RESEARCH ARTICLE

Association Between Consumption of Low- and No-Calorie Artificial Sweeteners and Cognitive Decline

An 8-Year Prospective Study

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Abstract

Background and Objectives

Consumption of low- and no-calorie sweeteners (LNCSs) has been associated with adverse health outcomes. However, little is known about the association between consumption of LNCSs and cognition. The aim of this study was to investigate the association between consumption of LNCSs and cognitive decline.

Methods

We conducted a longitudinal observational study using data from civil servants aged 35+ years at baseline who were enrolled in the Brazilian Longitudinal Study of Adult Health and evaluated across 3 study waves (2008–10, 2012–14, and 2017–19). Participants with incomplete dietary data, extreme caloric intake (<1st percentile or >99th percentile), and incomplete data for cognitive tests and covariates at baseline were excluded. A Food Frequency Questionnaire was used to calculate combined and individual consumption of 7 LNCSs (aspartame, saccharin, acesulfame k, erythritol, xylitol, sorbitol, and tagatose). We estimated *z*-scores across 6 cognitive tests. The association of LNCSs with cognitive decline was evaluated using linear mixed-effects models.

Results

Among 12,772 participants (mean age 51.9 ± 9.0 years, 54.8% women, 43.2% Black/mixed race), the mean consumption of LNCSs was 92.1 ± 90.1 mg/d. Among participants aged younger than 60 years, consumption of combined LNCSs in the highest tertiles was associated with a faster decline in verbal fluency (second tertile: β = −0.016, 95% CI −0.040 to −0.008; third tertile: β = −0.040, 95% CI −0.064 to −0.016) and global cognition (second tertile: β = −0.008, 95% CI −0.024 to 0.008; third tertile: β = −0.024, 95% CI −0.040 to −0.008). There was no association between tertiles of LNCSs and cognitive decline in participants aged 60+ years. Consumption of aspartame, saccharin, acesulfame k, erythritol, sorbitol, and xylitol was associated with a faster decline in global cognition, particularly in memory and verbal fluency domains. Consumption of combined LNCSs in the highest tertiles was associated with a faster decline in verbal fluency and global cognition in participants without diabetes and faster decline in memory and global cognition in participants with diabetes.

Discussion

Consumption of LNCSs was associated with an accelerated rate of cognitive decline during 8 years of follow-up. Our findings suggest the possibility of long-term harm from LNCS consumption, particularly artificial LNCSs and sugar alcohols, on cognitive function. Study limitations include self-reported dietary data, selection bias from attrition, and residual confounding from co-occurring health behaviors.

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Glossary

ADI = Acceptable Daily Intake; **BMI** = body mass index; **DASH** = Dietary Approach to Systolic Hypertension; **ELSA-Brasil** = Brazilian Longitudinal Study of Adult Health; **FFQ** = Food Frequency Questionnaire; **Hb** = hemoglobin; **IPW** = inverse probability weighting; **LMICs** = low- and middle-income countries; **LNCSs** = low- and no-calorie sweeteners; **MET** = metabolic equivalent of task; **MIND** = Mediterranean-DASH Intervention for Neurodegenerative Delay.

Introduction

Worldwide, the prevalence of dementia is expected to increase from 50 million in 2019 to 152 million in 2050.[1] Approximately 60% of people living with dementia live in low- and middle-income countries (LMICs), and this prevalence is expected to reach 68% in 2050.[1] A healthy lifestyle has been linked to a decreased risk of cognitive decline and dementia.[2] On the contrary, high consumption of ultraprocessed foods has been linked to accelerated cognitive decline and increased risk of dementia.[3,4]

Sugar-free ultraprocessed foods generally contain low- and no-calorie sweeteners (LNCSs) as part of their composition, such as diet beverages, yogurts, snacks, low-calorie desserts, and milk-based beverages.[5] LNCSs, such as aspartame, acesulfame k, saccharin, and sugar alcohols, are sugar substitutes that provide sweetness with no or few calories. Although the consumption of many LNCSs increased from 2008 to 2017 globally, mirroring worldwide increases in ultraprocessed food intake, this increased consumption did not exceed the Acceptable Daily Intakes (ADIs) suggested by the Joint Expert Committee on Food Additives.[6,7] However, consumption of LNCSs within the ADI has been associated with an increased risk of type 2 diabetes, cancer, cardiovascular disease, and depression.[8-10] Moreover, consumption of artificially sweetened beverages, as well as consumption of saccharin, has been associated with a higher risk of dementia, and consumption of sucralose has been associated with decreased performance in the memory and executive function domains, possibly linked to microbiome changes, neuroinflammation, and neurotoxicity from LNCS metabolites.[11-16]

Although some cross-sectional studies investigated the association of sucralose or saccharin consumption with cognitive performance and dementia, the association of several LNCSs with cognitive decline remains to be studied.[12,13] Moreover, many studies were limited by small sample sizes.[12,13] Therefore, we aimed to investigate the association of total and individual consumption of 7 LNCSs (aspartame, saccharin, acesulfame k, erythritol, xylitol, sorbitol, and tagatose) with cognitive decline in a large cohort of civil servants from the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) during a median follow-up of 8 years. We hypothesized a priori that higher consumption of LNCSs would be associated with faster cognitive decline.

Methods

Study Population

The ELSA-Brasil is a multicenter cohort of 15,105 active and retired civil servants from 6 cities in Brazil (Belo Horizonte, Porto Alegre, Rio de Janeiro, Salvador, São Paulo, and Vitoria). Data were collected across 3 waves: 2008–2010, 2012–2014, and 2017–2019. At the start of the study, participants were aged between 35 and 74 years and free of dementia. The assessment collected information about sociodemographics, clinical conditions, cognition, and laboratory tests. A comprehensive description of the study design and participant profile is available elsewhere.[17,18]

This study excluded participants who, at wave 1, had incomplete dietary data (n = 28), reported unusually high caloric intake (<1st percentile or >99th percentile, n = 302), had incomplete data for cognitive tests (n = 930) and covariates (n = 1,070), or had a history of Parkinson disease (n = 3). Therefore, we analyzed baseline data from 12,772 participants (Figure 1). In wave 2, 138 participants had died, 724 did not attend the examination, 5,869 participants younger than 55 years did not complete the cognitive assessment because it was only performed in participants aged 55 years or older, and 257 participants aged 55 years or older had incomplete cognitive data. Cognitive assessment was administered to all participants in wave 3, independent of age. In this wave, 200 participants had died, 1,021 were lost to follow-up, and 706 had missing cognitive data (Figure 1).

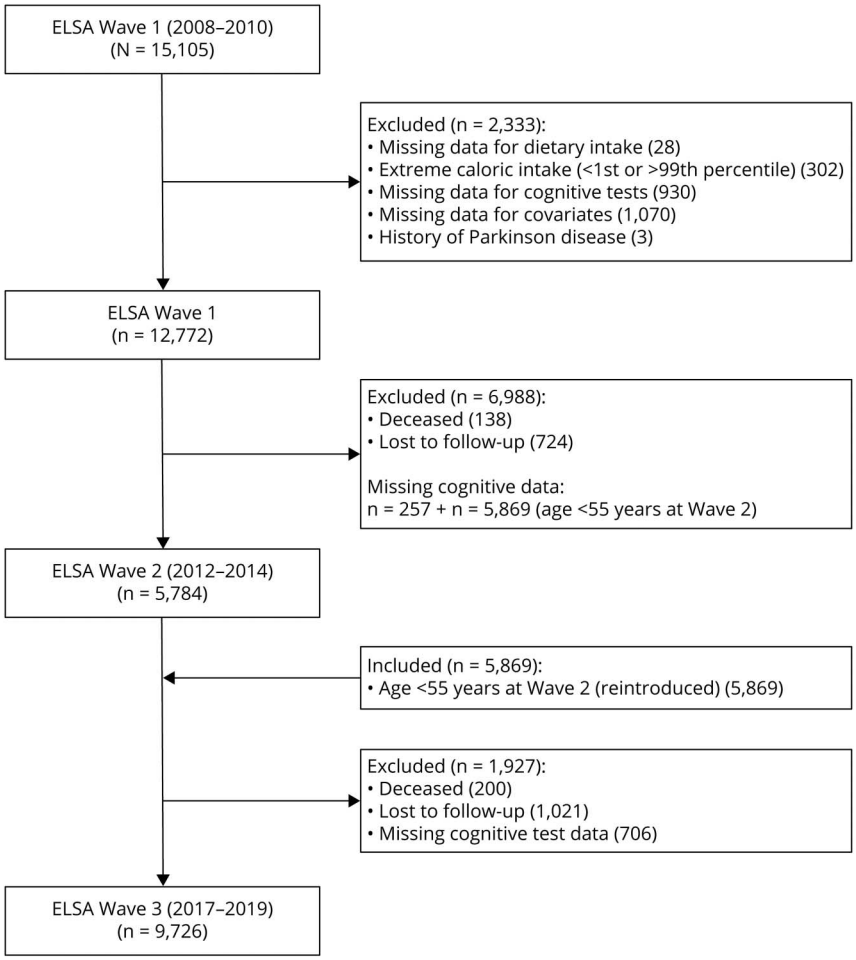
Standard Protocol Approvals, Registrations, and Patient Consents

The ELSA-Brasil study was conducted according to the guidelines of the Declaration of Helsinki. The ELSA-Brasil study was approved by the local institutional review boards, and all participants signed an informed consent.

Dietary Assessment

Food and drink consumption in the past 12 months was assessed at baseline using a validated Food Frequency Questionnaire (FFQ) with 114 items.[19] Details about the dietary assessment can be found in the eMethods. Seven LNCSs (aspartame, saccharin, acesulfame k, erythritol, sorbitol, xylitol, and tagatose) were identified from tabletop sweeteners and the composition of light and diet beverages, and their consumption was calculated in milligrams.[20] We calculated the combined consumption of LNCSs by summing the consumption of each of the 7 LNCSs and categorized participants into tertiles (first tertile: 0.02–37.2 mg, second tertile 2: 37.3–102.3 mg, third tertile: 102.4–856.5 mg). We also categorized participants according to their frequency of LNCS use into "no consumption/sporadic consumption" (less than once a day) and "daily consumption."

Figure 1 Flowchart of the Study Participants



Cognitive Assessment

Cognitive performance was assessed every 4 years across 3 study waves (2008–10, 2012–14, and 2017–19).[21] Episodic memory was evaluated with the Consortium to Establish a Registry for Alzheimer's Disease word list, validated for the Brazilian population.[22] The semantic and phonemic verbal fluency tests were used to assess language and executive function.[23] Because verbal fluency tests differed in wave 2 from waves 1 and 3, test scores were harmonized using the equipercentile equating technique to make all waves comparable.[24] Processing speed and executive function were evaluated with the Trail-Making Test version B.[25] We calculated *z*-scores for each wave, standardized to wave 1. Details about the cognitive assessment can be found in the eMethods.

Covariates

The sociodemographic variables were baseline age, sex, monthly per capita income (in US dollars), self-reported race (White, Black, mixed race, and other), and education (less than high school, high school graduate, college degree or more). Clinical variables included body mass index (BMI), calculated as the measured weight (in kilograms) divided by the squared measured height (in meters). Diabetes was categorized as no diabetes (no self-reported history of diabetes and glycated hemoglobin [Hb] <6.5%), undiagnosed diabetes (no self-reported history of diabetes and glycated Hb ≥6.5%), controlled diabetes (self-reported history of diabetes and glycated Hb <6.5%), and uncontrolled diabetes (self-reported history of diabetes and glycated Hb ≥6.5%). Hypertension was self-reported or defined by systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive drugs. Cardiovascular disease was defined by self-reported myocardial infarction, myocardial revascularization, or heart failure. Depression was evaluated using the Brazilian version of the Clinical Interview Scheduled Revised.[26]

Lifestyle factors included leisure physical activity, measured with the Physical Activity Questionnaire and categorized into light (<600 metabolic equivalent of task [MET]-min/week), moderate (600–2,999 MET-min/week), or vigorous (≥3,000 MET-min/week) physical activity.[27] Smoking status was self-reported as never smoked, former smoker, or current smoker. Alcohol consumption was self-reported as never,

former, or current drinker; total energy intake was measured in kilocalories; adhesion to the Mediterranean-Dietary Approach to Systolic Hypertension (DASH) diet intervention for neurodegenerative delay (MIND) diet was used as a proxy for healthy eating and was calculated as previously described.[28] The MIND diet is a dietary pattern that combines food items from the Mediterranean diet and the DASH diet, which encourages the consumption of green leafy vegetables, berries, nuts, olive oil, whole grains, fish, and poultry but recommends avoiding meats, fried foods, and pastries and sweets. We divided the sample into healthy (score >8) and unhealthy (score ≤8) diet groups using the median score of the MIND diet in the ELSA-Brasil cohort.

Statistical Analysis

Descriptive analyses were presented as mean and SD for continuous variables and percentages for categorical variables. We compared the tertiles of combined LNCS intake using ANOVA for continuous variables and the χ^2 test for categorical variables.

We used linear mixed-effects models with random intercepts and slopes to investigate the association between baseline consumption of LNCSs and cognitive decline. The timescale was the age of the participant in each wave. The longitudinal association between baseline consumption of LNCS and cognitive decline was evaluated by the interaction between the tertiles of LNCS consumption and the timescale, and the first tertile was used as reference. Model 1 was adjusted for age, sex, race/ethnicity, education, and income. Model 2 was further adjusted for physical activity, BMI (cubic function), hypertension, diabetes, cardiovascular disease, depressive symptoms, alcohol drinking, smoking, total calories, and the MIND diet. To calculate the percentage rate of cognitive decline, we subtracted each tertile slope from the first tertile slope, divided this difference by the first tertile slope, and multiplied it by 100.

We investigated the association of individual LNCS (aspartame, saccharin, acesulfame k, erythritol, sorbitol, xylitol, and tagatose) intake with cognitive decline and the association between frequency of LNCS intake and cognitive decline using the same procedure for each low-calorie sweetener. We also investigated whether obesity, diabetes, and a healthy diet, all evaluated in 2 categories (no/yes), modified the association between LNCS consumption and cognitive decline by adding a 3-way interaction among the consumption of LNCS, the timescale, and each modifier on model 2.

We used inverse probability weighting (IPW) to account for attrition.[29] We calculated the probability of survival and participation for each follow-up wave using separate logistic regressions. The weight numerator included baseline age, sex, education, and race. The weight denominator also incorporated time-varying factors such as income, BMI, alcohol consumption, smoking, diabetes, hypertension, cardiovascular disease, physical activity, depression, total calories, the MIND diet, the global cognitive score, and baseline LNCS consumption. The final stabilized weights were calculated by multiplying the weights for survival and participation.

We estimated the excess years of cognitive aging over an 8-year follow-up attributable to each tertile of LNCS consumption, assuming that the cognitive decline rate among participants in the first tertile trajectory represented normal cognitive aging. We calculated this by dividing the 8-year cognitive change associated with each trajectory by the annual cognitive decline rate observed in the first tertile group.

To verify the robustness of our analysis, we imputed cognitive data using next observation carried backward. This was performed by copying the scores from wave 3 to wave 2 for participants aged younger than 55 years in wave 2 because the cognitive performance of these participants was not evaluated in this wave. We assumed that this approach is conservative because cognitive performance is expected to decline over time in middle-aged and older adults.[30] In addition, we investigated the association between LNCS consumption and cognitive decline including only participants who were evaluated with the cognitive test battery across the 3 waves. We also investigated the association between LNCS consumption and cognitive decline stratified by age (<60 years and ≥60 years) after visual inspection suggested that this association differs between middle-aged and older adults (eFigure 1). The alpha level was set at 5%. All statistical analyses were performed using R version 4.1.2, using the lme4 package.

Results

Sample Characteristics

A total of 15,105 participants were recruited, and after exclusion of 2,333 individuals, 12,772 participants remained (Figure 1). The median (range) duration of follow-up was 8 (6–12) years. At baseline, the mean age was 51.9 ± 9.0 years, 54.8% of participants were women, 43.2% were Black/mixed race, and 56.3% had a college education or more (Table 1). The mean consumption of low-calorie sweeteners was 92.1 ± 90.1 mg/d, with sorbitol being the most consumed sweetener (mean consumption = 63.8 ± 69.1 mg/d) and erythritol the least consumed (0.1 ± 0.2 mg/d) (Table 1). Compared with the participants in the lower tertile of total low-calorie sweetener consumption, those in the highest tertile were more likely to be older, women, and White and have higher education and income (Table 1). They were also more likely to have a higher frequency of hypertension and uncontrolled diabetes and be physically active (Table 1).

Consumption of Low- and No-Calorie Sweeteners and Cognitive Decline

After a median follow-up of 8 years, participants in the highest tertile of combined LNCS consumption had a 32% higher rate of memory decline compared with those in the first tertile (second tertile: β = −0.008, 95% CI −0.032 to 0.008; third tertile: β = −0.024, 95% CI −0.040 to −0.004, p for trend = 0.058)

Table 1 Sample Characteristics at Baseline (n = 12,772)

	Total (n = 12,772)	First tertile (0.02–37.2 mg) (n = 4,258)	Second tertile (37.3–102.3 mg) (n = 4,257)	Third tertile (102.4–856.5 mg) (n = 4,257)	*p* Value
Age, y, mean (SD)	51.9 (9.0)	51.0 (8.9)	52.2 (9.2)	52.4 (9.0)	<0.001[a]
Women, %	54.8	49.7	57.7	57.1	<0.001[b]
Race, %					<0.001[b]
Black	15.1	17.1	13.7	14.4	
Mixed[c]	28.1	31.1	27.1	26.1	
White	53.4	48.2	55.8	56.2	
Other[d]	3.4	3.6	3.4	3.3	
Education, college or more, %	56.3	48.6	60.5	59.8	<0.001[b]
Per capita income, USD, mean (SD)	991.7 (795.3)	860.1 (722.4)	1,028.4 (806.5)	1,087.4 (835.0)	<0.001[a]
BMI, kg/m^2, mean (SD)	27.0 (4.7)	26.6 (4.6)	26.9 (4.7)	27.5 (4.8)	<0.001[a]
Daily calorie intake, kcal, mean (SD)	2,911.7 (1,064.0)	2,774.0 (1,011.0)	2,860.0 (1,020.0)	3,100.0 (1,129.0)	<0.001[a]
Hypertension, %	34.9	32.9	34.8	37.0	<0.001[b]
Diabetes, %[e]					<0.001[b]
No diabetes	89.0	92.0	89.1	85.8	
Undiagnosed diabetes	1.8	1.7	2.0	1.6	
Controlled diabetes	5.1	3.6	5.6	6.1	
Uncontrolled diabetes	4.1	2.7	3.3	6.5	
Cardiovascular disease, %[f]	6.4	5.8	6.3	7.0	0.082[b]
Alcohol consumption, %					<0.001[b]
Never	10.1	9.6	10.0	10.8	
Former	19.3	19.0	17.5	21.5	
Current	70.6	71.4	72.5	67.7	
Smoking, %					<0.001[b]
Never	57.6	53.9	59.8	59.1	
Former	29.7	28.3	28.8	31.9	
Current	12.7	17.8	11.4	9.0	
Physical activity, %					<0.001[b]
Light or none	76.3	82.3	75.9	70.7	
Moderate	16.4	12.6	17.3	19.5	
Vigorous	7.3	5.1	6.8	9.8	
Depression, %	12.9	14.0	12.6	12.3	0.050[b]
LCNS intake, mg, mean (SD)					
Total	92.1 (90.1)	19.9 (9.7)	65.6 (16.7)	191.0 (91.2)	<0.001[a]
Aspartame	12.8 (31.9)	0.9 (2.3)	6.2 (10.9)	31.2 (49.2)	<0.001[a]
Saccharin	4.6 (7.8)	1.3 (3.2)	3.9 (5.9)	8.5 (10.5)	<0.001[a]
Acesulfame k	6.3 (17.1)	0.5 (1.2)	2.7 (4.7)	15.8 (26.9)	<0.001[a]

Continued

Table 1 Sample Characteristics at Baseline (n = 12,772) *(continued)*

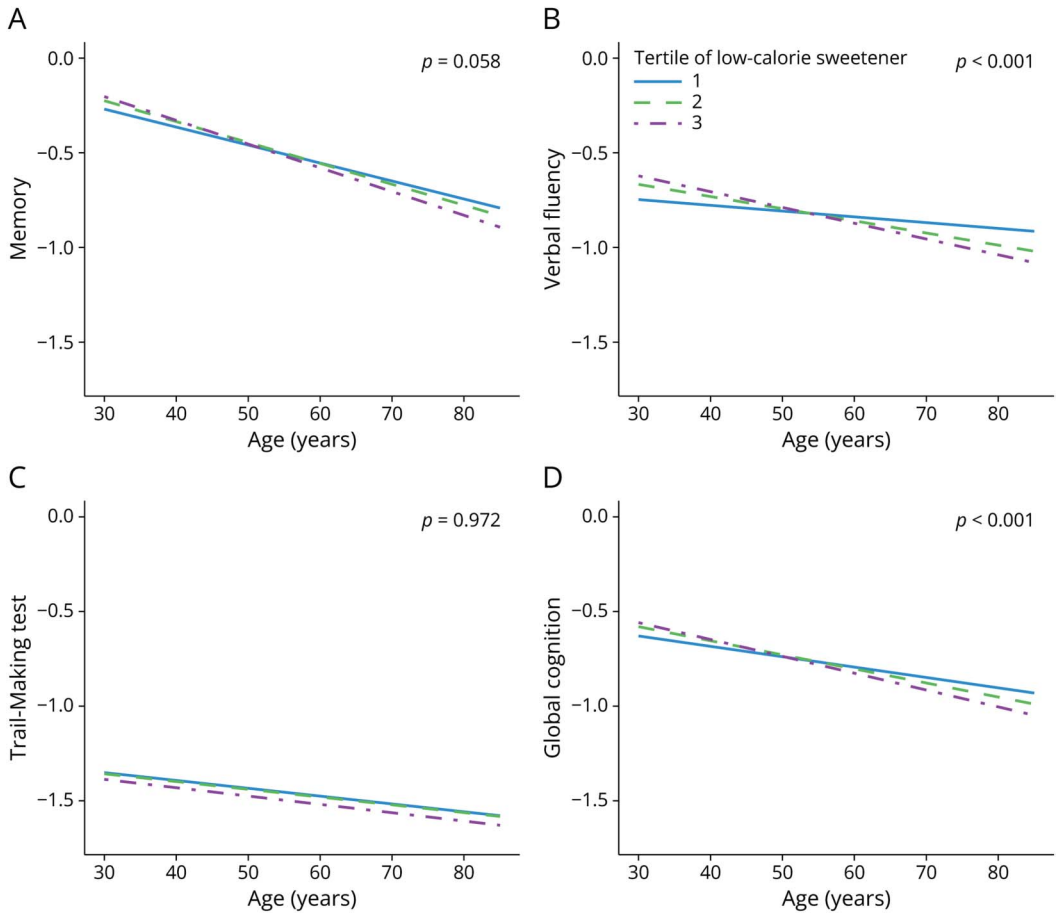
	Total (n = 12,772)	First tertile (0.02–37.2 mg) (n = 4,258)	Second tertile (37.3–102.3 mg) (n = 4,257)	Third tertile (102.4–856.5 mg) (n = 4,257)	*p* Value
Erythritol	0.1 (0.2)	0.1 (0.1)	0.1 (0.2)	0.2 (0.2)	<0.001[a]
Sorbitol	63.8 (69.1)	14.1 (8.4)	48.2 (20.0)	129.0 (82.7)	<0.001[a]
Xylitol	3.0 (2.1)	1.9 (1.2)	3.0 (1.8)	4.2 (2.6)	<0.001[a]
Tagatose	1.4 (1.7)	0.9 (1.4)	1.4 (1.6)	1.7 (1.9)	<0.001[a]
Immediate recall, mean (SD)[g]	21.3 (3.8)	21.0 (3.9)	21.5 (3.8)	21.4 (3.9)	<0.001[a]
Late recall, mean (SD)[g]	7.0 (1.9)	6.9 (2.0)	7.1 (1.9)	7.1 (1.9)	<0.001[a]
Word recognition, mean (SD)[g]	9.6 (0.9)	9.6 (0.9)	9.6 (0.9)	9.6 (0.9)	0.446[a]
Semantic verbal fluency, mean (SD)[g]	18.8 (5.2)	18.5 (5.2)	18.9 (5.1)	18.9 (5.3)	<0.001[a]
Phonemic verbal fluency, mean (SD)[g]	12.8 (4.3)	12.6 (4.4)	13.0 (4.3)	12.7 (4.3)	0.001[a]
Trail-Making Test score, s, mean (SD)	123.1 (86.8)	126.0 (92.0)	118.0 (78.7)	125.0 (89.1)	<0.001[a]

Abbreviations: BMI = body mass index; Hb = hemoglobin; LCNS = low- and no-calorie sweetener.
[a] Analysis of variance.
[b] Chi-square test.
[c] Mix of Black and White races.
[d] Includes Asian, Indigenous, and other races/ethnicities.
[e] No diabetes: no self-reported history of diabetes and glycated Hb <6.5%; undiagnosed diabetes: no self-reported history of diabetes and glycated Hb ≥6.5%; controlled diabetes: self-reported history of diabetes and glycated Hb <6.5%; uncontrolled diabetes: self-reported history of diabetes and glycated Hb ≥6.5%.
[f] Self-reported myocardial infarction, angina, or heart failure.
[g] Number of recorded words.

(Figure 2 and eTable 1). Participants in the 2 highest tertiles of combined LNCS consumption had 110% and 173% higher rates of verbal fluency decline, respectively (second tertile: β = −0.024, 95% CI −0.048 to −0.008; third tertile: β = −0.040, 95% CI −0.064 to −0.024, *p* for trend <0.001). Participants in the 2 highest tertiles of LNCS consumption had a 35% and 62% higher rate of global cognition decline, respectively (second tertile: β = −0.016, 95% CI −0.032 to −0.001, third tertile: β = −0.024, 95% CI −0.040 to −0.016, *p* for trend <0.001), corresponding to an excess 1.3 and 1.6 years of cognitive aging (Figure 2 and eTable 1). There was no association between the consumption of combined LNCSs and scores of the Trail-Making Test during the study period (Figure 2 and eTable 1). Sensitivity analysis using next observation carried backward yielded similar results (eTable 2). Compared with no use or sporadic consumption, daily frequency of LNCS intake was associated with accelerated decline in memory (β = −0.018, 95% CI −0.035 to 0.000, $p = 0.043$), verbal fluency (β = −0.029, 95% CI −0.045 to −0.012, $p < 0.001$), and global cognition (β = −0.021, 95% CI −0.034 to −0.009, $p = 0.001$) (eTable 3). In complete case analysis, there was no association between tertiles of LNCS consumption and cognitive decline (eTable 4).

Figure 3 shows the association between individual LNCS consumption and cognitive decline. There was a faster rate of decline in memory, verbal fluency, and global cognitive with higher consumption of aspartame (memory: β = −0.002, 95% CI −0.003 to −0.0004, verbal fluency: β = −0.001, 95% CI −0.002 to −0.0001, global cognition: β = −0.001, 95% CI −0.002 to −0.0004), saccharin (memory: β = −0.010, 95% CI −0.016 to −0.003, verbal fluency: β = −0.005, 95% CI −0.008 to −0.002, global cognition: β = −0.008, 95% CI −0.011 to −0.002), sorbitol (memory: β = −0.001, 95% CI −0.001 to −0.0001; verbal fluency: β = −0.0008, 95% CI −0.001 to −0.0003; global cognition: β = −0.0006, 95% CI −0.001 to −0.002), and xylitol (memory: β = −0.032, 95% CI −0.056 to −0.016; verbal fluency: β = −0.016, 95% CI −0.032 to −0.001; global cognition: β = −0.016, 95% CI −0.032 to −0.008) (Figure 3 and eTable 5). There was a higher rate of memory and global cognitive decline with higher consumption of acesulfame k (memory: β = −0.003, 95% CI −0.006 to −0.001; global cognition: β = −0.002, 95% CI −0.004 to −0.001) and erythritol (memory: β = −0.038, 95% CI −0.067 to −0.007; global cognition: β = −0.028, 95% CI −0.049 to −0.006) (Figure 3 and eTable 5). There was no association between consumption of tagatose and cognitive decline (Figure 3 and eTable 5). There was no association between the consumption of individual LNCSs and performance in the Trail-Making Test over time (Figure 3 and eTable 5).

Figure 2 Association Between Total Artificial Sweetener Consumption and Cognitive Decline in the Whole Sample



Association of tertiles of combined LCNS consumption at the study baseline with (A) memory, (B) verbal fluency, (C) Trail-Making Test scores, and (D) global cognition trajectories over a median of 8 years of follow-up (n = 12,772). *p* Values represent the interaction term between tertiles of LCNS consumption and the timescale using linear mixed-effects models adjusted for age, sex, race/ethnicity, education, income, physical activity, body mass index (cubic function), hypertension, diabetes, cardiovascular disease, depressive symptoms, alcohol consumption, smoking, total calories, and MIND diet. We used inverse probability weighting to correct for attrition bias related to mortality and missing participation at each wave. Consumption of combined LCNS in milligrams was categorized into tertiles (first tertile: 0.02–37.2 mg; second tertile: 37.3–102.3 mg; third tertile: 102.4–856.5 mg). LCNS = low- and no-calorie sweetener; MIND = Mediterranean-Dietary Approach to Systolic Hypertension Intervention for Neurodegenerative Delay.

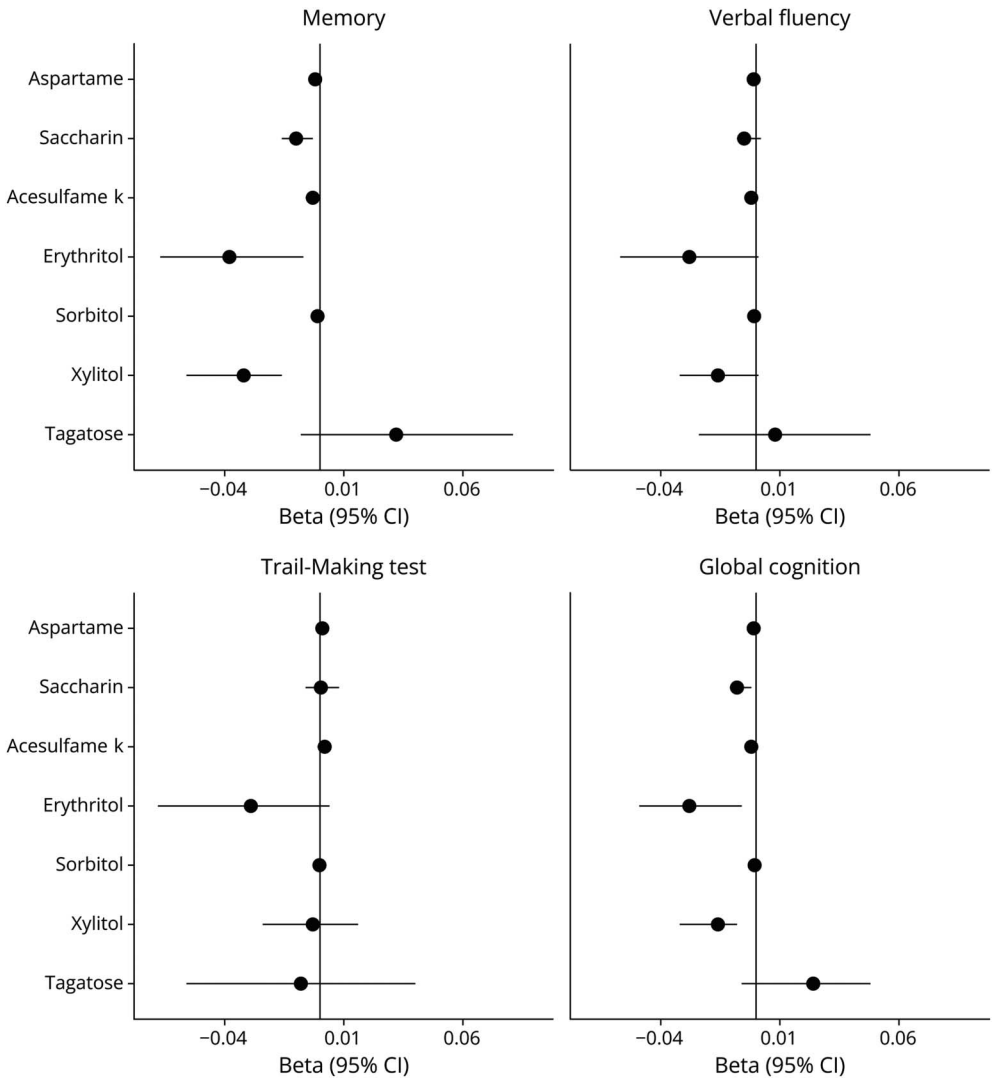
Stratified Analysis by Age

Age was a modifier in the association between LNCS consumption and cognitive decline ($p < 0.001$). In stratified analyses by age, consumption of combined LNCSs in the highest tertile was associated with a faster decline in verbal fluency (second tertile: β = −0.016, 95% CI −0.040 to −0.008; third tertile: β = −0.040, 95% CI −0.064 to −0.016) and global cognition (second tertile: β = −0.008, 95% CI −0.024 to 0.008; third tertile: β = −0.024, 95% CI −0.040 to −0.008) in participants aged younger than 60 years (eTable 6). There was no association between tertiles of LNCS consumption with memory and performance in the Trail-Making Test over time (e6) in this age group. There was no association between tertiles of LNCS and cognitive decline in participants aged 60 years and older (eTable 6). Regarding individual sweeteners, in participants aged younger than 60 years, there was a faster rate of decline in memory, verbal fluency, and global cognitive with higher consumption of sorbitol (memory: β = −0.001, 95% CI −0.002 to 0.000; verbal fluency: β = −0.001, 95% CI −0.002 to 0.000; global cognition β = −0.0005, 95% CI −0.001 to −0.0001) (eTable 7). In these participants, higher consumption of tagatose was associated with a slower rate of memory and global cognition decline (memory: β = 0.064, 95% CI 0.008–0.120; global cognition: β = 0.040, 95% CI 0.008–0.080) (eTable 7). There was no association between individual sweeteners and cognitive decline in participants aged 60 years and older (eTable 7).

Modifier Role of Obesity, Diabetes, and a Healthy Diet

While obesity and diet did not modify the association between LNCS consumption and cognitive decline (eFigure 2), diabetes modified the association between consumption of total LNCSs and global cognition decline ($p = 0.016$) (eFigure 2). In stratified analyses, consumption of combined LNCSs in the highest tertiles was associated with faster decline in verbal fluency (second tertile: β = −0.021, 95% CI −0.042 to −0.001; third tertile: β = −0.036, 95% CI −0.057 to −0.014) and global

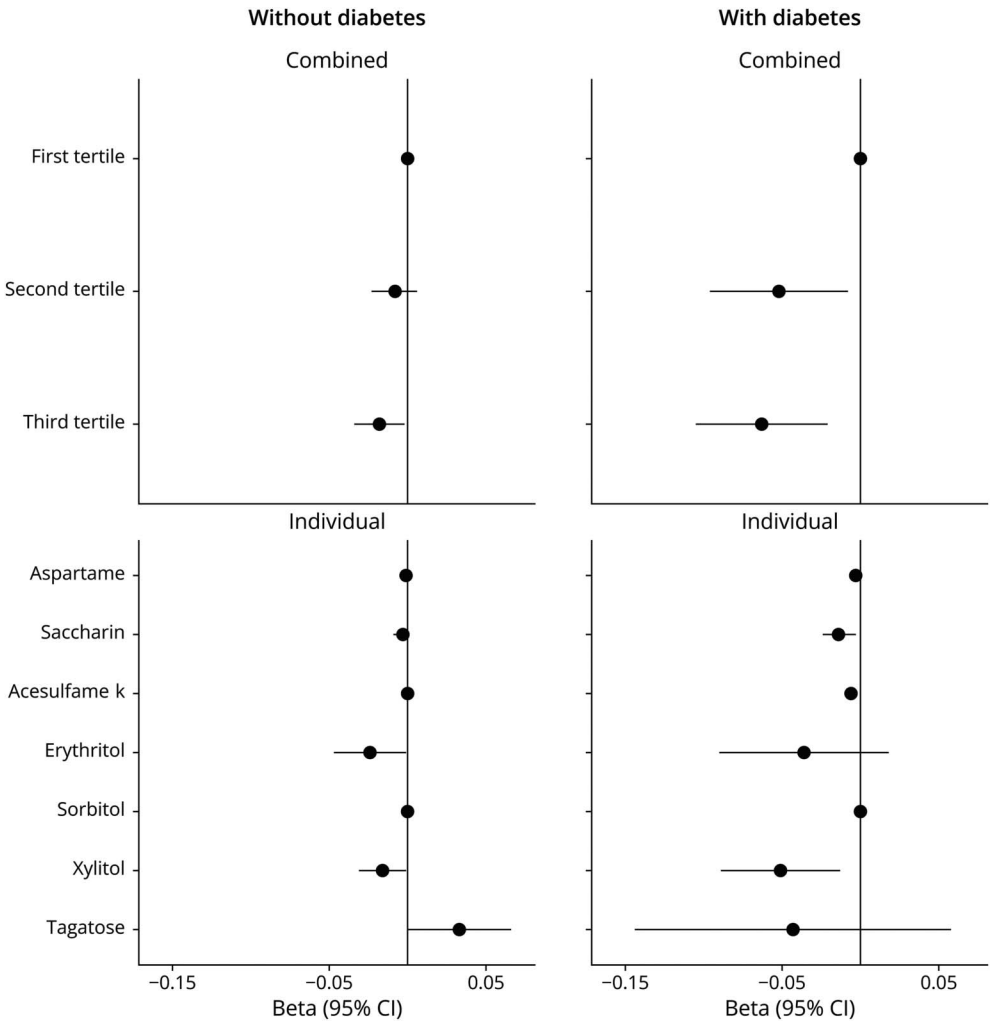
Figure 3 Association Between Individual Artificial Sweetener Consumption and Cognitive Decline in the Whole Sample



Association of individual LCNS consumption at the study baseline with memory, verbal fluency, Trail-Making Test scores, and global cognition trajectories over a median of 8 years of follow-up (n = 12,772). Linear mixed-effects models were adjusted for age, sex, race/ethnicity, education, income, physical activity, body mass index (cubic function), hypertension, diabetes, cardiovascular disease, depressive symptoms, alcohol consumption, smoking, total calories, and MIND diet. We used inverse probability weighting to correct for attrition bias related to mortality and missing participation at each wave. Consumption of aspartame, saccharin, acesulfame k, sorbitol, xylitol, and tagatose ranged from 0 to 550 mg and was categorized in intervals of 5 mg each and analyzed as a continuous variable. Consumption of erythritol consumption ranged from 0 to 1.8 mg and was categorized in intervals of 0.5 mg and analyzed as a continuous variable. LCNS = low- and no-calorie sweetener; MIND = Mediterranean-Dietary Approach to Systolic Hypertension Intervention for Neurodegenerative Delay.

cognition (second tertile: β = −0.008, 95% CI −0.023 to −0.006; third tertile: β = −0.018, 95% CI −0.034 to −0.002) in participants without diabetes (Figure 4 and eTable 8). In participants with diabetes, consumption of combined LNCSs in the highest tertiles was associated with a faster decline in memory (second tertile: β = −0.069, 95% CI −0.093 to −0.006; third tertile: β = −0.088, 95% CI −0.148 to −0.028) and global cognition (second tertile: β = −0.052, 95% CI −0.096 to −0.008; third tertile: β = −0.063, 95% CI −0.105 to −0.021) (Figure 4 and eTable 8). Regarding individual sweeteners, in participants without diabetes, there was a faster rate of memory and global cognitive decline with higher consumption of erythritol (memory: β = −0.038, 95% CI −0.070 to −0.004; global cognition: β = −0.024, 95% CI −0.047 to −0.001) and xylitol (memory: β = −0.029, 95% CI −0.049 to −0.007; global cognition: β = −0.016, 95% CI −0.031 to −0.001) (Figure 4 and eTable 9). Consumption of sorbitol was associated with a faster rate of decline in memory, verbal fluency, and global cognition (memory: β = −0.0007, 95% CI −0.001 to 0.000; verbal fluency: β = −0.0007, 95% CI −0.001 to 0.000; global cognition: β = −0.0005, 95% CI −0.001 to 0.000), in participants without diabetes (Figure 4 and eTable 9). In participants with diabetes, higher consumption of aspartame and acesulfame k was associated with faster memory (aspartame: β = −0.004, 95% CI −0.007 to −0.002; acesulfame k: β = −0.009, 95% CI −0.015 to −0.004), verbal fluency (aspartame: β = −0.003, 95% CI −0.006 to 0.000; acesulfame k: β = −0.007, 95% CI −0.012 to −0.002), and global cognition (aspartame: β = −0.003, 95% CI −0.005 to −0.001; acesulfame k: β = −0.006, 95% CI −0.010 to −0.002) decline (Figure 4 and eTable 9). Consumption of saccharin and xylitol was associated with faster memory (saccharin: β = −0.024, 95% CI −0.038 to −0.009; xylitol: β = −0.069, 95% CI −0.122 to −0.014) and global cognition (saccharin: β = −0.014, 95% CI −0.024 to −0.003; xylitol: β = −0.051, 95% CI −0.089

Figure 4 Association Between Individual Artificial Sweetener Consumption and Cognitive Decline in Stratified Analysis



Association of combined and individual LCNS consumption at the study baseline with global cognition decline over a median of 8 years of follow-up in participants without (n = 11,363) and with (n = 1,409) diabetes. Linear mixed-effects models were adjusted for age, sex, race/ethnicity, education, income, physical activity, body mass index (cubic function), hypertension, diabetes, cardiovascular disease, depressive symptoms, alcohol consumption, smoking, total calories, and MIND diet. We used inverse probability weighting to correct for attrition bias related to mortality and missing participation at each wave. Consumption of combined LCNSs in milligrams was categorized into tertiles (first tertile: 0.02–37.2 mg; second tertile: 37.3–102.3 mg; third tertile: 102.4–856.5 mg), and the first tertile was used as reference. Consumption of aspartame, saccharin, acesulfame k, sorbitol, xylitol, and tagatose ranged from 0 to 550 mg and was categorized in intervals of 5 mg each and analyzed as a continuous variable. Consumption of erythritol consumption ranged from 0 to 1.8 mg and was categorized in intervals of 0.5 mg and analyzed as a continuous variable. LCNS = low- and no-calorie sweetener; MIND = Mediterranean-Dietary Approach to Systolic Hypertension Intervention for Neurodegenerative Delay.

to −0.013) decline (Figure 4 and eTable 9). Consumption of tagatose was associated with faster executive function decline in participants with diabetes (β = −0.216, 95% CI −0.404 to −0.029) (Figure 4 and eTable 9).

Discussion

In this cohort study of 12,772 participants followed for a median of 8 years, we found that consumption of combined and individual LNCSs, particularly aspartame, saccharin, acesulfame k, erythritol, sorbitol, and xylitol, was associated with faster declines in global cognition and in memory and verbal fluency domains. Moreover, daily consumption of LNCSs was associated with accelerated decline in memory, verbal fluency, and global cognition. We also found that consumption of LNCSs was associated with cognitive decline in participants younger than 60 years, which suggests the importance of preventive interventions in middle-aged adults. Furthermore, the magnitude of the association of combined LNCS intake with cognitive decline was larger in participants with diabetes than in participants without diabetes.

In this study, the reported consumption of LNCSs was similar to that in a previous study in the Brazilian population.[6,31] Consumption of LNCSs has increased from 2008 to 2017 globally, with China and the United States being the highest consumers.[6,32] The main sources of LNCSs are low-calorie ultraprocessed foods, such as light bread, yogurt, candy bars, flavored water, sodas, and energy drinks.[31-33] However, many LNCSs are also used as tabletop sweeteners, notably aspartame and sucralose.[32,33] Indeed, previous evidence from the ELSA-Brasil study showed that a high percentage of LNCS consumption was from sweetened coffee.[20] Sucralose was approved by the National Agency for Health Surveillance (*Agência Nacional de Vigilância Sanitária*) in 2008, during which the FFQ administration of this study was ongoing.[34] Therefore, we were unable to assess the association between sucralose intake and cognitive decline.

Previous evidence showed that consumption of artificially sweetened beverages has also been associated with an increased risk of dementia.[11] In a study with 1,484 participants aged 60 years or older from the Framingham Heart Study, daily consumption of 1 or more artificially sweetened soft drinks was associated with an increased risk of dementia compared with no consumption, considering both recent consumption and cumulative consumption during 7 years.[11] On the contrary, consumption of artificially sweetened beverages was not associated with cognitive decline in 806 participants aged 55 years or older from the *Seguimiento Universidad de Navarra* cohort during 6 years of follow-up.[29] Previous evidence from a short clinical trial with 39 participants aged 18–35 years showed that consuming 4 g/d of sucralose for 6 weeks was associated with worse performance in the memory and executive function domains.[13] Moreover, sucralose consumption was associated with increased theta wave activity in quantitative electroencephalography, a measure that has been previously associated with faster cognitive decline.[13] In that trial, consumption of steviol glycosides was not associated with cognitive performance.[13] In a case-control study including 36 participants with dementia and 36 without dementia, consumption of saccharin was associated with an increased risk of dementia.[12] Besides the association between consumption of combined LNCSs and a faster rate of memory, verbal fluency, and global cognition decline, we found an association between individual LNCS consumption and cognitive decline. Similar to previous evidence, we found that saccharin consumption was associated with a faster decline in memory, verbal fluency, and global cognition. Previous studies have not investigated the association of aspartame, acesulfame k, erythritol, sorbitol, xylitol, and tagatose with cognitive decline. We found that, except for tagatose, all other investigated LNCSs were associated with faster cognitive decline.

Possible mechanisms that might explain our findings are neurotoxicity and neuroinflammation induced by toxic metabolites from artificial sweeteners. Consumption of aspartame was metabolized into neurotoxic compounds, leading to microglia-mediated neuroinflammation and cognitive decline in rodents.[14] Consumption of aspartame and stevia was also associated with an increased rate of cellular apoptosis in the hippocampus.[15] Moreover, a cafeteria diet rich in artificial flavorings, emulsifiers, and sweeteners caused gut dysbiosis in rats, which was linked to altered claudin-5 expression, negatively affecting blood-brain barrier integrity.[16] This diet was also associated with decreased hippocampal synaptophysin, indicating impaired synaptic function.[16]

Artificial sweeteners have been shown to cause glucose intolerance in mice by altering gut microbiota.[35] In humans, long-term consumption of artificial sweeteners was associated with impaired glucose tolerance and increased glycated Hb in participants without diabetes.[35,36] In a systematic review investigating the association of LNCSs with several health outcomes, consumption of 330 mL/d of artificially sweetened soft drinks was associated with an increased risk of type 2 diabetes.[8] However, the authors pointed out high heterogeneity among studies.[8] A systematic review and meta-analysis reported that consumption of artificially sweetened beverages was associated with incident diabetes, but the authors pointed out the possibility of publication bias and residual confounding.[37] Conversely, high doses of aspartame consumption (40 mg/kg of body weight per day) during 20 days were not associated with impaired glucose metabolism in 48 healthy adults aged 18–35 years.[38]

In this study, diabetes modified the association between LCNS intake and cognitive decline. Stratified analyses showed that the association between consumption of combined LNCSs and cognitive decline was stronger in participants with diabetes than in participants without diabetes. Although consumption of aspartame, saccharin, and acesulfame k was associated with a faster decline in memory and global cognition in participants with diabetes, it was not associated with cognitive decline in participants without diabetes. On the contrary, consumption of erythritol and sorbitol was associated with faster cognitive decline in participants without diabetes but not in participants with diabetes. We cannot exclude the possibility of residual confounding because people at higher risk of type 2 diabetes may be more likely to consume LNCSs instead of sugar.[39] However, evidence from a previous study investigating the association between artificial sweeteners and diabetes, where the authors excluded diabetes cases occurring during the first 6 years of follow-up, showed that consumption of artificial sweeteners remained associated with an increased risk of type 2 diabetes.[40] In addition, a clinical trial that investigated the effects of artificial sweeteners on the microbiome in 120 healthy adults showed that consumption of saccharin and sucralose impaired glycemic responses.[36] Furthermore, our results that different individual LNCSs are associated with cognitive decline in participants with and without diabetes suggest that residual confounding is unlikely to fully explain the observed findings. Diabetes has been associated with faster cognitive decline.[41] Patients with diabetes are also more likely to use LNCSs as alternatives to refined sugar. Therefore, our finding that consumption of certain LNCSs was associated with faster cognitive decline in participants with diabetes may have implications for clinical practice. If these findings are confirmed in other studies, practitioners may recommend that patients with diabetes avoid certain LNCSs that may be detrimental to their cognitive function. In addition, our findings highlight the detrimental association of artificial sweeteners (aspartame, saccharin, acesulfame k) and sugar alcohols (erythritol, sorbitol, xylitol) with accelerated cognitive decline, while tagatose, a natural LNCS, was not associated with cognitive decline in participants with or without diabetes. Therefore, choosing natural sweeteners may be a good way to avoid the potentially harmful association observed.

This study has strengths. First, this is a large racially/ethnically diverse sample. In addition, the dietary assessment used

a validated questionnaire.[19] Moreover, we found that consumption of LNCSs was associated with cognitive decline in middle-aged participants. The cognitive function related to memory, attention, and processing speed peaks during early adulthood and declines gradually during aging, starting in the third decade of life.[42] Therefore, it is important to include younger participants in studies of cognitive aging. Furthermore, including middle-aged adults may provide insights into preventive measures, as dementia biomarkers become evident 20–30 years before onset of clinical disease.[43] However, our study also has some limitations. First, long-term studies are prone to attrition. Nevertheless, the application of IPW may mitigate some of the selection bias. Furthermore, sensitivity analysis imputing missing cognitive data for wave 2 yielded consistent results. Second, while a validated FFQ was used, the possibility of misreporting bias cannot be ruled out. Third, many of our covariates were self-reported, which may introduce social desirability bias. Fourth, although we adjusted the regression models for several clinical and lifestyle variables, we cannot exclude the possibility of residual confounding, particularly because health behaviors may co-occur and some groups may consume more LCNSs because of their lifestyle and clinical history.[44] In addition, diet was assessed only at baseline, which may not reflect longitudinal diet changes and may lead to an underestimation of the associations between LNCS and cognition.[45] Finally, owing to unavailability of neuroimaging, we were unable to investigate structural brain changes and potential mechanisms that may explain the associations between the LNCS intake and cognitive decline in specific groups.

In conclusion, consumption of LNCS was associated with an accelerated rate of cognitive decline during 8 years of follow-up in this large cohort of middle-aged and older adults. Our findings suggest the possibility of long-term harm from consumption of LNCSs, particularly artificial LNCSs and sugar alcohols, on cognitive function. Therefore, opting for natural sweeteners, such as tagatose, or other sugar alternatives may help mitigate the potentially harmful association observed. Future research is needed to confirm our findings and to investigate whether other refined sugar alternatives, such as applesauce, honey, maple syrup, or coconut sugar, may be effective alternatives to avoid the detrimental association between LNCS consumption and cognitive function.

Author Contributions

N.G. Gonçalves: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. E. Martinez-Steele: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. P.A. Lotufo: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. I. Bensenor: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. A.C. Goulart: drafting/revision of the manuscript for content, including medical writing for content. S.M. Barreto: drafting/revision of the manuscript for content, including medical writing for content. L. Giatti: drafting/revision of the manuscript for content, including medical writing for content. C.P. de Faria: drafting/revision of the manuscript for content, including medical writing for content. M.C.B. Molina: drafting/revision of the manuscript for content, including medical writing for content. P. Caramelli: drafting/revision of the manuscript for content, including medical writing for content. D.M. Marchioni: drafting/revision of the manuscript for content, including medical writing for content. C.K. Suemoto: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data.

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