Sugary beverage intake and genetic risk of dementia in relation to incident dementia and brain structure: evidence from the UK Biobank

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Abstract

Importance: Sugary beverage intake was associated with higher risk of dementia, but the specific amounts and types related to it and its interactions with genetic predisposition to dementia remained poorly understood.

Objective: To investigate the relation of sugary beverage intake and genetic preposition to the long-term risk of dementia and brain structure.

Design, Setting, and Participants: We leveraged data of 187,994 UK Biobank participants without dementia at baseline and followed them until March 2021.

Exposures: Intake of sugary beverages (SBs, one unit=250 ml), including sugar-sweetened beverages (SSB), artificially-sweetened beverages (ASB), and natural sweet juices (NSJ), was assessed using repeated web-based 24-h dietary recall from 2009 to 2012. A polygenic risk score (PRS) was calculated to capture each participant's load of common genetic variants related to the risk of dementia.

Main Outcomes and Measures: Incident dementia was identified through hospital admissions and death registries. Brain magnetic resonance imaging was conducted in a subgroup of 12,566 participants in 2014.

Results: During a total of 1,790,996 person-years of follow up, 1,351 incident dementia cases were identified. Higher intake of SSB and ASB (>2 units/d v. none) was independently associated with a substantially increased risk of dementia (p-trend=0.013 for SSB, and <0.001 for ASB). The corresponding multivariable-adjusted hazard ratio [HR] and 95% confidence intervals [CI] were 1.47 (1.13~1.92), and 1.41 (1.00~1.99), respectively. The significant association of ASB was observed among ASB consumptions regardless of the intake level. In contrast, moderate intake of NSJ (0~1 unit/d v. none) was related to a decreased risk of dementia (HR=0.80, 0.71~0.90) and a larger volume of brain grey matter (beta=0.03, 0.01~0.06) and a lower volume of white matter hyperintensities (beta=-0.08, -0.13~-0.02). Moreover, the genetic risks were significantly magnified by higher intake of SSB and ASB, and was instead attenuated by moderate intake of NSJ (*P*-interaction<0.002).

Conclusions and Relevance: Higher intake of SSB and ASB was associated with higher risk of dementia, especially among individuals at high genetic risk for dementia. Inversely, moderate NSJ intake was associated with a reduced risk of dementia, possibly through the beneficial role maintaining brain grey matter volume and reducing white matter hyperintensities.

Key Points

Question: How are sugary beverage intake and genetic risk relate to dementia incidence and brain structure?

Findings: Among 187,994 participants, higher intake of sugar-sweetened beverage and artificially-sweetened beverage was associated with a higher risk of dementia, especially among individuals with a higher genetic predisposition. Inversely, moderate intake of natural sweet juice was associated with a reduced risk, possibly through the beneficial role in maintaining brain grey matter volume and reducing white matter hyperintensities.

Meaning: The findings support a potential detrimental role of SSB and ASB and a beneficial role of a moderate level of NSJ in preventing dementia.

Introduction

Dementia, a major type of neurodegenerative disease, poses great burdens on the well-being and economic cost of caring for older people worldwide as lifespan continues to increase[1–3]. Considering its limited therapy, it is thus crucial to identify the risk factors, especially modifiable ones, of dementia for prevention measures. Recent population-based studies[4–6] supported that dietary habits are associated with dementia risk in late life. Among multiple dietary factors identified, sugary beverages (SBs) intake is widely recognized worldwide as a driver of poor cardiometabolic health[7–9], with uncertain relation to neurological health.

Prior findings[10,11], although scarce in well-designed cohort settings, generated a plethora of discourse on whether SB is a risk factors for dementia. A prospective study[10] of 1,484 adults found that artificially-sweetened beverage (ASB) intake (> 0 serving/week vs. none), but not sugar-sweetened beverage (SSB) intake, was associated with a 98%-159% increased risk of dementia. Another cross-sectional study[11] suggested that sugary beverages, including fruit juice, are associated with lower brain volume and poorer cognitive performance. However, evidence was conflicting, with other studies finding that fruit intake and fruit juice intake was inversely associated with poor cognitive function [12,13] and dementia[14,15]. Hence, we investigated the long-term association of sugary beverages, including SSB, ASB, and naturally sweet juices (NSJ), with incident dementia and brain structural markers in UK Biobank, a large population-based prospective study in the UK.

Methods

Study population

This study was based on the UK Biobank (UKB), a population-based cohort study in the UK with deep genetic and phenotypic data collected[16]. Commenced in 2006, UKB recruited over 500,000 UK residents aged over 40 at 22 assessment centers, as described in more detail elsewhere on the UK Biobank website (http://www.ukbiobank.ac.uk/resources/). Ethical approval was granted by the North West-Haydock Research Ethics Committee (REC reference: 16/NW/0274).

We included 187,994 participants in the UKB (**Figure S1**) who: 1) finished the Oxford WebQ, a web-based 24-h dietary assessment tool, at least once; and 2) did not exit the program until March 2021. To minimize measurement error, we excluded non-typical diet records and records with extreme energy intake (> 20MJ/d) [17]. To reduce reverse causation, we excluded participants who developed dementia within the two years subsequent to dietaryassessment.

Sugary beverage intake

Repeated web-based 24h diet recall questionnaires (Oxford WebQ) were introduced to the assessment, with invitations being emailed to participants every 3–4 month (mean repetition = 1.93). Participants recalled how

much SBs they consumed in questionaires that have been validated using biomarkers [18] and by interviewer-administered 24 h recalls[19] and showed good reproducibility[20]. In this study, SBs consisted of sugar-sweetened beverage (SSB, i.e. fizzy drinks and squash), artificially-sweetened beverage (ASB, such as diet fizzy), and naturally sweet juices (NSJ, consisting of fruit and vegetable juices). The intake level of them were comparable with national data in UK[21]. We categorized daily intake of these beverages into 4 groups: 0, 0 ~ 1 (> 0 but < = 1) unit/d, 1 ~ 2 (> 1 but < = 2) units/d, or > 2.0 units/d, in which a unit refers to one glass/can/carton or 250 mL of the beverages, and their correlation was presented in **Table S2**.

Dementia and its subtypes

Dementia cases in the UK Biobank were linked to hospital admissions and death registries. We identified Alzheimer's Dementia (AD), and vascular dementia (VD), and other types or undefined dementia from International Classification of Diseases (ICD) codes of hospital inpatient admission data (**Table S1**). In this study, health conditions were updated in the linkage to the healthcare system to March 2021.

Brain structure

Brain structure data in the UK Biobank sample were obtained from magnetic resonance imaging (MRI) since 2014[22]. Our study used imaging-derived phenotypes generated by an image-processing pipeline developed and ran on behalf of UKB. In this study, the volumes (in mm^3) of the whole brain, white matter, grey matter were derived from T1 structural brain MRI, and the volume of white matter hyperintensities (WMHs) was derived from T2-weighted brain MRI. The external surface of the skull was estimated from the T1 and used to normalize brain tissue volumes for head size. Head-size adjusted brain volumes were added correspondingly (left and right sides) and then z-standardized. For WMH, the volume was transformed by taking the logarithm before z-standardized because of its skewed distribution.

Polygenic Risk Score

A polygenic risk score (PRS) capturing each participant's load of common genetic variants related to the risk of Alzheimer's disease and dementia was constructed in the UK Biobank sample[23], with details being described in a previous study[4]. Briefly, the analysis was constrained to participants with white backgrounds. Single-nucleotide polymorphisms (SNPs) were selected using "clumped" results so that the remaining SNPs were the most significant variant per linkage disequilibrium block, common, and available in the UK Biobank. The threshold of inclusion for a *P*-value was < 0.5. The number of associated alleles at each SNP was weighted according to the regression coefficient with AD in the discovery stage of GWAS results, summed, z-standardized, and then divided into tertiles.

Covariates

Demographic characteristics, including age, sex defined by self-reported identity, race, education level, and Townsend deprivation index (indicating the social deprivation status), and lifestyle factors, including smoking status, body mass index (BMI), alcohol drinking status, and physical activity levels, were collected at baseline. Bodyweight status of participants was categorized into underweight (BMI < = 20.0 kg/m^2), normal weight (BMI > 20.0 but < = 25.0 kg/m^2), or overweight (BMI > 25.0 kg/m^2). Alternative healthy eating index (AHEI) excluding sugary beverage component was calculated as suggested by a previous study [17].

Statistical analyses

Participants' baseline characteristics were presented by their SB intake. Continuous variables were displayed as means (standard deviations, SDs), and categorical variables were shown as numbers (percentages). Cox proportional hazard models were used to estimate the hazard ratios (HRs) and confidence intervals (CIs) for SBs intake and incident dementia, with person-years being calculated from date of the first 24-h diet recall report to the diagnosis of dementia, the ascertainment of death, or loss to follow-up, whichever came first. Missing values were imputed to median or class with the most participants. Proportional hazard assumption was tested by entering an exposure-time interaction term in the model. The HR were adjusted for age, age-square and sex in model 1. Model 2 was additionally adjusted for Townsend deprivation index (low, medium, or high deprivation), education (college or above, or high school or below), physical activity (low, medium, high), smoking (ever smoked or not), alcohol intake (currently drinking or not), total energy intake, and alternative healthy eating index (AHEI) excluding sugary beverage component. Bodyweight status categories (underweight, normal weight, or overweight) were further adjusted for in model 3. Penalized splines were used to explore the potential non-linearity, with maximal Akaike information criterion (AIC) being used to choose an optimal degree of freedom[24]. We tested the mediation effect of incident diabetes using "mediation" package[25] and reported the quasi-Bayesian estimates.

In the secondary analysis, we investigated the association of SBs with AD and VD using model 3 mentioned above. To explore the joint association of polygenic risk and SBs with dementia, we categorized participants into 12 groups by crossing 3 PRS quantiles and four intake levels for each type. Specifying the non-intakers with low PRS as the reference group, we estimated the HRs using model 3 mentioned above and further adjusted the association for 20 principal components of population structure, number of risk bases, and kinship. To explore potential effect modifications by major covariates, we conducted subgroup analyses stratified by multiple factors, including age, sex, educational levels, PRS, etc. *P* for interactions between these covariates and SBs were calculated by entering a multiplication term in model 3.

In assessing the relation of SBs to the brain structure, since total and regional brain volume was only available for participants undergoing image assessment, we used data of a subgroup of participants (N = 12,566) for analyses. Linear regression was used to estimate the beta coefficients of SBs with brain volume measurements, with the differences in z-score being presented.

To assess the robustness of our findings, we conduct several sensitivity analyses in several steps: 1) adding baseline comorbidities (cancer, cardiovascular diseases, hypertension, and diabetes), which may lie within the causal pathway of SBs and dementia, in the models; 2) mutually adjust the models for three types of sugary beverages; 3) further adjust the relation for total sugar intake; and 4) assess the association of SBs with brain structure restricted to participants aged over 60 years at baseline.

Statistical analyses were performed using R 3.6.0, and two-sided *P*-values below 0.05 were considered statistically significant.

Results

Participant Characteristics

Of the 187,994 dementia-free participants, the mean (SD) age at baseline was 56.2 (7.9). Among them, 44.9 % were female, and 96.4 % were White/Caucasian (Table 1 **& Table S3**). During the follow-up period (mean = 9.5 y), a total of 1,351 (0.72 %) dementia cases were reported. Participants who consumed more SSB were more likely to be female, younger, and had higher income.

Table 1
Baseline characteristics of participants according to sugar-sweetened beverage intake (N = 187,994)

	Overall	By sugar-sweetened beverage categories				
		None	0 ~ 1 unit/d	1 ~ 2 unit/d	> 2 unit/d	P-value
n	187994	132710	6959	35146	13179	
Female (%)	84499 (44.9)	57371 (43.2)	3950 (56.8)	16372 (46.6)	6806 (51.6)	< 0.001
White ethnicity (%)	181155 (96.4)	128379 (96.7)	6595 (94.8)	33623 (95.7)	12558 (95.3)	< 0.001
Age at baseline (mean (SD))	56.2 (7.9)	56.5 (7.8)	53.5 (8.1)	56.1 (8.0)	54.8 (8.2)	< 0.001
Total Energy, kJ (mean (SD))	8664.9 (2460.2)	8471.7 (2436.1)	9782.8 (2587.8)	8920.6 (2406.6)	9338.9 (2435.5)	< 0.001
Townsend deprivation index (%)						
High	62582 (33.3)	43856 (33.0)	2651 (38.1)	11498 (32.7)	4577 (34.7)	< 0.001
Medium	62779 (33.4)	44316 (33.4)	2270 (32.6)	11846 (33.7)	4347 (33.0)	
Low	62633 (33.3)	44538 (33.6)	2038 (29.3)	11802 (33.6)	4255 (32.3)	
Highest education (%)						
Below high school	108674 (57.8)	75433 (56.8)	4435 (63.7)	20849 (59.3)	7957 (60.4)	< 0.001
College or above	79320 (42.2)	57277 (43.2)	2524 (36.3)	14297 (40.7)	5222 (39.6)	
Physical activity (%)						
High	63005 (33.5)	44349 (33.4)	2498 (35.9)	11623 (33.1)	4535 (34.4)	< 0.001
Medium	95997 (51.1)	68055 (51.3)	3254 (46.8)	18041 (51.3)	6647 (50.4)	
Low	28992 (15.4)	20306 (15.3)	1207 (17.3)	5482 (15.6)	1997 (15.2)	
Ever smoked (%)	80949 (43.1)	58092 (43.8)	3071 (44.1)	14406 (41.0)	5380 (40.8)	< 0.001

SD, standard deviation; AHEI, Alternative Heathy Eating Index (with sugary beverages being excluded)

[a] Body weight status was defined by BMI (< = 20 kg/m2 to be underweight, > 20 and < = 25 to be normal weight, > 25 to be overweight)

	Overall	By sugar-sweetened beverage categories				
		None	0 ~ 1 unit/d	1 ~ 2 unit/d	> 2 unit/d	P-value
Current alcohol drinker (%)	175793 (93.5)	124816 (94.1)	6253 (89.9)	32581 (92.7)	12143 (92.1)	< 0.001
Body weight status[a] (%)						
Underweight	5049 (2.7)	3806 (2.9)	126 (1.8)	842 (2.4)	275 (2.1)	< 0.001
Normal weight	65496 (34.8)	47392 (35.7)	1869 (26.9)	12018 (34.2)	4217 (32.0)	
Overweight	117449 (62.5)	81512 (61.4)	4964 (71.3)	22286 (63.4)	8687 (65.9)	
AHEI (mean (SD))	24.4 (11.4)	25.1 (11.4)	21.9 (11.4)	23.2 (11.3)	22.4 (11.2)	< 0.001
Hypertension (%)	45912 (24.4)	32175 (24.2)	1848 (26.6)	8579 (24.4)	3310 (25.1)	< 0.001
Heart diseases (%)	8092 (4.3)	5601 (4.2)	338 (4.9)	1593 (4.5)	560 (4.2)	0.008
Cancer (%)	14094 (7.5)	10129 (7.6)	473 (6.8)	2545 (7.2)	947 (7.2)	0.004
Diabetes (%)	7572 (4.0)	5564 (4.2)	303 (4.4)	1204 (3.4)	501 (3.8)	< 0.001

SD, standard deviation; AHEI, Alternative Heathy Eating Index (with sugary beverages being excluded)

[a] Body weight status was defined by BMI (< = 20 kg/m2 to be underweight, > 20 and < = 25 to be normal weight, > 25 to be overweight)

Sugary beverages and incident dementia

All three types of SBs were associated with the incident dementia (Table 2). Participants reporting to be consuming > 2 units/d of SSB were at higher dementia risk (HR = 1.47; 95% CI, 1.13 ~ 1.92) compared to those who did not drink any, partially mediated by type 2 diabetes (proportion = 1.81%, *P*-mediation = 0.02). ASB intake was also associated with a dementia risk, with its intake of 0 ~ 1 unit/d being associated with 1.21-fold hazard (95%CI, 1.03–1.43), intake of 1 ~ 2 units/d with 1.50-fold odds (95%CI, 1.19 ~ 1.90), and the HR for intake over 2 units/d being 1.41 (95%CI, 1.00 ~ 1.99). On the contrary, participants with moderate NSJ intake (0 ~ 1 unit/d) were at a decreased risk (HR = 0.80; 95%CI, 0.71 ~ 0.90) compared with non-drinkers. We did not observe a significantly higher risk for participants who consumed NSJ more than 1 unit per day. No mediation effect of type 2 diabetes was detected for ASB or NSJ. When merging all three types of beverages into one (**Table S4**), we found that higher total sugary beverage intake was associated with an elevated dementia risk (HR = 1.25; 95%CI, 1.06 ~ 1.46).

Table 2
Hazard ratios (HRs) for sugary beverages intake and incident dementia (N = 187,994)

	Events	Person-Years	Model 1[a]		Model 2[b]		Model 3[c]	
			HR [95% CI]	P-value	HR [95% CI]	P-value	HR [95% CI]	P-value
Sugar-sweetened beverage								
None	947	1262675	Ref		Ref		Ref	
0 ~ 1 unit/d	254	335689	1.00 [0.88, 1.15]	0.962	0.98 [0.86, 1.13]	0.800	0.99 [0.86, 1.13]	0.836
1 ~ 2 unit/d	94	126221	1.21 [0.98, 1.48]	0.071	1.16 [0.94, 1.42]	0.165	1.16 [0.95, 1.43]	0.149
> 2 unit/d	56	66412	1.59 [1.22, 2.06]	< 0.001	1.45 [1.12, 1.89]	0.005	1.47 [1.13, 1.92]	0.004
Artificially-sweetened beverage								
None	1088	1448058	Ref		Ref		Ref	
0 ~ 1 unit/d	158	208717	1.22 [1.04, 1.44]	0.017	1.19 [1.01, 1.40]	0.035	1.21 [1.03, 1.43]	0.020
1 ~ 2 unit/d	73	87222	1.53 [1.21, 1.93]	< 0.001	1.47 [1.16, 1.86]	0.001	1.50 [1.19, 1.90]	0.001
> 2 unit/d	32	47000	1.48 [1.05, 2.09]	0.024	1.37 [0.97, 1.93]	0.071	1.41 [1.00, 1.99]	0.050
Naturally sweet juices								
None	709	904274	Ref		Ref		Ref	
0 ~ 1 unit/d	467	669844	0.78 [0.69, 0.87]	< 0.001	0.80 [0.72, 0.90]	< 0.001	0.80 [0.71, 0.90]	< 0.001
1 ~ 2 unit/d	131	169407	0.90 [0.75, 1.08]	0.240	0.92 [0.76, 1.11]	0.374	0.92 [0.76, 1.11]	0.370
> 2 unit/d	44	47472	1.17 [0.87, 1.58]	0.298	1.16 [0.86, 1.57]	0.338	1.16 [0.85, 1.57]	0.344

HR, hazard ratio; CI, confidence interval

[a] Model 1 was adjusted for age, age-square, and sex.

[b] Model 2 was additionally adjusted for Townsend deprivation index, education level, physical activity, smoking, alcohol intake, total energy intake, and alternative healthy eating index (AHEI) excluding sugary beverages.

[c] Model 3 was further adjusted for body weight status.

We used penalized splines to estimate the potential non-linear associations (Fig. 1), we found that SSB and ASB were linearly associated with higher incident dementia risk (*P*-nonlinearity = 0.09 for SSB, and 0.17 for ASB). Also, daily sugar intake over 100 g was associated with a higher dementia risk. We found a non-linear J-shaped curve (*P*-nonlinearity < 0.001) for NSJ, with the trough of HR being observed at approximately 1 unit/d.

When taking polygenic risk score (PRS) into account, the corresonidng associations were significantly altered by genetic risk of dementia (*P*-interaction = 0.0016 for SSB and PRS, 0.0013 for ASB and PRS, and 0.0010 for NSJ and PRS), with stronger associations of all three types of SBs being observed among individuals with medium and higher genetic risk (**Figure S2**). Viewed differently, the genetic risks were significantly magnified by higher intake of SSB (HR = 1.70; 95%CI: 1.05 ~ 2.75 for > 2 unit/d and high PRS) and ASB (HR = 2.16; 95%CI: 1.24 ~ 3.77 for > 2 unit/d and high PRS), and was instead attenuated by moderate intake of NSJ (Fig. 2).

We conducted additional analyses on the association of SBs with Alzheimer's disease and vascular dementia, two major subtypes of dementia (**Table S5**). Higher intake of ASB was associated with higher risks of both Alzheimer's disease (HR = 1.82; 95% CI, 1.00 ~ 3.34) and vascular dementia (HR = 1.90; 95% CI, 0.77 ~ 4.68), whereas higher SSB intake was only significantly associated with risk of Alzheimer's disease (HR = 2.02; 95% CI, 1.27 ~ 3.19). The significant association of moderate intake of NSJ was also only observed for Alzheimer's disease (HR = 0.65; 95% CI, 0.43, 0.97).

Sugary beverages and brain structure

The associations of SBs with brain structure measurements were shown in Table 3. Adjusted for multiple potential sociodemographic, lifestyle, total energy and dietary confounders, higher SSB consumption was related to marginally smaller volume of whole-hippocampus ($beta_{1 \sim 2\ unit/d}$=-0.08; 95% CI, -0.14~-0.01) and grey matter in hippocampus ($beta_{>2\ unit/d}$=-0.07; 95% CI, -0.15 ~ 0.01). Higher ASB consumption was related to larger volume of white matter hyperintensities ($beta_{>2\ unit/d}$=0.06; 95% CI, -0.03 ~ 0.16). Moderate NSJ intake was associated with larger volume of grey matter ($beta_{1 \sim 2\ unit/d}$=0.06; 95% CI, 0.02 ~ 0.11) and smaller volume of white matter hyperintensities ($beta_{1 \sim 2\ unit/d}$=-0.08; 95% CI, -0.13~-0.02). The results were similar among participants over 60 (**Table S6**).

Table 3

Association[a] of sugary beverages intake with brain structure (N = 12,566)

	N	Difference in z-score[b] [95% confidence interval]					
		Total brain volume	Volume of white matter	Volume of grey matter	Volume of white matter hyperintensities	Volume of Whole-hippocampus	Volume of grey matter in Hippocampus
Sugar-sweetened beverage							
None	8685	ref					
0 ~ 1 unit/d	2440	0.01 [-0.03, 0.05]	-0.00 [-0.05, 0.04]	0.02 [-0.02, 0.05]	0.03 [-0.01, 0.07]	-0.02 [-0.06, 0.02]	-0.01 [-0.06, 0.03]
1 ~ 2 unit/d	963	0.03 [-0.02, 0.09]	0.03 [-0.03, 0.10]	0.02 [-0.03, 0.07]	-0.01 [-0.07, 0.05]	-0.08 [-0.14, -0.01]	-0.04 [-0.10, 0.02]
> 2 unit/d	478	-0.02 [-0.10, 0.06]	-0.02 [-0.11, 0.07]	-0.02 [-0.09, 0.05]	-0.01 [-0.09, 0.08]	-0.02 [-0.11, 0.07]	-0.07 [-0.15, 0.01]
Artificially-sweetened beverage							
None	10098	ref					
0 ~ 1 unit/d	1480	0.01 [-0.04, 0.06]	0.04 [-0.02, 0.09]	-0.02 [-0.06, 0.03]	0.01 [-0.04, 0.06]	0.01 [-0.04, 0.07]	0.02 [-0.03, 0.06]
1 ~ 2 unit/d	649	-0.03 [-0.10, 0.04]	0.01 [-0.07, 0.08]	-0.05 [-0.11, 0.01]	0.06 [-0.01, 0.13]	-0.02 [-0.09, 0.06]	-0.02 [-0.09, 0.05]
> 2 unit/d	339	0.01 [-0.08, 0.10]	0.07 [-0.04, 0.17]	-0.04 [-0.13, 0.04]	0.06 [-0.03, 0.16]	0.07 [-0.04, 0.17]	0.04 [-0.05, 0.14]
Natural sweet juice							
None	5999	ref					

[a] Beta coefficients calculated by linear regression models adjusted for age, age-square, sex, Townsend deprivation index, education level, physical activity, smoking, alcohol intake, total energy intake, alternative healthy eating index (AHEI) excluding sugary beverages, and body weight status.

[b] Volume of white matter hyperintensities was log-transformed. All measures were then scaled to z-score.

	N	Difference in z-score[b] [95% confidence interval]					
		Total brain volume	Volume of white matter	Volume of grey matter	Volume of white matter hyperintensities	Volume of Whole-hippocampus	Volume of grey matter in Hippocampus
0 ~ 1 unit/d	5016	0.01 [-0.02, 0.05]	-0.01 [-0.05, 0.02]	0.03 [0.01, 0.06]	-0.03 [-0.06, 0.01]	-0.02 [-0.06, 0.01]	-0.01 [-0.05, 0.02]
1 ~ 2 unit/d	1229	0.02 [-0.03, 0.08]	-0.03 [-0.09, 0.03]	0.06 [0.02, 0.11]	-0.08 [-0.13, -0.02]	-0.02 [-0.08, 0.04]	-0.03 [-0.09, 0.03]
> 2 unit/d	322	0.02 [-0.08, 0.11]	0.03 [-0.08, 0.14]	-0.00 [-0.09, 0.08]	0.05 [-0.05, 0.15]	0.06 [-0.05, 0.16]	-0.07 [-0.17, 0.03]

[a] Beta coefficients calculated by linear regression models adjusted for age, age-square, sex, Townsend deprivation index, education level, physical activity, smoking, alcohol intake, total energy intake, alternative healthy eating index (AHEI) excluding sugary beverages, and body weight status.

[b] Volume of white matter hyperintensities was log-transformed. All measures were then scaled to z-score.

Subgroup and sensitivity analyses

Generally, the primary findings were consistently observed across major subgroups of participants stratified by age, sex, Townsend deprivation index, education level, smoking status, alcohol drinking, and BMI categories (**Table S7**). ASB consumption was less associated with dementia in participants with low deprivation level (*P*-interaction < 0.001). The association of SSB and NSJ with dementia was consistent among all subgroups (*P*-interaction > 0.05 in all tests). In the sensitivity analyses (**Table S8**) the association of SBs with dementia remained similar.

Discussion

In this prospective study of adults in the UK, higher SSB (> 2 unit/day) and ASB (> 0 unit/day) intake were associated with higher dementia risk, while consuming moderate NSJ (0–1 unit/day) was associated with a lower risk and lower level of suboptimal brain structural markers. These associations were similar across major subgroups but was significantly altered by genetic risk of dementia. In aggregate, the findings of this study underscored the detrimental role of SSB and ASB and the potential beneficial role of moderate intake of NSJ in the prevention of dementia.

To our knowledge, this study is one of the few to explore the relation of type-specific SBs with dementia. Looking at prior findings, among 2,888 participants aged over 60 years[10], researchers discovered that higher consumption of ASB is associated with a higher risk of Alzheimer's disease during 9.5 years of follow-up. The estimated HR was 2.89 (95% CI, 1.18 ~ 7.07) for Alzheimer's disease, while SSB was not significantly related. Another study conducted among 1,865 participants in Framingham Heart Study[26] added that consuming sugar from beverages over 7 servings/week was associated with a substantially higher risk of all-cause dementia (HR = 2.80, 95%CI, 2.24 ~ 3.50). Our study, using data of a well-administered population-based cohort, provided further and strong evidence on brain structure to support the hypothesis that ASB intake as well as SSB intake was associated with a higher risk of dementia, although both HRs were not as high as in previous findings.

In our research on NSJ, which have been consumed as an substitute for SSB [27], moderate intake of it was associated with decreased risk of dementia, which was in concordance with several previous studies. For example, in a prospective study of 1,836 Japanese Americans, drinking juices > = 3 times/week were related to a substantially reduced risk of Alzheimer's disease[28]. Other short-term interventional studies also presented similar results that juice intake was associated with slowed cognitive decline and lowered risk of cognitive impairment[29,30]. In another prior study among men in US, fruit juice intake was related with subjective cognitive decline in a dose-response manner from 0 to 1serving/d [12]. Our study extended that while moderate intake of 0 ~ 1 units/d was associated with lower dementia risk, participant taking NSJ > 2 units/d was approximately at an as high dementia risk as those who did not drink any. Given that excessive fruit juice intake could be associated with higher diabetes risk[31] or other co-morbidity, there awaits further investigation to define the optimal level.

Although the biological pathway of the relation between SBs and dementia was not fully understood, several possible mechanisms could shed light on the results. For SSB, excessive sugar intake might induce a rapid rise in blood glucose and insulin[32], thus causing brain dysfunction[33]. For ASB, aspartame could be linked to

energy production disruption and increased oxidative stress[34], and thus contributed to a higher risk of dementia[35] Also, the phenylalanine in aspartame could directly affect the synthesis of inhibitory monoamine neurotransmitters and induce neural degeneration[36]. Therefore, its neurological harm may outweigh benefits from reduced caloric intake. Conversely, rich contents of vitamins[37–39], minerals[40], carotenoids[41–43], and flavornoids[44] in NSJ may have advantaged the effects of excessive sugar and thus protected brain health. And oxidative damage caused by the β-amyloid peptide in the pathogenesis of dementia may be hydrogen peroxide mediated[45].

Findings in the present study were of timely social and public health significance. For SSB which has long been considered as an excessive energy source, our findings provided evidence of it being a risk factor of dementia. While the food administration department in some western countries has advocated sugar reduction[46], the risk of excessive added sugar intake remained inadequately noticed by more developing countries. In the meantime, the widely used artificial sweetener aspartame as a substitution for sugar was quite controversial. Although aspartame has been suggested to be related to neural dysfunction[39] through abnormal blood glucose level and direct neurological effect, epidemiological evidence remained very scarce in the past. Our findings suggested that the chronic safety of aspartame needs to be reassessed. For NSJ recommended as a potential healthy beverage alternative, our results also suggest that excessive intake may not play a protective role. Therefore, it is necessary to emphasize a moderate quantity when recommending fruit and vegetable juice intake.

The present study has several strengths. First, the large sample size and relatively long-term follow-up enabled us to explore a comprehensive relation between sugary beverages and dementia incidence. To the best of our knowledge, our research is one of the largest of its kind, and the population-based design with high representativity ensured the generalizability of the results in the UK. The availability of genetic data and brain images in the database also allowed in-depth analyses. Secondly, linkage to registered healthcare records, low rate of loss to follow-up, less affected by selection bias. Insufficient reliability of results due to underestimation of dementia cases in other studies is theoretically avoided in this study. Third, the availability of multiple covariates and careful control in regression models minimized potential confounding effects.

Limitations

This study has several limitations. First, 24h diet recall was poor at representing a long-term dietary habit. Although using repeated daily records over 2 years, the measurement error was attenuated[18,19], and the intake levels in this study were comparable with the national data of UK[21], there warrants further investigation using dietary assessments that could better represent a long-term status, such as food frequency questionaire. Secondly, a relatively young age at baseline meant that a large proportion of participants had yet reached an age of prevalent dementia, although subgroup analyses among participants with a baseline age over 60 did demonstrate similar results as that of the whole population. And because the participants undergoing MRI may be healthier and more tolerant to sugar or aspartame than the general population, our results on brain structure need to be further verified. Third, milder dementia cases were likely to be underreported when patients did not acquire medical assistance, considering only participants' registration data was used to define dementia cases in this study. Moreover, our results may still be subjective to reverse causality, although we

have excluded the dementia incidences within the two years after dietary assessment. Due to the long-term development of dementia, early cognitive decline may precede dietary changes, and there awaits further research to confirm these associations and help explain the underlying mechanisms.

Conclusions

The present study discovered that higher SSB and ASB intake were associated with higher dementia risk, while moderate intake of NSJ was associated with a lower risk. These associations were similar across major subgroups defined by sociodemographic features but could be altered by genetic predisposition. Our observational findings provided evidence for revised thinking in the balance of reducing the consumption of sugar and artificially-sweetener.

Declarations

Declarations of interest: None

Author contributions: HC, JC and CY designed the study; HC performed the statistical analyses; JC, YC, and JS provided statistical support; JC and YS helped visualize the results and interpreted the data; HC drafted and JC, JJ, and LH revised the manuscript; CY supervised the data analysis and interpretation; CY had the primary responsibility for the final content. All authors critically reviewed the manuscript and approved the final draft.

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Figures

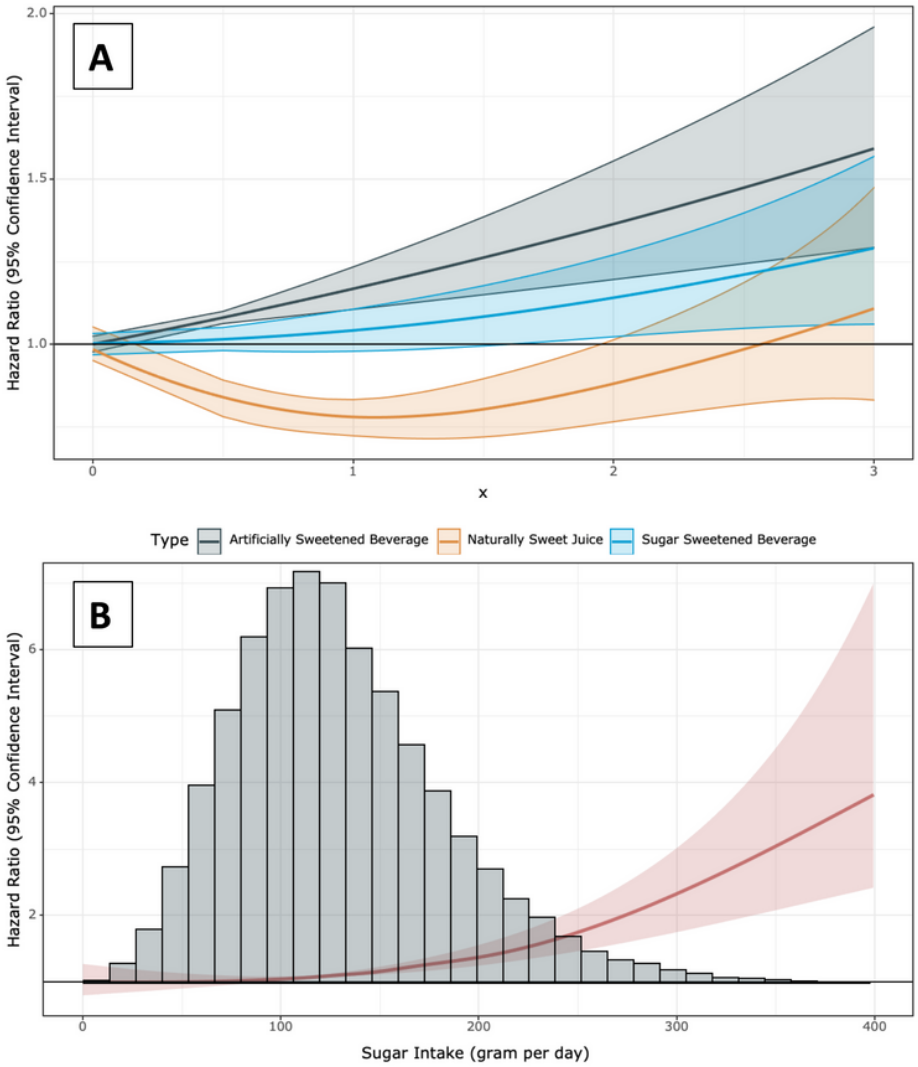

Figure 1

Curvesa for the association of sugary beverages intake and total sugar intake with risk of incident dementia (N=187,994). a Penalized splines of hazard ratio adjusted for Townsend deprivation index, education level, physical activity, smoking, alcohol intake, total energy intake, alternative healthy eating index (AHEI) excluding sugary beverages, and body weight status.

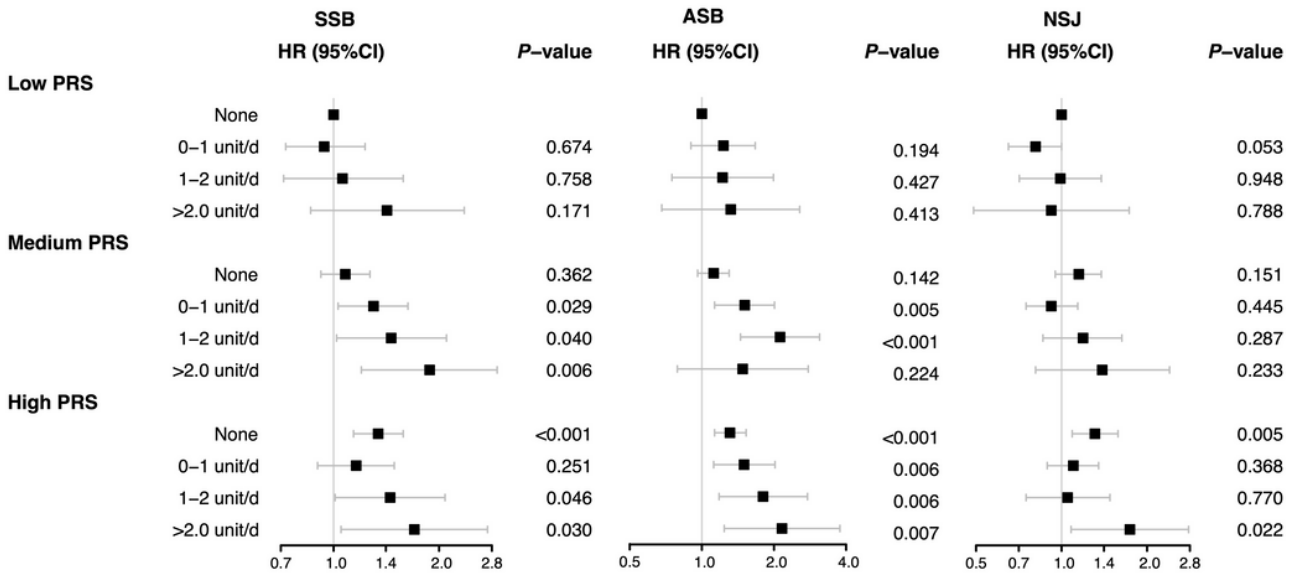

Figure 2

Hazard ratiosa for the joint associationsb of sugary beverages and polygenic risk score (PRS) with incident dementia (N=184,024). SSB, sugar-sweetened beverage; ASB, artificially-sweetened beverage; NSJ, natural sweet juices; HR, hazard ratio; CI, confidence interval a adjusted for age, age-square, sex, Townsend deprivation index, education level, physical activity, smoking, alcohol intake, total energy intake, alternative healthy eating index (AHEI) excluding sugary beverages, and bodyweight status. b P-interaction = 0.0016 for SSB and PRS, 0.0013 for ASB and PRS, and 0.0010 for NSJ and PRS.

Supplementary Files

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