61 (0.25–1.49)	0.28	0.61 (0.23–1.61)	0.32
0/wk (ref)	3								
>0–3/wk		1.22 (0.78–1.92)	0.38	1.25 (0.76–2.04)	0.38	1.14 (0.70–1.85)	0.60	1.20 (0.70–2.05)	0.51
>3/wk		0.88 (0.43–1.78)	0.71	0.84 (0.38–1.86)	0.67	0.80 (0.38–1.67)	0.55	0.81 (0.36–1.83)	0.61
Artificially sweetened soft drinks									
0/wk (ref)	2								
>0–6/wk		2.09 (1.24–3.51)	0.005	2.47 (1.39–4.40)	0.002	1.78 (0.98–3.23)	0.06	2.62 (1.26–5.45)	0.01
≥1/d		1.95 (1.02–3.73)	0.045	2.27 (1.11–4.64)	0.03	1.87 (0.90–3.90)	0.10	2.96 (1.26–6.97)	0.01
0/wk (ref)	3								
>0–6/wk		1.83 (1.14–2.93)	0.01	2.02 (1.19–3.43)	0.01	1.59 (0.92–2.75)	0.10	1.98 (1.03–3.78)	0.01
≥1/d		1.97 (1.10–3.55)	0.02	2.34 (1.24–4.45)	0.01	1.79 (0.91–3.52)	0.09	2.59 (1.21–5.57)	0.01

Model 1 is reported in the online-only Data Supplement. Model 2 adjusts for age, sex, total caloric intake, the dietary guidelines adherence index, self-reported physical activity, and smoking status. Model 3 adjusts for age, sex, total caloric intake, systolic blood pressure, treatment of hypertension, prevalent cardiovascular disease, atrial fibrillation, left ventricular hypertrophy, total cholesterol, high-density lipoprotein cholesterol, prevalent diabetes mellitus, and waist to hip ratio. For recent intake: N/events for all strokes were 76/2225 for Model 2 and 93/2729 for Model 3. N/events for ischemic stroke were 64/2225 for Model 2 and 78/2729 for Model 3. For cumulative intake: N/events for all strokes were 70/2137 for Model 2 and 85/2598 for Model 3. N/events for ischemic stroke were 58/2137 for Model 2 and 70/2598 for Model 3. CI indicates confidence interval; and HR, hazard ratio.

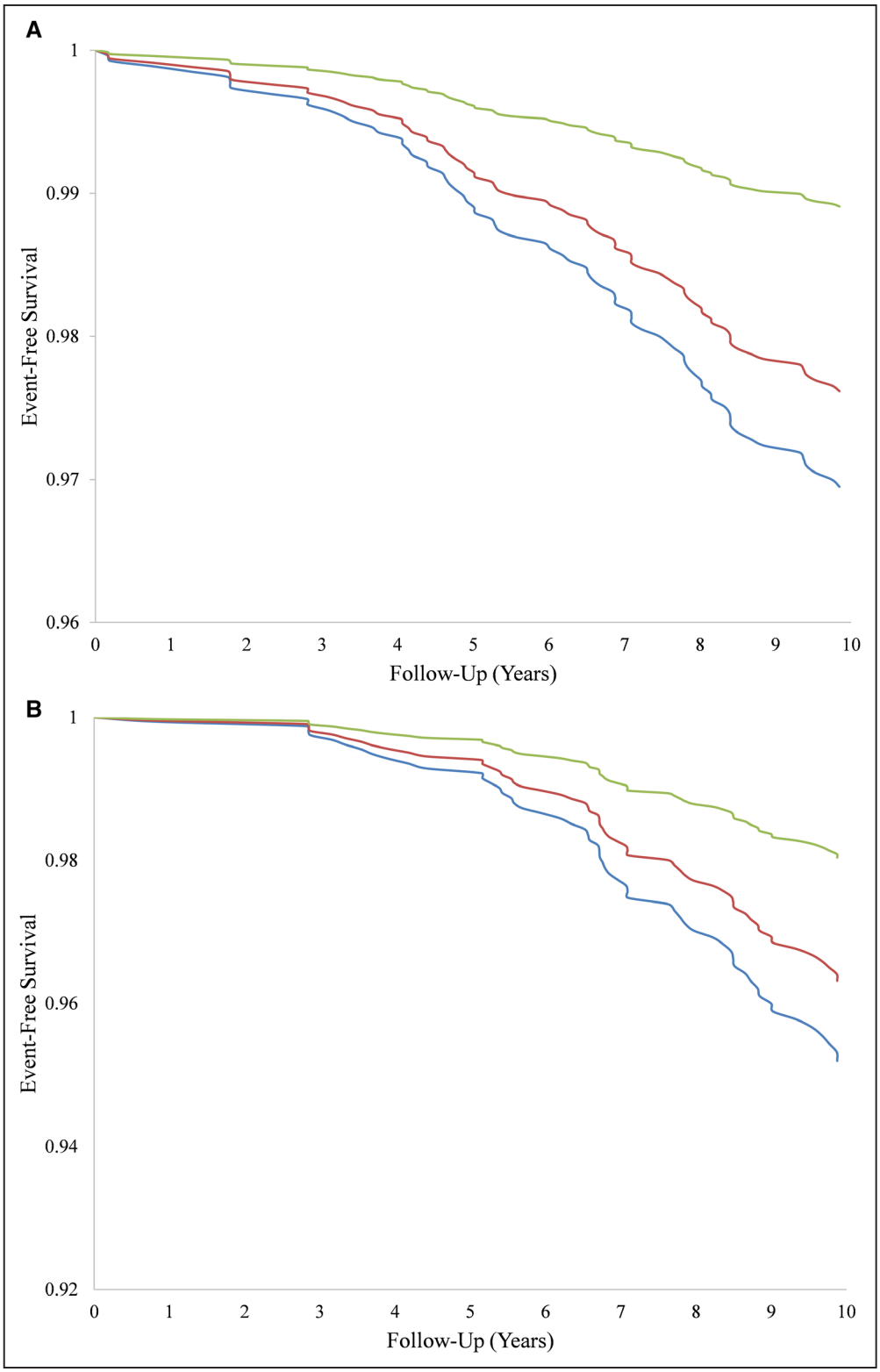

Figure 2. Cumulative consumption of artificially sweetened soft drinks and event-free survival of incident (**A**) all stroke and (**B**) all-cause dementia. Green, red, and blue lines denote intake of 0/wk, >0 to 6/wk, and ≥1/d, respectively. Incidence curves are adjusted for age, sex, and total caloric intake (as well as education for dementia as an outcome).

sweetened beverage intake and incident all-stroke, but not ischemic stroke (see Results in the online-only Data Supplement). After excluding people with prevalent hypertension, and after adjustment for Model 1 covariates, the association between artificially sweetened beverage intake and incident all-stroke was attenuated (0 per week, reference; >0–6 per week: HR, 1.53; 95% CI, 0.58–4.02; ≥1 per day: HR, 1.43; 95% CI, 0.40–5.11; N/events, 23/1456). No other mediation was identified.

Table 3. Beverage Intake and the Risk of Dementia

		Recent Intake				Cumulative Intake			
		All-Cause Dementia		AD Dementia		All-Cause Dementia		AD Dementia	
	Model	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Total sugary beverages									
<1/d (ref)	2								
1–2/d		0.92 (0.53–1.58)	0.75	0.95 (0.51–1.78)	0.88	0.72 (0.41–1.27)	0.26	0.69 (0.35–1.33)	0.26
>2/d		1.23 (0.59–2.58)	0.59	1.75 (0.81–3.81)	0.16	0.59 (0.24–1.47)	0.26	0.78 (0.31–2.01)	0.61
<1/d (ref)	3								
1–2/d		1.09 (0.67–1.76)	0.73	1.21 (0.69–2.13)	0.50	0.86 (0.52–1.40)	0.53	0.89 (0.50–1.59)	0.69
>2/d		1.19 (0.58–2.44)	0.63	1.90 (0.89–4.05)	0.10	0.61 (0.25–1.53)	0.29	0.92 (0.36–2.38)	0.87
Sugar-sweetened soft drinks									
0/wk (ref)	2								
>0–3/wk		0.86 (0.48–1.51)	0.59	0.91 (0.47–1.74)	0.77	0.75 (0.42–1.33)	0.32	0.88 (0.45–1.70)	0.69
>3/wk		1.15 (0.49–2.68)	0.75	1.56 (0.64–3.76)	0.33	0.82 (0.35–1.96)	0.66	1.23 (0.50–3.06)	0.65
0/wk (ref)	3								
>0–3/wk		1.06 (0.64–1.77)	0.82	1.11 (0.62–2.00)	0.73	0.80 (0.48–1.33)	0.39	0.88 (0.49–1.59)	0.68
>3/wk		0.94 (0.41–2.13)	0.87	1.30 (0.56–3.04)	0.54	0.77 (0.35–1.70)	0.52	0.91 (0.37–2.24)	0.84
Artificially sweetened soft drinks									
0/wk (ref)	2								
>0–6/wk		1.39 (0.79–2.43)	0.25	1.48 (0.78–2.82)	0.23	1.41 (0.77–2.59)	0.27	1.68 (0.82–3.43)	0.15
≥1/d		2.20 (1.09–4.45)	0.03	2.53 (1.15–5.56)	0.02	2.47 (1.15–5.30)	0.02	2.89 (1.18–7.07)	0.02
0/wk (ref)	3								
>0–6/wk		1.00 (0.60–1.67)	0.99	1.05 (0.59–1.87)	0.87	1.30 (0.74–2.29)	0.36	1.66 (0.86–3.20)	0.13
≥1/d		1.08 (0.54–2.17)	0.83	1.29 (0.59–2.80)	0.53	1.70 (0.80–3.61)	0.17	2.03 (0.83–4.97)	0.12

Model 1 is reported in the online-only Data Supplement. Model 2 adjusts for age, sex, total caloric intake, education, the dietary guidelines adherence index, self-reported physical activity, and smoking status. Model 3 adjusts for age, sex, education, total caloric intake, systolic blood pressure, treatment of hypertension, prevalent cardiovascular disease, atrial fibrillation, left ventricular hypertrophy, total cholesterol, high-density lipoprotein cholesterol, prevalent diabetes mellitus, waist to hip ratio, and positivity for at least 1 APOE ε4 allele. For recent intake: N/events for all-cause dementia were 66/1135 for Model 2 and 81/1348 for Model 3. N/events for AD dementia were 52/1135 for Model 2 and 63/1348 for Model 3. For cumulative intake: N/events for all-cause dementia were 61/1087 for Model 2 and 75/1285 for Model 3. N/events for AD dementia were 47/1087 for Model 2 and 57/1285 for Model 3. APOE indicates apolipoprotein E; CI, confidence interval; and HR, hazard ratio.

Discussion

In our community-based cohort, higher consumption of artificially sweetened soft drink was associated with an increased risk of both stroke and dementia. Neither total sugary beverages nor sugar-sweetened soft drink consumption was associated with the risks of stroke or dementia.

The Nurses Health Study and Health Professionals Follow-Up Study reported that greater consumption of sugar- and artificially sweetened soft drinks was each independently associated with a higher risk of incident stroke over 28 years of follow-up for women (N=84 085) and 22 years of follow-up for men (N=43 371).[5] The Northern Manhattan Study, a population-based multiethnic cohort (N=2564), reported that daily consumption of artificially sweetened soft drink was associated with a higher risk of combined vascular events but not stroke when examined as an independent outcome.[6] Our study provides further evidence to link consumption of artificially sweetened beverages with the risk of stroke, particularly ischemic stroke. To our knowledge, our study is the first to report an association between daily intake of artificially sweetened soft drink and an increased risk of both all-cause dementia and dementia because of AD.

Our observation that artificially sweetened, but not sugar-sweetened, soft drink consumption was associated with an increased risk of stroke and dementia is intriguing. Sugar-sweetened beverages provide a high dose of added sugar, leading to a rapid spike in blood glucose and insulin,[17] providing a plausible mechanism to link consumption to the development of stroke and dementia risk factors. Like sugar-sweetened soft drinks, artificially sweetened soft drinks are associated with risk factors for stroke and dementia,[1,14,15] although the mechanisms are incompletely understood, and inconsistent findings have been reported.[18]

Artificially sweetened beverages are typically sweetened with non-nutritive sweeteners, such as saccharin, acesulfame, aspartame, neotame, or sucralose. At the time of FFQ administration in this study, saccharin, acesulfame-K, and aspartame were Food and Drug Administration approved, whereas sucralose was approved in 1999, neotame in 2002, and stevia in 2008.[18] Collectively, these synthetic substances are much

more potent than sucrose, with only trace amounts needed to generate the sensation of sweetness.[17]

Previous studies linking artificially sweetened beverage consumption to negative health consequences have been questioned based on concerns regarding residual confounding and reverse causality, whereby sicker individuals consume diet beverages as a means of negating a further deterioration in health.[19] Indeed, in our study, diabetes mellitus—a known risk factor for dementia[20]—was more prevalent in those who regularly consumed artificially sweetened soft drinks. Diabetes mellitus status also partially mediated the association between artificially sweetened soft drink intake and incident dementia. Because our study was observational, we are unable to determine whether artificially sweetened soft drink intake increased the risk of incident dementia through diabetes mellitus or whether people with diabetes mellitus were simply more likely to consume diet beverages. Some studies have provided evidence for the former.[21] Artificial sweeteners have been shown to cause glucose intolerance in mice by altering gut microbiota and are associated with dysbiosis and glucose intolerance in humans.[21] A systematic review and meta-analysis reported that artificially sweetened beverage consumption was associated with incident diabetes mellitus, although publication bias and residual confounding were considered possible.[14] Clinical trials are needed to establish whether the consumption of artificially sweetened beverages is causally related to dementia or surrogate end points, such as cognitive decline or brain atrophy.

In our study, prevalent hypertension, the single most important stroke risk factor, attenuated the association between artificially sweetened beverage intake and incident all-stroke, although not ischemic stroke. Prospective cohort studies, such as the Nurses Health Study, have demonstrated associations between higher intake of artificially sweetened beverages and an increased risk of incident hypertension.[22] However, it remains unclear whether artificial sweeteners cause hypertension or whether diet beverages are favored by those most at risk. Given that clinical trials involving stroke end points are large and costly, clinical trials should investigate whether artificially sweetened beverages are associated with important stroke risk factors, such as high blood pressure.

Limitations of the study include the absence of ethnic minorities, which limits the generalizability of our findings to populations of non-European decent. Second, the observational nature of our study precludes us from inferring causal links between artificially sweetened beverage consumption and the risks of stroke and dementia. Third, the use of a self-report FFQ to obtain dietary intake data may be subject to recall bias, thus, introducing error into our estimated models. Fourth, although we addressed confounding in numerous ways, we cannot exclude the possibility of residual confounding. Finally, we did not adjust for multiple comparisons meaning that some findings may be attributable to chance.

In conclusion, artificially sweetened soft drink consumption was associated with an increased risk of stroke and dementia. Sugar-sweetened beverages were not associated with an increased risk of such outcomes. As the consumption of artificially sweetened soft drinks is increasing in the community,[23] along with the prevalence of stroke[24] and dementia,[25] future research is needed to replicate our findings and to investigate the mechanisms underlying the reported associations.

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Disclosures

None.

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Sugar- and Artificially Sweetened Beverages and the Risks of Incident Stroke and Dementia: A Prospective Cohort Study

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SUPPLEMENTAL MATERIAL

Sugar- and artificially-sweetened beverages and the risks of incident stroke and dementia: A prospective cohort study

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Supplemental Methods

Methods for determining incident stroke and incident dementia

Supplemental Table Legend

Supplemental Table I. Beverage intake and the risk of stroke using a minimally adjusted model

Supplemental Table II. Beverage intake and the risk of dementia using a minimally adjusted model

Supplemental Table III. Cohort demographics at examination cycle 7 for the dementia study sample

Supplemental Results

Mediation analysis

Methods for determining incident stroke and incident dementia

Surveillance for incident stroke was conducted by monitoring hospital admissions in Framingham, reviewing available medical records and results, and by questioning about stroke and stroke symptoms during annual health status updates and routine Heart Study examination cycles. Participants with a suspected stroke were evaluated by a Framingham study stroke physician (within 48 hours where feasible). We defined stroke as the rapid onset of focal neurological symptoms of presumed vascular origin, lasting >24 hours or resulting in death. Our diagnosis of stroke was determined by a review committee comprised of at least 3 Framingham Heart Study investigators, including at least two vascular neurologists. The committee adjudicated after reviewing all available medical records, imaging studies, and neurological reports.

Surveillance for incident dementia was conducted using routine cognitive screening at each Heart Study examination cycle with the Mini-Mental State Examination (MMSE)[1] and with complete neuropsychological testing at selected examination cycles. Participants were flagged for cognitive evaluation using the MMSE if (i) performance fell below education-based cut-off scores at any exam,[2] (ii) a decline of >3 points was observed between consecutive exams or (iii) a decline of >5 points was observed from the participants highest previously obtained MMSE score. Participants were also flagged for cognitive review following referrals or concern expressed by the participant, their family or a health care professional. Participants flagged with suspected cognitive impairment underwent complete neuropsychological and neurological evaluation before referral to the study dementia review committee. Persons flagged with suspected cognitive impairment were also examined annually with neurological and neuropsychological evaluations until they developed dementia or were adjudicated to be normal. A diagnosis of dementia was made in line with the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition.*[3] A diagnosis of Alzheimer's disease (AD) dementia was based on the criteria of the *National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association for definite, probable, or possible AD.*[4] Dementia diagnosis was the responsibility of a study committee comprising at least a neurologist and a neuropsychologist.

Supplemental Table I. Beverage intake and the risk of stroke using a minimally adjusted model

	Recent Intake				Cumulative Intake			
	All Stroke		Ischemic Stroke		All Stroke		Ischemic Stroke	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Total Sugary Beverages								
<1/day (ref)								
1-2/day	1.25 (0.80, 1.94)	0.33	1.26 (0.78, 2.02)	0.34	1.26 (0.80, 2.00)	0.32	1.20 (0.73, 1.98)	0.53
>2/day	1.22 (0.65, 2.28)	0.53	0.94 (0.46, 1.95)	0.88	0.81 (0.39, 1.69)	0.58	0.65 (0.28, 1.52)	0.98
Sugar-Sweetened Soft Drinks								
0/week (ref)								
>0-3/week	1.21 (0.78, 1.86)	0.39	1.24 (0.77, 1.97)	0.68	1.12 (0.70, 1.79)	0.65	1.18 (0.70, 1.98)	0.54
>3/week	0.89 (0.44, 1.79)	0.74	0.85 (0.39, 1.86)	0.38	0.82 (0.40, 1.69)	0.59	0.83 (0.37, 1.86)	0.66
Artificially-Sweetened Soft Drinks								
0/week (ref)								
>0-6/week	**1.88 (1.19, 3.00)**	**0.01**	**2.08 (1.25, 3.45)**	**0.005**	**1.75 (1.02, 2.99)**	**0.04**	**2.20 (1.16, 4.17)**	**0.02**
≥1/day	**2.17 (1.24, 3.79)**	**0.01**	**2.55 (1.39, 4.67)**	**0.003**	**1.96 (1.02, 3.79)**	**0.04**	**2.82 (1.34, 5.95)**	**0.01**

Models are adjusted for age, sex, and total caloric intake. For recent intake, N/events for all strokes and ischemic strokes were 97/2888 and 82/2888 respectively. For cumulative intake, N/events for all strokes and ischemic strokes were 87/2690 and 72/2690, respectively.

Supplemental Table II. Beverage intake and the risk of dementia using a minimally adjusted model

	Recent Intake				Cumulative Intake			
	All-Cause Dementia		AD Dementia		All-Cause Dementia		AD Dementia	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Total Sugary Beverages								
<1/day (ref)								
1-2/day	1.13 (0.70, 1.82)	0.62	1.21 (0.70, 2.10)	0.50	0.90 (0.56, 1.47)	0.68	0.90 (0.51, 1.59)	0.72
>2/day	1.06 (0.53, 2.13)	0.87	1.62 (0.78, 3.38)	0.20	0.54 (0.22, 1.32)	0.18	0.80 (0.32, 1.99)	0.63
Sugar-Sweetened Soft Drinks								
0/week (ref)								
>0-3/week	0.98 (0.60, 1.61)	0.94	1.03 (0.59, 1.81)	0.91	0.79 (0.48, 1.31)	0.36	0.93 (0.52, 1.67)	0.82
>3/week	0.77 (0.34, 1.74)	0.53	1.04 (0.45, 2.40)	0.93	0.76 (0.35, 1.64)	0.48	0.88 (0.36, 2.11)	0.77
Artificially-Sweetened Soft Drinks								
0/week (ref)								
>0-6/week	1.24 (0.76, 2.03)	0.40	1.25 (0.71, 2.21)	0.44	1.57 (0.90, 2.71)	0.11	1.89 (0.99, 3.62)	0.05
≥1/day	1.58 (0.81, 3.07)	0.18	1.79 (0.85, 3.74)	0.12	**2.28 (1.11, 4.67)**	**0.02**	**2.48 (1.06, 5.84)**	**0.04**

Models are adjusted for age, sex, education, and total caloric intake. For recent intake, N/events for all-cause dementia and Alzheimer's disease dementia were 81/1442 and 63/1442, respectively. For cumulative intake, N/events for all-cause dementia and Alzheimer's disease dementia were 75/1356 and 57/1356, respective.

Supplemental Table III. Cohort demographics at examination cycle 7 for the dementia study sample (N=1484)

	Total Sugary Beverages			Artificially-Sweetened Soft Drinks		
	<1/day	**1-2/day**	**>2/day**	**0/week**	**1-6/week**	**≥1/day**
N (%)	634 (43)	621 (42)	229 (15)	683 (46)	575 (39)	225 (15)
Age, years	68 (6)	69 (5)	69 (6)	69 (6)	68 (6)	67 (5)
Male, n (%)	267 (42)	292 (47)	127 (55)	297 (43)	268 (47)	120 (53)
No HS degree	33 (5)	31 (5)	11 (5)	44 (7)	18 (3)	13 (6)
Waist/Hip, ratio, median (Q1, Q3)	0.97 (0.92, 1.01)	0.98 (0.93, 1.01)	0.97 (0.93, 1.01)	0.97 (0.91, 1.01)	0.98 (0.93, 1.02)	0.99 (0.94, 1.03)
BMI, ratio, median (Q1, Q3)	28 (25, 31)	27 (24, 30)	28 (25, 31)	26 (24, 30)	28 (25, 31)	29 (26, 33)
SBP, mmHg	132 (20)	133 (19)	134 (19)	132 (20)	133 (20)	133 (18)
Rx Hyp, n (%)	277 (44)	270 (43)	100 (44)	268 (39)	273 (48)	106 (47)
TC, mg/dL	202 (37)	198 (36)	196 (35)	203 (35)	197 (38)	195 (35)
HDL-C, mg/dL	55 (17)	53 (16)	50 (16)	54 (17)	53 (17)	51 (16)
DM, n (%)	112 (18)	93 (15)	23 (10)	58 (9)	113 (20)	57 (26)
AF, n (%)	27 (4)	41 (7)	15 (7)	31 (5)	35 (6)	17 (8)
CVD, n (%)	125 (20)	102 (16)	39 (17)	106 (15)	114 (20)	46 (20)
Smoker[a], n (%)	57 (9)	45 (7)	16 (7)	69 (10)	33 (6)	16 (7)
APOE ε4[b], n (%)	138 (22)	131 (21)	53 (23)	138 (20)	131 (23)	52 (24)
PAI, units, median (Q1, Q3)	37 (33, 42)	37 (34, 42)	38 (35, 43)	38 (34, 43)	37 (34, 41)	37 (33, 41)
Total caloric intake, Cal/day	1646 (491)	1786 (538)	2169 (587)	1811 (563)	1757 (558)	1783 (518)
DGAI, units	9 (3)	10 (3)	10 (3)	10 (3)	10 (3)	9 (3)
Saturated fat, gm/d	20 (9)	21 (9)	24 (11)	21 (10)	21 (9)	22 (9)
Trans fat, gm/d	2 (1)	3 (1)	3 (1)	3 (1)	3 (1)	3 (1)
Omega-3, gm/d	11 (5)	12 (5)	12 (5)	12 (5)	11 (5)	12 (5)
Dietary fiber, gm/d	18 (8)	19 (8)	21 (7)	19 (8)	19 (7)	18 (7)
Alcohol, gm/d	10 (16)	10 (14)	9 (14)	9 (15)	10 (15)	10 (16)

Mean (SD) reported unless specified otherwise. AF = atrial fibrillation; CVD = prevalent cardiovascular disease; DGAI = dietary guidelines adherence index; DM = diabetes mellitus; HDL-C = high-density lipoprotein cholesterol; HS = high school; PAI = physical activity index; Rx Hyp= treatment for hypertension; SBP = systolic blood pressure; TC = total cholesterol. [a]defined as current smoker, [b]presence of at least one APOE ε4 allele. Sugar sweetened soft drink consumption was as follows for the stroke analysis sample: never, 1539 (53%); up to 3 times/week, 936 (32%); ≥3 times/week, 412 (14%); and for the dementia analysis sample: never, 821 (55%); up to 3 times/week, 493 (33%); ≥3 times/week, 169 (11%).

Supplemental results: Mediation analysis

We performed mediation analyses to examine if prevalent hypertension, prevalent cardiovascular disease, prevalent diabetes, waist to hip ratio, total cholesterol, or HDL cholesterol mediated any of the observed associations between cumulative intake of artificially-sweetened soft drink and the outcomes. All models were adjusted for age, sex, education (for incident dementia), and total caloric intake. First, we examined the association between each potential mediator and each outcome. Potential mediators that were not associated the incidence of stroke or dementia were not considered further. Next, we examined the association between artificially-sweetened beverage intake and each potential mediator. We then examined the association between artificially-sweetened beverage intake and each outcome and observed the effect size. Next, we separately added each potential mediator to the model and observed the change in effect size between intake of artificially-sweetened beverage and each outcome. Attenuation of the effect size was taken to indicate potential mediation.

Diabetes status potentially mediated the association between artificially-sweetened beverage intake and incident all-cause dementia: Prevalent diabetes was associated with an increased risk of dementia (HR 2.62, 95% CI 1.58-4.35). Daily intake of artificially-sweetened beverages was associated with a higher risk of incident all-cause dementia (0/week, reference; >0-6/week, HR 1.57, 95% CI 0.90-2.71; ≥1/day, HR 2.28, 95% CI 1.11-4.67). After the addition of prevalent diabetes status to the model, the association between artificially-sweetened beverage intake and incident all-cause dementia was attenuated (0/week, reference; >0-6/week, HR 1.34, 95% CI 0.77-2.35; ≥1/day, HR 1.77, 95% CI 0.85-3.70).

Diabetes status potentially mediated the association between artificially-sweetened beverage intake and incident Alzheimer's disease dementia: Prevalent diabetes was associated with an increased risk of Alzheimer's disease dementia (HR 2.56, 95% CI 1.46-4.63). Daily intake of artificially-sweetened beverages was associated with a higher risk of incident Alzheimer's disease dementia (0/week, reference; >0-6/week HR 1.89, 95% CI 0.99-3.62; ≥1/day, HR 2.48; 95% CI 1.06-5.84). After the addition of prevalent diabetes status to the model, the association between artificially-sweetened beverage intake and incident Alzheimer's disease dementia was attenuated (0/week, reference; >0-6/week HR 1.64, 95% CI 0.85-3.17; ≥1/day, HR 1.93, 95% CI 0.80-4.64).

Hypertension potentially mediated the association between artificially-sweetened beverage intake and incident all-stroke: Prevalent hypertension was associated with an increased risk of incident all-stroke (HR 2.37, 95% CI 1.45-3.88). Higher intake of artificially-sweetened beverages was associated with a higher risk of incident all-stroke (0/week, reference; >0-6/week, HR 1.75, 95% CI 1.02-2.99; ≥1/day, HR 1.96, 95% CI 1.02-3.79). After the addition of prevalent hypertension status to the model, the association between artificially-sweetened beverage intake and incident all-stroke was attenuated (0/week, reference; >0-6/week, HR 1.68, 95% CI 0.98-2.87; ≥1/day, HR 1.83, 95% CI, 0.94-3.53).

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