



Featured Article

Sugary beverage intake and preclinical Alzheimer's disease in the community

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Abstract

Introduction: Excess sugar consumption has been linked with Alzheimer's disease (AD) pathology in animal models.

Methods: We examined the cross-sectional association of sugary beverage consumption with neuropsychological ($N = 4276$) and magnetic resonance imaging ($N = 3846$) markers of preclinical Alzheimer's disease and vascular brain injury (VBI) in the community-based Framingham Heart Study. Intake of sugary beverages was estimated using a food frequency questionnaire.

Results: Relative to consuming less than one sugary beverage per day, higher intake of sugary beverages was associated with lower total brain volume (1–2/day, $\beta \pm$ standard error [SE] = -0.55 ± 0.14 mean percent difference, $P = .0002$; >2/day, $\beta \pm$ SE = -0.68 ± 0.18 , $P < .0001$), and poorer performance on tests of episodic memory (all $P < .01$). Daily fruit juice intake was associated with lower total brain volume, hippocampal volume, and poorer episodic memory (all $P < .05$). Sugary beverage intake was not associated with VBI in a consistent manner across outcomes.

Discussion: Higher intake of sugary beverages was associated cross-sectionally with markers of preclinical AD.

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Keywords:

Sugar; Diet; Dementia; Alzheimer's disease; Framingham Heart Study

1. Introduction

Sugar consumption is excessive in Western society [1], contributing to the burden of cardiometabolic disease [2,3]. Consumption of sugary beverages, including sugar-sweetened soft drinks, fruit drinks with added sugar, and 100% fruit juice, are major contributors to excess sugar

intake [1]. Studies in animal models suggest that excess sugar intake, including from sugary beverages, leads to the development of Alzheimer's disease (AD) pathology [4–7]. However, little is known about the long-term effect of sugary beverage intake on the human brain. Examining intake of sugary beverages provides a proxy for excess dietary intake of sugar. Using detailed neuropsychological assessments and brain magnetic resonance imaging (MRI), we examined the cross-sectional association between sugary beverage consumption and phenotypes of preclinical AD

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and vascular brain injury in the Framingham Heart Study (FHS)—a large, community-based, prospective cohort study from Massachusetts, USA. We hypothesized that higher consumption of sugary beverages would be associated with greater evidence of both subclinical vascular brain injury and preclinical AD.

2. Methods

The FHS commenced in 1948 with the aim to identify factors that contribute to cardiovascular disease [8]. At enrollment, the Original cohort comprised 5209 community-dwelling participants who did not yet have overt signs of cardiovascular disease. Surviving participants continue to be examined approximately every 2 years. In 1971, following a need to study younger adults, the children of the Original cohort and their spouses were invited to form the Offspring cohort [9]. The Offspring cohort enrolled 5124 participants who have been studied across nine quadrennial examination cycles. In 2002, a subset of the grandchildren of the Original cohort (the children of the Offspring cohort) was enrolled into the Third Generation cohort [10]. This cohort comprised 4095 participants at the initial examination and has now been studied twice, with a third examination cycle currently underway. All cohorts are observational with information collected on a wide variety of demographic, medical, and lifestyle indicators. Participants are also under constant surveillance for incident events such as myocardial infarction, stroke, and dementia. For the

present study, we examined food frequency questionnaire (FFQ) data collected during examination cycle 7 (1998–2001) for the Offspring cohort and during examination cycle 2 (2008–2011) for the Third Generation cohort. We excluded persons with prevalent dementia, stroke, or other significant neurological disease, those younger than 30 years of age, and participants who reported improbably high or low total energy intakes, suggesting that they had not filled out the FFQ accurately. A comparison of participants included in analysis versus excluded because of prevalent stroke, dementia, or other neurological disease can be seen in [Supplementary Table 1](#).

Participants underwent neuropsychological assessment and a brain MRI an average of 2 years (standard deviation [SD] = 1) from the examination cycle at which the FFQ was administered; most participants completed cognitive assessment and brain MRI on the same day (98%). The study flow diagram is presented in [Fig. 1](#). There were 4276 and 3846 participants available for analysis of the neuropsychological and MRI outcomes, respectively. All participants provided written informed consent, and the study was approved by the institutional review board and Boston University Medical Center.

2.1. Assessment of sugary beverage intake

Participants completed the Harvard semiquantitative FFQ at examination 7 for the Offspring cohort and examination 2 for the Third Generation cohort. This FFQ is designed to

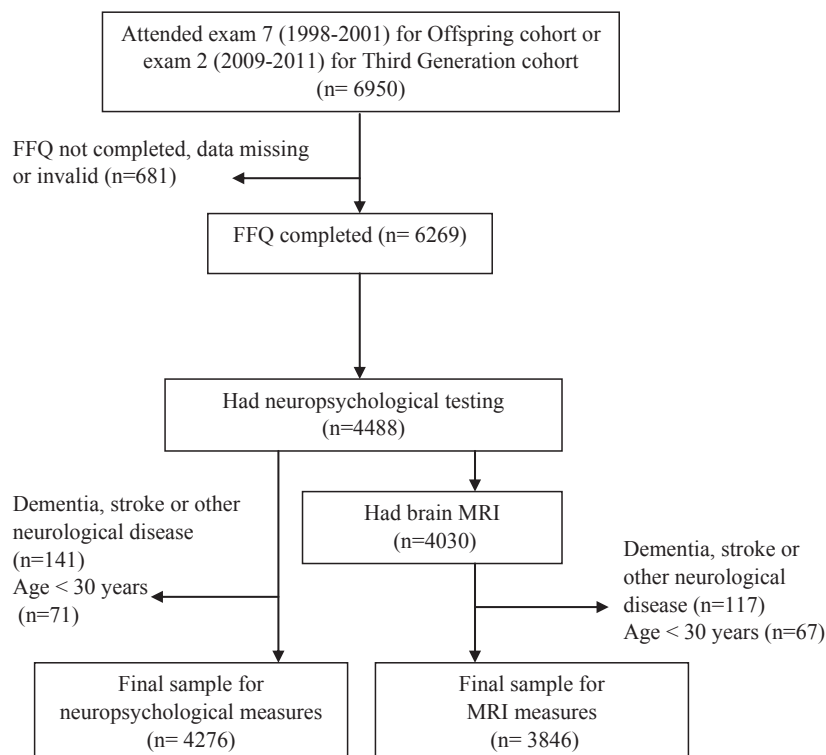


Fig. 1. Study flow diagram. Abbreviations: FFQ, food frequency questionnaire; MRI, magnetic resonance imaging.

measure dietary intake over the past year and has been validated extensively [11–13]. Participants were asked how often they consumed one glass, bottle, or can of each sugary beverage item, on average, across the previous year. Each item was scored according to nine responses spanning from “never or almost never” to “6+ per day.” Participants were presented with three items on sugar-sweetened soft drink (“Coke, Pepsi, or other cola with sugar,” “caffeine-free Coke, Pepsi, or other cola with sugar,” and “other carbonated beverages with sugar”), four items on fruit juice (“apple juice,” “orange juice,” “grapefruit juice,” and “other juice”), one item on sugar-sweetened fruit drinks and three items on diet soft drink (“low-calorie cola with caffeine,” “low-calorie caffeine-free cola,” and “other low-calorie beverages”).

We summed the individual items to create exposure variables reflecting intake of (I) total sugary beverages (excluding diet soft drinks), (II) fruit juice, (III) sugar-sweetened soft drinks (all sugary beverages excluding diet soft drink, fruit juice, and fruit drinks), and (IV) diet soft drinks. For each of the four exposure variables, participant responses were aggregated and new intake categories were created ensuring an adequate number of participants in each intake group for each variable. These new intake categories were based on the distribution of each variable. Total sugary beverage consumption was examined as a three-level variable: <1/day (reference), 1–2/day, and >2/day; fruit juice intake was categorized as a dichotomous variable: <1/day (reference) and \geq 1/day. Sugar-sweetened soft drink intake was examined as a three-level variable: 0/week (reference), up to 3/week, and >3/week. Diet soft drink was also examined as a three-level variable: 0/week (reference), up to 6/week, and \geq 1/day. Intake of sugary beverages using the FFQ has been compared against dietary records, with correlation coefficients ranging from 0.84 for cola and 0.74 to 0.76 for fruit juice [14,15]. Moreover, intake of sugary beverages ascertained via the FFQ is reliable when measurements are repeated after 12 months, with correlation coefficients ranging from 0.85 for cola and 0.86 for fruit juice [14,15].

2.2. Structural brain MRI

Total brain volume and hippocampal volume are sensitive to early neurodegeneration [16] and were measured as markers of preclinical AD. Silent brain infarcts and white-matter hyperintensity volume (WMHV) are indicative of cerebral small vessel disease [17] and were measured as sub-clinical markers of vascular brain injury. For the Offspring study participants, we used a Siemens 1-Tesla or 1.5-Tesla field strength machine with a T2-weighted double spin-echo (DSE) coronal imaging sequence in contiguous slices of 4 mm. For the Third Generation participants, we used a 1.5-Tesla Siemens Avanto scanner with three-dimensional T1-weighted coronal spoiled gradient-recalled echo acquisition and fluid-attenuated inversion recovery (FLAIR)

sequences. Total brain volume, hippocampal volume, and WMHV were calculated relative to total cranial volume to adjust for differences in head size. Given that intracranial volume signifies the largest brain size achieved during life, total brain volume provides an indicator of global brain atrophy. Hippocampal volume was calculated using a semiautomatic multiatlas segmentation algorithm [18]. The methods used to segment WMHV have been described previously [19]. We harmonized differences in WMHV between the DSE and FLAIR sequences by applying formulae developed from statistical modeling. WMHV was first expressed as a percent of total cranial volume and log transformed to normalize its distribution. The resulting variable, logWMHV-DSE, was converted to predicted FLAIR logWMHV using simple linear conversion models within 5-year age bins. Silent brain infarcts were counted manually in accordance with the STRIVE criteria [17]. Comprehensive details of the imaging methodology, including intrarater reliabilities, are published elsewhere [19–22]. Scans were read blinded to dietary intake scores.

2.3. Neuropsychological testing

Subtle deficits in episodic (verbal) memory can precede the clinical diagnosis of AD dementia by up to a decade [23] and are useful in identifying persons at the highest risk of developing clinical AD [24]. We examined episodic memory, using the tests of Logical Memory Immediate and Delayed from the Wechsler Memory Scales, as markers of preclinical AD. Based on our extensive past work relating vascular risk factors to cognitive function [25,26], we included tasks of Trail Making B minus A (processing speed and executive function), Similarities (verbal abstract reasoning) from the Wechsler Adult Intelligence Scale and Visual Reproductions Delayed (visual memory) from the Wechsler Memory Scales as markers of vascular cognitive impairment. Values of Trails B-A were natural logarithmically transformed to restore normality and then the mathematical sign was reversed, such that higher scores on all tasks indicate superior performance. All neuropsychological tests have adequate reliability and construct validity [27,28]. Further details of the neuropsychological protocol can be seen elsewhere [28].

2.4. Statistical analysis

Statistical models were estimated using SAS Software (SAS Institute, Cary, NC, USA). We used separate multivariable linear (for continuous measures) and logistic (for binary outcomes) regression models to examine the associations between the four dietary exposure variables and the MRI and neuropsychological outcomes. Missing data were excluded from analysis. All models included adjustments for age, sex, total caloric intake, and the time interval between completion of the FFQ and the measurement of the imaging/neuropsychological outcomes. All models involving

the neuropsychological outcomes were further adjusted for education, whereas all models involving the MRI outcomes were further adjusted for age squared given that the association between age and brain volume is nonlinear [19]. A second statistical model included additional adjustments for systolic blood pressure, treatment of hypertension, current smoking status, prevalent cardiovascular disease, atrial fibrillation, left ventricular hypertrophy, total cholesterol, high-density lipoprotein cholesterol, prevalent diabetes mellitus, depressive symptoms (Center for Epidemiologic Studies Depression Scale scores ≥ 16) and waist-to-hip ratio. A third statistical model included the covariates outlined in model one plus intake of saturated fat, trans-fat, and dietary fiber and self-reported physical activity. We performed a sensitivity analysis by repeating statistical analyses (for model 1) after excluding persons with prevalent diabetes or cardiovascular disease. We also performed a sensitivity analysis by adjusting for fasting blood glucose levels in model 2 in place of diabetes status. To provide some clinical context to our results, we expressed some of our main findings in terms of years of brain aging. For this purpose, we regressed each outcome score on age and compared differences in means attributable to the different categories of sugary

beverage intake. We considered results statistically significant if a two-sided $P < .05$.

3. Results

3.1. Cohort demographics

The clinical characteristics of our study sample are displayed in Table 1. Across the sample, the mean total caloric intake was 1942 calories (SD = 670) per day, which is similar to other US cohorts of comparable ages [29]. Total caloric intake and saturated fat, but not trans-fat, tended to be higher with increasing intake of sugary beverages. Total sugary beverages were consumed less than once per day, once to twice per day, and greater than twice per day by 2395 (56%), 1239 (29%), and 641 (15%) participants, respectively. Fruit juice was consumed one or more times per day by 1330 (31%) participants. Most participants reported consuming no sugar-sweetened soft drinks ($n = 2326$, 54%), with 1359 (32%) participants consuming sugar-sweetened soft drinks up to 3 times per week, and 588 (14%) participants consuming sugar-sweetened soft drinks greater than three times per week. Diet soft drinks

Table 1
Characteristics of the larger study sample

Variable	Total sugary beverage intake			Total ($N = 4276$)*
	<1/day ($n = 2395$)	1–2/day ($n = 1239$)	>2/day ($n = 641$)	
Clinical characteristics				
Age, years, mean (SD)	53 (11)	56 (12)	54 (12)	54 (11)
Male, n (%)	936 (39)	648 (52)	380 (59)	1965 (46)
Education, n (%)				
No high school degree	41 (2)	25 (2)	10 (2)	76 (2)
High school degree	518 (22)	262 (21)	128 (20)	908 (21)
Some college	759 (32)	365 (29)	178 (28)	1303 (31)
College graduate	1073 (45)	587 (47)	325 (51)	1985 (46)
Waist/hip ratio, mean (SD)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)
Systolic BP, mm Hg, mean (SD)	120 (17)	123 (18)	122 (17)	121 (17)
Hypertension treatment, n (%)	594 (25)	326 (26)	143 (22)	1063 (25)
Fasting blood glucose, mg/dL, mean (SD)	100.0 (24.5)	99.7 (20.7)	98.1 (14.3)	99.6 (22.2)
Total cholesterol, mg/dL, mean (SD)	194.9 (37.5)	193.6 (35.1)	193.6 (38.0)	194.3 (36.9)
HDL cholesterol, mg/dL, mean (SD)	58.9 (18.1)	54.9 (16.7)	52.4 (15.5)	56.8 (17.5)
Diabetes mellitus, n (%)	218 (9)	96 (8)	28 (4)	342 (8)
Atrial fibrillation, n (%)	43 (2)	41 (3)	15 (2)	99 (2)
Prevalent CVD, n (%)	149 (6)	92 (7)	29 (5)	270 (6)
Current smoker, n (%)	257 (11)	106 (9)	71 (11)	434 (10)
PAI, score, median (Q1, Q3)	36 (32, 39)	36 (33, 40)	36 (33, 41)	37 (33, 40)
Depression [†] , n (%)	204 (9)	86 (7)	70 (11)	360 (8)
Dietary variables				
Total caloric intake, calories/day, mean (SD)	1782 (594)	2007 (626)	2413 (767)	1942 (670)
Saturated fat, g/day, mean (SD)	22 (10)	24 (11)	27 (12)	23 (11)
Trans-fat, g/day, mean (SD)	3 (1)	3 (2)	3 (2)	2 (1)
Dietary fiber, g/day, mean (SD)	20 (10)	21 (9)	22 (9)	20 (9)

Abbreviations: SD, standard deviation; BP, blood pressure; CVD, cardiovascular disease; PAI, physical activity index; MRI, magnetic resonance imaging; CESD, Center for Epidemiologic Studies Depression Scale.

*Table based on the larger (neuropsychological outcome) sample. MRI outcomes were reported on a subsample of this population ($N = 3846$) with comparable characteristics.

[†]Defined as CESD scores ≥ 16 .

were consumed more regularly than sugar-sweetened soft drinks, with 2081 (49%), 1495 (35%), and 698 (16%) participants consuming no diet soft drinks, up to six per week, and one or more per day, respectively. [Supplementary Table 2](#) displays the unadjusted values of the outcome measures, stratified by total sugary beverage intake.

3.2. Sugar-sweetened beverage consumption and markers of preclinical AD

Greater consumption of total sugary beverages was associated with lower total brain volume and lower scores on Logical Memory Immediate and Delayed Recall ([Table 2](#)). There was also a borderline statistically significant association between the highest intake of total sugary beverages and lower hippocampal volume. Adjusted least square means and standard errors are displayed in [Fig. 2](#) (adjusted for model 1 covariates). Relative to no intake, the difference in total brain volume associated with consuming 1–2 or greater than 2 sugary beverages per day was equivalent to 1.6 and 2.0 years of brain aging, respectively. Relative to no intake, the difference in Logical Memory Delayed Recall scores associated with consuming 1–2 or greater than 2 sugary beverages per day was equivalent to 5.8 and 11.0 years of brain aging, respectively.

One or more servings per day of fruit juice were associated with lower total brain volume, hippocampal volume, and poorer Immediate and Delayed Logical Memory scores. The difference in total brain volume and Logical Memory Delayed scores associated with daily fruit juice intake was equivalent to 1.5 and 3.5 years of brain aging, respectively. Relative to no intake, consuming more than three sugar-sweetened soft drinks per week was associated with lower total brain volume and lower Logical Memory Immediate scores, with differences equivalent to 2.6 (for total brain volume) and 13.0 (for Logical Memory Immediate) years of brain aging, when comparing the highest intake group to the reference group. However, the association between sugar-sweetened soft drinks and total brain volume was no longer significant after adjustment for other dietary factors and physical activity (model 3).

3.3. Consumption of sugary beverages and vascular brain injury

Consuming more than two sugary beverages per day or more than three sugary soft drinks per week was associated with greater WMHV in models 1 and 2 although not model 3 ([Table 3](#)). There was also a borderline statistically significant association between greater consumption of soft drinks with sugar and poorer performance on the test of similarities.

3.4. Consumption of diet soft drink, preclinical AD, and vascular brain injury

Higher diet soft drink intake was associated with smaller total brain volume and poorer performance on the test of

similarities ([Supplementary Tables 3 and 4](#)). There were no other associations between diet soft drink intake and the outcomes evaluated.

3.5. Sensitivity analysis

Excluding 540 persons from analyses of the neuropsychological outcomes and 463 persons from analyses of the MRI outcomes (due to prevalent diabetes or cardiovascular disease) did not change the observed pattern of results (data not shown). Adjusting for fasting blood glucose levels in place of prevalent diabetes status (in model 2) did not change the significance or direction of the reported results for any of the AD markers, with the exception that consuming more than two sugary beverages per day was associated with smaller hippocampal volume ($\beta \pm SE = 0.005 \pm 0.002, P = .04$). After adjustment for fasting blood glucose, consuming more than two sugary beverages per day was no longer associated with WMHV ($\beta \pm SE = 0.05 \pm 0.07, P = .48$).

4. Discussion

In our cross-sectional analysis of a large community-based sample, we observed that higher consumption of sugary beverages was associated with smaller total brain volume, poorer episodic memory, and smaller hippocampal volume (for higher fruit juice intake), a pattern of findings consistent with preclinical AD. These findings were striking given that they were evident in a middle-aged sample and were observed even after statistical adjustment for numerous confounding factors such as prevalent diabetes, total caloric intake, and physical activity. The magnitudes of the associations observed were the equivalent of 1.5–2.6 years of brain aging for total brain volume and 3.5–13 years of brain aging for episodic memory.

Excess sugary beverage intake is known to be associated with cardiovascular disease [2,3], which, in turn, is associated with vascular brain injury [30]. Although this suggests a possible link between sugary beverage consumption and vascular brain injury, we observed more striking associations between sugary beverage intake and markers of preclinical AD. These results add to a growing body of pre-clinical research suggesting that high sugar intake is associated with the correlates of AD in mice. Research using mice highly predisposed to developing AD pathology demonstrated that high sucrose intake increased A β aggregation and tau phosphorylation via signaling of the mammalian target of rapamycin [4], a protein that regulates cell proliferation and survival as well as energy homeostasis. Similarly, a study using a transgenic mouse model of AD demonstrated that the long-term consumption of sucrose-sweetened water, relative to control water, led to poorer memory and a near three-fold increase in A β aggregation [7]. Also in animal models, high fat refined sugar diets increase A β aggregation and tau phosphorylation [5], hippocampal atrophy [6], and

Table 2
Sugary beverage intake and markers of preclinical AD

Exposure	Model	Total brain volume, %		Hippocampal volume, %		Logical memory, <i>n</i> details recalled immediately		Logical memory, <i>n</i> details recalled after delay	
		$\beta \pm SE$	<i>P</i>	$\beta \pm SE$	<i>P</i>	$\beta \pm SE$	<i>P</i>	$\beta \pm SE$	<i>P</i>
Total sugary beverages									
<1/day (ref)	1								
1–2/day		–0.55 ± 0.14	.0002	0.00002 ± 0.002	.99	–0.41 ± 0.12	.001	–0.37 ± 0.12	.003
>2/day		–0.68 ± 0.18	<.0001	–0.004 ± 0.002	.06	–0.67 ± 0.16	<.0001	–0.69 ± 0.16	<.0001
<1/day (ref)	2								
1–2/day		–0.53 ± 0.14	.0002	0.0004 ± 0.002	.82	–0.37 ± 0.12	.002	–0.36 ± 0.13	.005
>2/day		–0.69 ± 0.18	.0002	–0.004 ± 0.002	.08	–0.66 ± 0.16	<.0001	–0.69 ± 0.17	<.0001
<1/day (ref)	3								
1–2/day		–0.47 ± 0.14	.001	0.00001 ± 0.002	.96	–0.38 ± 0.12	.002	–0.36 ± 0.12	.005
>2/day		–0.43 ± 0.19	.02	–0.004 ± 0.002	.11	–0.59 ± 0.12	.0004	–0.61 ± 0.17	.0004
Fruit Juice									
<1/day (ref)	1								
≥1/day		–0.53 ± 0.13	<.0001	–0.004 ± 0.002	.01	–0.41 ± 0.11	.0003	–0.39 ± 0.12	.001
<1/day (ref)	2								
≥1/day		–0.57 ± 0.13	<.0001	–0.004 ± 0.002	.03	–0.40 ± 0.12	.001	–0.40 ± 0.12	.001
<1/day (ref)	3								
≥1/day		–0.57 ± 0.13	<.0001	–0.004 ± 0.002	.02	–0.35 ± 0.12	.003	–0.34 ± 0.12	.006
Soft drink with sugar									
0/week (ref)	1								
>0–3/week		–0.37 ± 0.13	.01	–0.002 ± 0.002	.16	–0.02 ± 0.12	.84	–0.02 ± 0.12	.86
>3/week		–0.92 ± 0.19	<.0001	–0.003 ± 0.002	.27	–0.50 ± 0.16	.002	–0.32 ± 0.17	.06
0/week (ref)	2								
>0–3/week		–0.33 ± 0.14	.02	–0.002 ± 0.002	.22	–0.01 ± 0.12	.93	–0.01 ± 0.12	.91
>3/week		–0.82 ± 0.19	<.0001	–0.003 ± 0.002	.26	–0.44 ± 0.17	.01	–0.28 ± 0.17	.11
0/week (ref)	3								
>0–3/week		–0.03 ± 0.13	.82	–0.001 ± 0.002	.39	0.02 ± 0.12	.87	–0.004 ± 0.13	.97
>3/week		–0.23 ± 0.19	.24	–0.002 ± 0.002	.53	–0.44 ± 0.17	.01	–0.28 ± 0.18	.12

Abbreviations: AD, Alzheimer's disease; Ref, reference category; SE, standard error; CESD, Center for Epidemiologic Studies Depression Scale.

NOTE. Model 1 is adjusted for age, sex, time to outcome assessment, total caloric intake, as well as education (for neuropsychological outcomes) and age squared (for the MRI outcomes). Model 2 included additional adjustments for systolic BP, treatment for hypertension, current smoking status, history of cardiovascular disease, atrial fibrillation, left ventricular hypertrophy, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, CESD scores ≥16 and waist-to-hip ratio. Model 3 included the covariates outlined in model one plus intake of saturated fat, intake of trans-fat, intake of dietary fiber, and the physical activity index. Samples sizes for the largest statistical model are as follows: total sugary beverages, 2395, 1239, and 641 for <1/day, 1–2/day and >2 per day respectively; fruit juice, 2944 and 1330 for <1/day and ≥1/day; soft drink with sugar, 2326, 1359 and 588 for 0/week, 0–3/week, and >3/week, respectively.

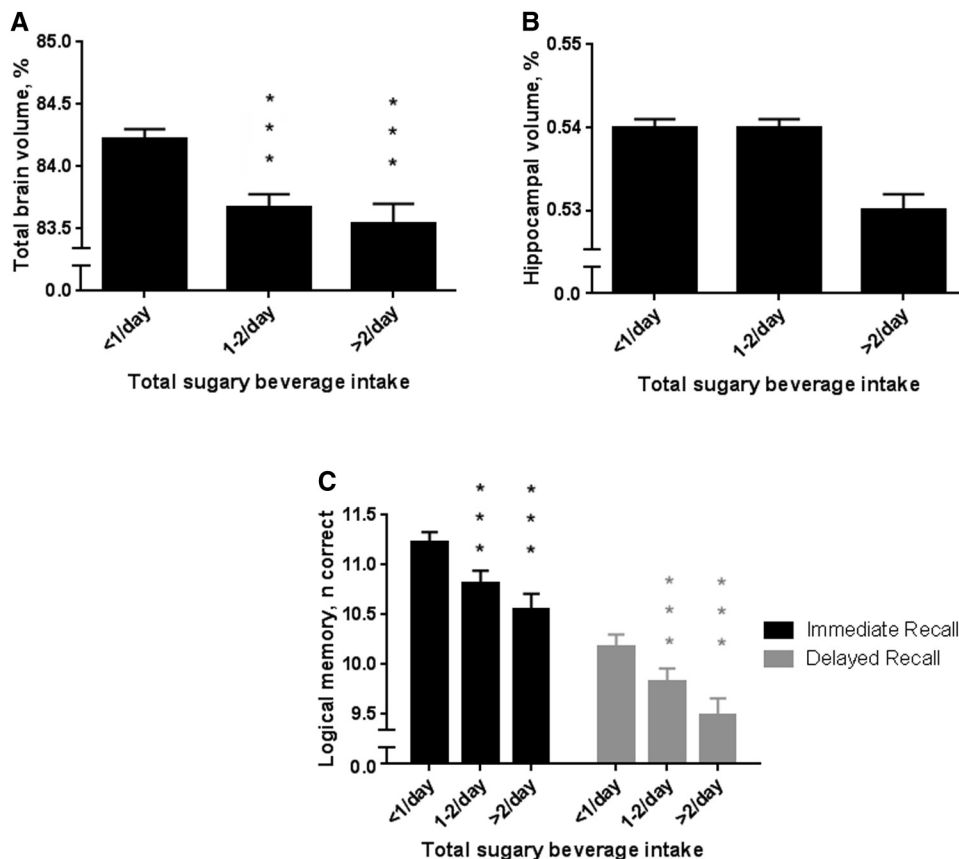


Fig. 2. Association between total sugary beverage consumption and (A) total brain volume, (B) hippocampal volume, and (C) Logical Memory. Bars and whiskers represent adjusted least square means and standard error. Means are adjusted for model 1 covariates. Intake of <1/day serves as the reference group. *** $P < .001$.

reduce levels of brain-derived neurotrophic factor (BDNF) [6,31], a molecular correlate of preserved synaptic integrity, and improved neuronal survival [32], leading to impaired memory performance and reduced synaptic plasticity within the hippocampus [6,31]. Our previous work demonstrated that each SD increment in BDNF was associated with a 33% lower risk of AD dementia [33], suggesting that BDNF may partly mediate the association between high fat refined sugar diets and AD pathology.

In humans, the emerging pattern of results is consistent with the aforementioned preclinical work. In a sample of 737 middle-aged community-dwelling participants without diabetes, the Boston Puerto Rican Health Study reported that higher total sugar intake was cross-sectionally associated with an AD-like pattern of poorer verbal memory and phonemic fluency, whereas domains of cognition typically associated with vascular cognitive impairment, such as executive function and attention, were spared [34]. In a sample of 141 adults, impaired glucose tolerance and chronically elevated blood glucose levels were linked to poor memory, with results partially mediated by changes in hippocampal volume and microstructure [35]. By combining MRI and neuropsychological outcomes in a large, dementia-free community-dwelling cohort, our results provide further evidence

that sugary beverage consumption is associated with markers of preclinical AD in humans. These findings are highly relevant given that AD is one of the largest growing disease burdens facing our aging population [36].

Excess consumption of sugar throughout the Western world has prompted action and debate from various Governments on how to lower sugar intake at the population level. In the United States, newly released dietary guidelines advise that adults should consume less than 10% of calories from added sugar [37]. In Britain, the Government recently announced a forthcoming sugar tax on soft drinks. According to the US National Nutrient Database, cola contains approximately 9 g of sugar/100 g, and unsweetened apple juice contains nearly 10 g of sugar/100 g [38]. Although soft drinks are not celebrated for their health benefits, fruit juices are often touted as a healthy alternative [39]. In one survey, the general public overestimated the sugar content of soft drinks but underestimated the sugar content of fruit juices by an average of 48% [40]. Even without added sugar, 100% fruit juice contains the fructose from multiple portions of fruit but with negligible fiber content. Worryingly, the average 100% fruit juice marketed to children contains more than a day recommended sugar allowance per 200 mL serving [39]. Our findings demonstrate that daily

Table 3
Sugary beverage intake and subclinical markers of vascular brain injury

Exposure	Model	WMHV, %		Silent brain infarcts, <i>n</i>		Similarities, <i>n</i> correct		Trail Making, B-A score		Visual Reproductions, <i>n</i> correct after delay	
		$\beta \pm SE$	<i>P</i>	OR (95% CI)	<i>P</i>	$\beta \pm SE$	<i>P</i>	$\beta \pm SE$	<i>P</i>	$\beta \pm SE$	<i>P</i>
Total sugary beverages											
<1/day (ref)	1										
1–2/day		0.03 ± 0.03	.32	1.18 (0.88, 1.59)	.53	−0.14 ± 0.11	.21	−0.0003 ± 0.01	.97	−0.11 ± 0.10	.27
>2/day		0.08 ± 0.04	.03	1.16 (0.78, 1.73)	.74	−0.17 ± 0.15	.25	−0.01 ± 0.01	.33	−0.10 ± 0.13	.45
<1/day (ref)	2										
1–2/day		0.02 ± 0.03	.41	1.19 (0.88, 1.83)	.57	−0.13 ± 0.11	.24	−0.005 ± 0.01	.52	−0.13 ± 0.10	.20
>2/day		0.09 ± 0.04	.03	1.22 (0.81, 1.83)	.61	−0.21 ± 0.15	.16	−0.01 ± 0.01	.36	−0.16 ± 0.13	.24
<1/day (ref)	3										
1–2/day		−0.03 ± 0.06	.56	1.18 (0.87, 1.59)	.46	−0.09 ± 0.11	.42	0.002 ± 0.01	.74	−0.10 ± 0.11	.33
>2/day		0.02 ± 0.07	.79	1.10 (0.72, 1.70)	.93	−0.002 ± 0.16	.99	−0.004 ± 0.01	.68	−0.04 ± 0.14	.76
Fruit juice											
<1/day (ref)	1										
≥1/day		0.04 ± 0.03	.22	1.10 (0.83, 1.45)	.52	−0.05 ± 0.11	.62	0.002 ± 0.01	.73	−0.06 ± 0.10	.51
<1/day (ref)	2										
≥1/day		0.04 ± 0.03	.18	1.12 (0.84, 1.50)	.44	−0.07 ± 0.11	.53	0.0001 ± 0.01	.99	−0.10 ± 0.10	.32
<1/day (ref)	3										
≥1/day		−0.02 ± 0.06	.66	1.09 (0.82, 1.45)	.57	0.01 ± 0.11	.90	0.006 ± 0.01	.39	−0.02 ± 0.10	.80
Soft drink with sugar											
0/week (ref)	1										
>0–3/week		0.001 ± 0.03	.96	1.40 (1.02, 1.92)	.04	−0.18 ± 0.11	.09	0.001 ± 0.01	.91	0.17 ± 0.10	.08
>3/week		0.12 ± 0.04	.003	1.04 (0.74, 1.47)	.44	−0.38 ± 0.15	.01	−0.01 ± 0.01	.21	−0.13 ± 0.14	.35
0/week (ref)	2										
>0–3/week		−0.01 ± 0.03	.81	1.36 (0.98, 1.89)	.05	−0.22 ± 0.11	.05	−0.001 ± 0.01	.88	0.14 ± 0.10	.16
>3/week		0.09 ± 0.04	.02	1.01 (0.70, 1.44)	.38	−0.41 ± 0.15	.01	−0.01 ± 0.01	.24	−0.16 ± 0.14	.25
0/week (ref)	3										
>0–3/week		−0.03 ± 0.05	.54	1.35 (0.98, 1.86)	.05	−0.12 ± 0.11	.26	0.004 ± 0.01	.57	0.19 ± 0.10	.06
>3/week		0.13 ± 0.08	.09	0.99 (0.69, 1.42)	.36	−0.30 ± 0.16	.06	−0.01 ± 0.01	.57	−0.09 ± 0.14	.54

Abbreviations: Ref, reference category; SE, standard error; WMHV, white-matter hyperintensity volume; CESD, Center for Epidemiologic Studies Depression Scale.

NOTE. Model 1 is adjusted for age, sex, time to outcome assessment, total caloric intake, as well as education (for neuropsychological outcomes) and age squared (for the MRI outcomes). Model 2 included additional adjustments for systolic BP, treatment for hypertension, current smoking status, history of cardiovascular disease, atrial fibrillation, left ventricular hypertrophy, total cholesterol, high-density lipoprotein cholesterol, diabetes mellitus, CESD scores ≥16, and waist-to-hip ratio. Model 3 included the covariates outlined in model 1 plus intake of saturated fat, intake of trans-fat, intake of dietary fiber, and the physical activity index. Samples sizes for the largest statistical model are as follows: total sugary beverages, 2395, 1239, and 641 for <1/day, 1–2/day, and >2 per day, respectively; fruit juice, 2944 and 1330 for <1/day and ≥1/day; soft drink with sugar, 2326, 1359, and 588 for 0/week, 0–3/week, and >3/week, respectively.

consumption of total sugary beverages and fruit juice were both linked to markers of preclinical AD. Diet soft drink was also associated with lower total brain volume. However, it is unclear whether the association between diet soft drinks and brain volume is mediated by concomitant higher intake of sugary beverages either at present or in the past.

The main strength of our study was the use of a large and well-characterized community-based sample free of clinical stroke and dementia. Limitations of our study include the observational and cross-sectional nature of the study, which precludes conclusions about causality and the temporal associations between sugary beverage intake, brain atrophy, and cognitive decline. Second, ethnic minorities were not well represented in our sample, limiting the generalizability of our results to nonwhite populations. Third, sugary beverage intake was quantified using a self-report FFQ, which may be subject to recall bias. However, sugary beverage intake estimated using our FFQ has been validated previously against dietary records [14,15]. Our FFQ also did not differentiate between fruit juice with and without added sugar, although both contain high amounts of fructose. Regarding the outcomes evaluated, we did not implement positron emission tomography to characterize the burden of A β and tau pathology in the brain, which would help further clarify the association between sugary beverage intake and AD pathology. Finally, we did not adjust for multiple statistical testing, and we cannot rule out the possibility that some of the findings are due to chance.

In our cross-sectional observations in a large community-based sample, higher sugary beverage intake was associated with markers of preclinical AD, including brain atrophy and poorer episodic memory. Greater intake of total sugary beverages, fruit juice, and soft drinks were all associated with characteristics of preclinical AD. Additional studies are warranted to confirm our findings and evaluate if sugary beverages are associated longitudinally with worsening of subclinical AD measures and with incident AD.

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Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jalz.2017.01.024>.

RESEARCH IN CONTEXT

1. Systematic review: We searched for relevant literature using online databases such as SCOPUS and PubMed. Although studies have investigated the associations of sugary beverage intake with cardiometabolic disease and stroke, the association of sugary beverage with subclinical brain injury and dementia remains little examined in humans.
2. Interpretation: Our findings indicate an association between higher sugary beverage intake and markers of preclinical Alzheimer's disease, including lower brain volume and poorer memory.
3. Future directions: Prospective studies are needed to examine whether higher intake of sugary beverages leads to the progression of Alzheimer's disease pathology and incident dementia.

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