Artificial sweeteners and sugar alcohols are associated with cognitive decline: an 8-year prospective cohort study

Supplementary Material

Supplemental Methods

Dietary assessment

Food and drink consumption in the last 12 months was assessed at baseline using a validated Food Frequency Questionnaire (FFQ) with 114 items. For each food item, the frequency of consumption ("more than 3 times/day, "2-3 times/day, "once/day", "5-6 times/week", "2-4 times/week", "once/week", "1-3 times/month", and "never/rarely") and the number of portions consumed (using standardized portion sizes) were obtained. The amount (grams/day) of each food item was calculated by multiplying the consumption frequency (3 for >3 times/day, 2 for 2-3 times/day, 1 for 1 time/day, 0.8 for 5-6 times/week, 0.4 for 2-4 times/week, 0.1 for 1 time/week, 0.07 for 1-3 times/month, and 0 for never/almost never) by the number of portions and the portion weight. The energy content of the food and drink items in kcal was calculated using the information on energy in 100g estimated by the University of Minnesota Nutrition Data System for Research (NDSR) software. All mixed dishes identified through the FFQ were decomposed into individual ingredients based on household standard recipes according to the national literature.

Cognitive assessment

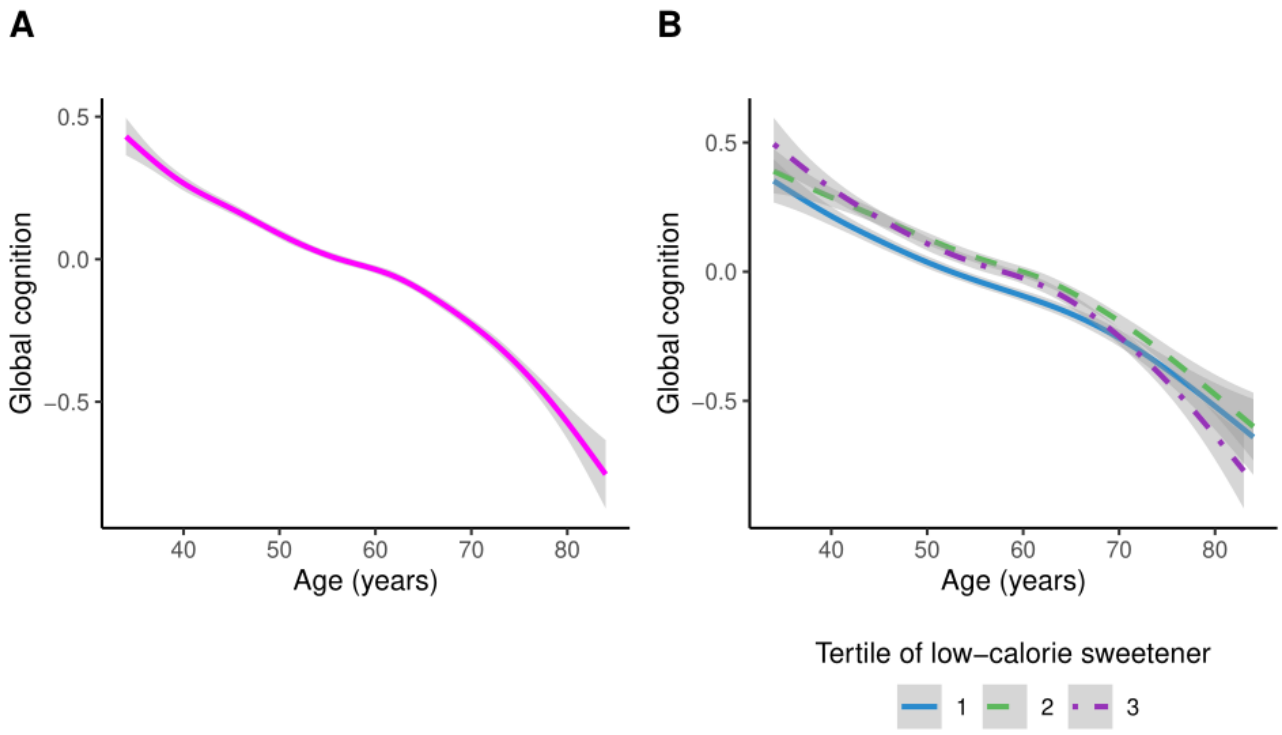
The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word list, validated for the Brazilian population, was used to assess episodic memory. For the immediate recall, participants were required to recall ten words from a list, presented three times, immediately after their presentations. In each trial, the words were displayed in a different order. The score was calculated as the sum of the correctly recalled words from the three trials (0-30). After a 5-minute distraction period, participants were required to recall the words from the same list without a new presentation.

The delayed memory score was calculated as the number of correctly recalled words (0-10 words). Participants were then asked to recognize the previously presented words from a list of 20 words - the original ones plus ten distracting words. The recognition score was calculated as the number of correctly recognized words minus the number of incorrectly selected words (0-10 words). The final memory score was computed by summing all partial scores from the word list tests (0-50 words). The semantic and phonemic verbal fluency tests were used to assess language and executive function. For semantic fluency, participants were asked to name as many animals as possible in 60 seconds in waves 1 and 3; in wave 2, the vegetable category was used instead. For phonemic fluency, participants were asked to name as many words starting with the letter F as possible in 60 seconds in waves 1 and 3; in wave 2, the letter A was used instead. The score for each test was the number of correct words produced. Verbal fluency categories differed in wave 2 to attenuate learning effects. Therefore, test scores from wave 2 were harmonized using the equipercentile equating technique to make them comparable to scores from waves 1 and 3. Finally, the Trail-Making Test version B was used to assess processing speed and executive function. Participants were instructed to draw a line connecting numbers and letters, placed randomly on a paper, in ascending and alternating order, and as quickly as possible (e.g., 1-A-2-B-3-C. Numbers ranged from 1 to 13 and letters from A to L). The test score was the time in seconds the participants took to complete the task.

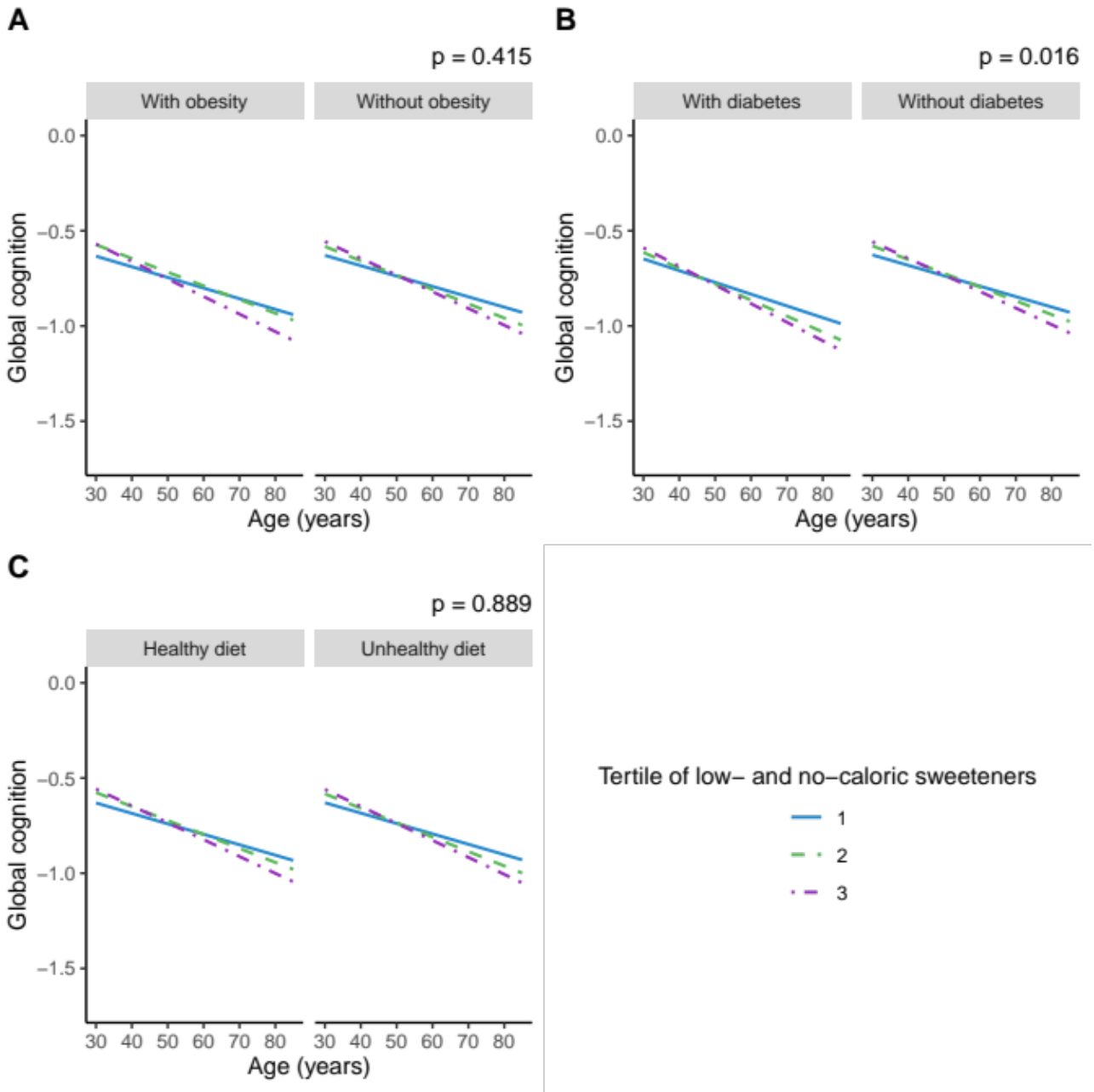
We calculated z-scores for each wave standardized to wave 1. For each test, the z-score was calculated by subtracting the sample mean for that test in wave 1 from the participants' score at each wave and dividing this difference by the sample standard deviation (SD) for the same test in wave 1. Different from the other tests, higher scores in the Trail-Making Test represent poorer performance. To make it comparable to the other tests, the z-scores were multiplied by -1. A composite memory z-score was created for each wave by averaging the z-scores from the memory tests at each wave, a composite verbal fluency z-score by averaging the z-scores from the two

verbal fluency tests at each wave, and a global cognitive score by averaging the z-scores from all the cognitive tests at each wave.

Supplemental Figures



eFigure 1. Association of low and no-caloric sweeteners consumption at the study baseline and trajectories of global cognition over a median of eight years of follow-up. **(A)** Total low and no caloric sweeteners and **(B)** tertiles of combined low and no-caloric sweeteners (1st tertile: 0.02mg to 37.2mg; 2nd tertile: 37.3mg to 102.3mg; 3rd tertile: 102.4mg to 856.5mg).



e**Figure 2.** Association of tertiles of combined low and no-caloric sweeteners at the study baseline and trajectories of global cognition over a median of eight years of follow-up considering the interaction with (A) obesity, (B) diabetes, and (C) diet. P-values represent the interaction terms among tertiles of low-calorie sweeteners, each modifier, and the timescale calculated 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 low and no-caloric sweeteners in mg was categorized into

tertiles (1st tertile: 0.02mg to 37.2mg; 2nd tertile: 37.3mg to 102.3mg; 3rd tertile: 102.4mg to 856.5mg). Obesity was defined as body mass index ≥ 30. Diabetes was self-reported or defined by glycated hemoglobin ≥ 6.5%. The healthy diet score was calculated by using the median score of the MIND diet, dividing the sample into healthy (score > 8) and unhealthy (score ≤ 8) diet groups.

Supplemental Tables

eTable 1. Association between baseline tertiles of combined low and no-caloric sweeteners and cognitive decline during eight years of follow-up (n = 12,772).

	Unadjusted		Model 1		Model 2		
	β (95% CI)	**p**	**β (95% CI)**	**p**	**β (95% CI)**	**p**	**%**
Memory							
Tertile 1*Time	Reference		Reference		Reference		
Tertile 2*Time	-0.004 (-0.024; 0.016)	0.680	-0.016 (-0.032; 0.004)	0.129	-0.008 (-0.032; 0.008)	0.219	16.0
Tertile 3*Time	-0.024 (-0.048; -0.002)	0.033	-0.032 (-0.048; -0.008)	0.005	-0.024 (-0.040; -0.004)	0.017	32.0
Verbal fluency							
Tertile 1*Time	Reference		Reference		Reference		
Tertile 2*Time	-0.016 (-0.032 0.008)	0.137	-0.024 (-0.048; -0.008)	0.005	-0.024 (-0.048; -0.008)	0.006	110.0
Tertile 3*Time	-0.032 (-0.056; -0.016)	<0.001	-0.040 (-0.056; -0.016)	<0.001	-0.040 (-0.064; -0.024)	<0.001	173.0
Executive function							
Tertile 1*Time	Reference		Reference		Reference		
Tertile 2*Time	0.016 (0.002; 0.048)	0.088	-0.001 (-0.024; 0.024)	0.931	0.000 (-0.024; 0.024)	0.976	0.9
Tertile 3*Time	0.008 (-0.016; 0.032)	0.576	-0.008 (-0.024; 0.016)	0.651	-0.002 (-0.024; 0.016)	0.852	6.3
Global cognition							
Tertile 1*Time	Reference		Reference		Reference		
Tertile 2*Time	-0.006 (-0.024; 0.008)	0.436	-0.016 (-0.024; -0.002)	0.024	-0.016 (-0.032; -0.001)	0.030	35.0
Tertile 3*Time	-0.024 (-0.040; -0.008)	0.002	-0.024 (-0.040; -0.016)	<0.001	-0.024 (-0.040; -0.016)	<0.001	62.0

β: estimate, CI: confidence interval

Tertiles of low and no-caloric sweeteners: 1st tertile: 0.02mg to 37.2mg; 2nd tertile: 37.3mg to 102.3mg; 3rd tertile: 102.4mg to 856.5mg

Model 1: linear mixed models adjusted for age, sex, race/ ethnicity, education, and income.

Model 2: linear mixed models additionally adjusted for 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.

eTable 2. Association between baseline tertiles of combined low and no-caloric sweeteners and cognitive decline during eight years of follow-up using next observation carried backward* (n = 12,772).

	Unadjusted		Model 1		Model 2	
	β (95% CI)	**p**	**β (95% CI)**	**p**	**β (95% CI)**	**p**
Memory						
Tertile 1*Time	Reference		Reference		Reference	
Tertile 2*Time	-0.004 (-0.024; 0.016)	0.632	-0.016 (-0.032; 0.001)	0.198	-0.008 (-0.032; 0.008)	0.209
Tertile 3*Time	-0.016 (-0.040; -0.002)	0.044	-0.024 (-0.048; -0.004)	0.017	-0.024 (-0.040; -0.002)	0.027
Verbal fluency						
Tertile 1*Time	Reference		Reference		Reference	
Tertile 2*Time	-0.016 (-0.032; 0.003)	0.115	-0.024 (-0.044; -0.007)	0.005	-0.024 (-0.040; -0.007)	0.007
Tertile 3*Time	-0.032 (-0.056; -0.016)	<0.001	-0.040 (-0.056; -0.024)	<0.001	-0.040 (-0.056; -0.024)	<0.001
Executive function						
Tertile 1*Time	Reference		Reference		Reference	
Tertile 2*Time	0.024 (0.001; 0.048)	0.037	0.004 (-0.016; 0.024)	0.674	0.006 (-0.016; 0.024)	0.595
Tertile 3*Time	0.002 (-0.016; 0.024)	0.861	-0.008 (-0.032; 0.008)	0.395	-0.006 (-0.024; 0.016)	0.538
Global cognition						
Tertile 1*Time	Reference		Reference		Reference	
Tertile 2*Time	-0.006 (-0.021; 0.008)	0.439	-0.016 (-0.024; -0.001)	0.033	-0.014 (-0.028; 0.000)	0.040
Tertile 3*Time	-0.024 (-0.039; -0.008)	0.002	-0.024 (-0.040; -0.016)	<0.001	-0.026 (-0.048; -0.013)	<0.001

β: estimate, CI: confidence interval

* Next observation carried backward by replacing missing cognitive scores from wave 3 to wave 2 for those aged less than 55 years in wave 2.

Tertiles of low- and no-caloric sweeteners: 1st tertile: 0.02mg to 37.2mg; 2nd tertile: 37.3mg to 102.3mg; 3rd tertile: 102.4mg to 856.5mg

Model 1: linear mixed models adjusted for age, sex, race/ ethnicity, education, and income.

Model 2: linear mixed models additionally adjusted for 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.

eTable 3. Association between baseline daily consumption of low- and no-caloric sweeteners and cognitive decline during eight years of follow-up (n = 12,772).

	Unadjusted		**Model 1**		**Model 2**	
	β (95% CI)	**p**	**β (95% CI)**	**p**	**β (95% CI)**	**p**
Memory	-0.029 (-0.048; -0.010)	0.002	-0.022 (-0.038; -0.004)	0.014	-0.018 (-0.035; 0.000)	0.043
Verbal fluency	-0.040 (-0.058; -0.022)	<0.001	-0.032 (-0.049; -0.016)	<0.001	-0.029 (-0.045; -0.012)	<0.001
Trail-Making test	-0.019 (-0.042; 0.002)	0.084	-0.018 (-0.037; 0.001)	0.069	-0.013 (-0.032; 0.006)	0.187
Global cognition	-0.030 (-0.044; -0.017)	<0.001	-0.024 (-0.037; -0.012)	<0.001	-0.021 (-0.034; -0.009)	0.001

β: estimate, CI: confidence interval

No consumption/ sporadic consumption was used as reference

Model 1: linear mixed models adjusted for age, sex, race/ ethnicity, education, and income.

Model 2: linear mixed models additionally adjusted for 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.

eTable 4. Association between baseline tertiles of combined low and no-caloric sweeteners and cognitive decline during eight years of follow-up using complete-case analysis (n = 6,041).

	Unadjusted		Model 1		Model 2	
	β (95% CI)	**p**	**β (95% CI)**	**p**	**β (95% CI)**	**p**
Memory						
Tertile 1*Time	Reference		Reference		Reference	
Tertile 2*Time	-0.008 (-0.048; 0.024)	0.511	-0.016 (-0.048; 0.024)	0.491	-0.008 (-0.048; 0.024)	0.568
Tertile 3*Time	-0.048 (-0.088; -0.008)	0.013	-0.040 (-0.072; 0.000)	0.050	-0.036 (-0.072; -0.000)	0.059
Verbal fluency						
Tertile 1*Time	Reference		Reference		Reference	
Tertile 2*Time	-0.016 (-0.056; 0.016)	0.388	-0.024 (-0.056; 0.008)	0.206	-0.016 (-0.056; 0.008)	0.192
Tertile 3*Time	-0.008 (-0.048; 0.024)	0.584	0.000 (-0.032; 0.032)	0.876	0.000 (-0.040; 0.032)	0.823
Executive function						
Tertile 1*Time	Reference		Reference		Reference	
Tertile 2*Time	-0.008 (-0.049; 0.040)	0.819	0.000 (-0.048; 0.040)	0.858	0.000 (-0.048; 0.040)	0.889
Tertile 3*Time	-0.008 (-0.056; 0.040)	0.678	0.000 (-0.048; 0.040)	0.911	0.000 (-0.048; 0.040)	0.954
Global cognition						
Tertile 1*Time	Reference		Reference		Reference	
Tertile 2*Time	-0.008 (-0.040; 0.016)	0.387	-0.016 (-0.040; 0.008)	0.268	-0.008 (-0.040; 0.008)	0.293
Tertile 3*Time	-0.024 (-0.048; 0.000)	0.053	-0.016 (-0.048; 0.008)	0.145	-0.016 (-0.048; 0.008)	0.139

β: estimate, CI: confidence interval

* Next observation carried backward by replacing missing cognitive scores from wave 3 to wave 2 for those aged less than 55 years in wave 2.

Tertiles of low- and no-caloric sweeteners: 1st tertile: 0.02mg to 37.2mg; 2nd tertile: 37.3mg to 102.3mg; 3rd tertile: 102.4mg to 856.5mg

Model 1: linear mixed models adjusted for age, sex, race/ ethnicity, education, and income.

Model 2: linear mixed models additionally adjusted for 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.

eTable 5. Association of individual low and no-caloric sweeteners* at the study baseline and cognitive decline during eight years of follow-up (n = 12,772).

	Memory		Verbal fluency		Executive function		Global cognition	
	β (95% CI)	**p**	**β (95% CI)**	**p**	**β (95% CI)**	**p**	**β (95% CI)**	**p**
Aspartame	-0.002 (-0.003; -0.0004)	0.005	-0.001 (-0.002; -0.0001)	0.038	0.001 (-0.001; 0.002)	0.347	-0.001 (-0.002; -0.0004)	0.004
Saccharin	-0.010 (-0.016; -0.003)	0.003	-0.005 (-0.008; 0.002)	0.154	0.0004 (-0.006; 0.008)	0.889	-0.008 (-0.011; -0.002)	0.003
Acesulfame-k	-0.003 (-0.006; -0.001)	0.003	-0.002 (-0.004; 0.0003)	0.095	0.002 (-0.001; 0.004)	0.318	-0.002 (-0.004; -0.001)	0.007
Erythritol	-0.038 (-0.067; -0.007)	0.015	-0.028 (-0.057; 0.001)	0.061	-0.029 (-0.068; 0.004)	0.083	-0.028 (-0.049; -0.006)	0.010
Sorbitol	-0.001 (-0.001; -0.0001)	0.009	-0.0008 (-0.001; -0.0003)	0.002	-0.0002 (-0.001; 0.0004)	0.443	-0.0006 (-0.001; -0.0002)	0.002
Xylitol	-0.032 (-0.056; -0.016)	<0.001	-0.016 (-0.032; 0.001)	0.059	-0.003 (-0.024; 0.016)	0.749	-0.016 (-0.032; -0.008)	<0.001
Tagatose	0.032 (-0.008; 0.081)	0.148	0.008 (-0.024; 0.048)	0.594	-0.008 (-0.056; 0.040)	0.737	0.024 (-0.006; 0.048)	0.118

β: estimate, CI: confidence interval

* Apartame, Saccharin, Acesulfame-k, Sorbitol, Xylitol, and Tagatose consumption ranged from 0 to 550 mg and were categorized in intervals of 5 mg each and analyzed as a continuous variable. Erythritol consumption raged from 0 to 1.8 mg and was categorized in intervals of 0.5 mg and analyzed as a continuous variable

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.

eTable 6. Association between baseline tertiles of combined low and no-caloric sweeteners and cognitive decline during eight years of follow-up stratified by baseline age (n = 12,772).

	< 60 years (n = 10,103)		**60+ years (2,669)**	
	β (95% CI)	**p**	**β (95% CI)**	**p**
Memory				
Tertile 1*Time	Reference		Reference	
Tertile 2*Time	0.000 (-0.024; 0.024)	0.867	-0.024 (-0.096; 0.048)	0.507
Tertile 3*Time	-0.024 (-0.048; 0.000)	0.055	-0.024 (-0.096; 0.048)	0.529
Verbal fluency				
Tertile 1*Time	Reference		Reference	
Tertile 2*Time	-0.016 (-0.040; -0.008)	0.234	-0.024 (-0.088; 0.032)	0.430
Tertile 3*Time	-0.040 (-0.064; -0.016)	0.001	0.000 (-0.056; 0.064)	0.879
Trail-making test				
Tertile 1*Time	Reference		Reference	
Tertile 2*Time	-0.008 (-0.032; 0.016)	0.574	-0.008 (-0.096; 0.080)	0.843
Tertile 3*Time	-0.008 (-0.032; 0.024)	0.668	-0.032 (-0.120; 0.048)	0.450
Global cognition				
Tertile 1*Time	reference		Reference	
Tertile 2*Time	-0.008 (-0.024; 0.008)	0.303	-0.016 (-0.064; 0.032)	0.513
Tertile 3*Time	-0.024 (-0.040; -0.008)	0.003	-0.016 (-0.064; 0.032)	0.520

β: estimate, CI: confidence interval
Tertiles of low and no-caloric sweeteners: 1st tertile: 0.02mg to 37.2mg; 2nd tertile: 37.3mg to 102.3mg; 3rd tertile: 102.4mg to 856.5mg
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.

eTable 7. Association of individual low and no-caloric sweeteners* at the study baseline and cognitive decline during eight years of follow-up stratified by baseline age. (n = 12,772).

	< 60 years (n = 10,103)		60+ years (2,669)	
	β (95% CI)	**p for trend**	**β (95% CI)**	**p for trend**
Memory				
Aspartame	-0.016 (-0.001; 0.001)	0.107	0.000 (-0.008; 0.001)	0.382
Saccharin	-0.008 (-0.016; 0.001)	0.058	-0.008 (-0.032; 0.008)	0.419
Acesulfame-k	0.000 (-0.008; 0.000)	0.083	-0.008 (-0.016; 0.000)	0.219
Erythritol	-0.032 (-0.065; 0.008)	0.142	0.008 (-0.080; 0.096)	0.898
Sorbitol	-0.001 (-0.002; 0.000)	0.015	0.000 (0.000; 0.000)	0.814
Xylitol	-0.032 (-0.056; -0.008)	0.016	0.008 (-0.056; 0.064)	0.779
Tagatose	0.064 (0.008; 0.120)	0.011	-0.168 (-0.320; -0.004)	0.043
Verbal fluency				
Aspartame	0.000 (0.000; 0.000)	0.366	0.000 (0.000; 0.000)	0.831
Saccharin	0.000 (-0.008; 0.008)	0.397	0.016 (-0.001; 0.032)	0.088
Acesulfame-k	0.000 (0.000; 0.000)	0.484	0.000 (-0.008; 0.008)	0.841
Erythritol	-0.024 (-0.080; 0.001)	0.051	0.008 (-0.064; 0.088)	0.731
Sorbitol	-0.001 (-0.002; 0.000)	0.032	0.000 (0.000; 0.000)	0.573
Xylitol	-0.008 (-0.032; 0.016)	0.485	-0.016 (-0.032; 0.064)	0.462
Tagatose	0.008 (-0.040; 0.064)	0.708	0.040 (-0.044; 0.176)	0.527
Executive function				
Aspartame	0.000 (0.000; 0.002)	0.226	0.000 (-0.008; 0.001)	0.293
Saccharin	0.008 (-0.001; 0.008)	0.249	-0.008 (-0.040; 0.008)	0.316
Acesulfame-k	0.000 (-0.001; 0.008)	0.253	-0.008 (-0.016; 0.000)	0.235
Erythritol	-0.024 (-0.064; 0.016)	0.275	-0.040 (-0.152; 0.072)	0.480
Sorbitol	0.000 (-0.001; 0.001)	0.482	0.000 (-0.002; 0.001)	0.613
Xylitol	0.024 (0.000; 0.056)	0.084	-0.016 (-0.088; 0.056)	0.649
Tagatose	0.000 (-0.056; 0.056)	0.949	0.048 (-0.144; 0.248)	0.606
Global cognition				
Aspartame	0.000 (-0.002; 0.001)	0.214	0.000 (-0.008; 0.001)	0.111
Saccharin	0.000 (-0.008; 0.001)	0.126	0.000 (-0.016; 0.008)	0.528
Acesulfame-k	0.000 (-0.003; 0.008)	0.222	0.000 (-0.008; 0.001)	0.087
Erythritol	-0.024 (-0.048; 0.000)	0.054	0.008 (-0.048; 0.064)	0.798
Sorbitol	-0.0005 (-0.001; -0.0001)	0.016	0.000 (0.000; 0.000)	0.611
Xylitol	-0.008 (-0.024; 0.008)	0.187	0.008 (-0.032; 0.048)	0.738
Tagatose	0.040 (0.008; 0.080)	0.023	-0.048 (-0.168; 0.056)	0.328

β: estimate, CI: confidence interval

* Apartame, Saccharin, Acesulfame-k, Sorbitol, Xylitol, and Tagatose consumption ranged from 0 to 550 mg and were categorized in intervals of 5 mg each and analyzed as a continuous variable. Erythritol consumption raged from 0 to 1.8 mg and was categorized in intervals of 0.5 mg and analyzed as a continuous variable

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.

eTable 8 Association between baseline tertiles of combined low and no-caloric sweeteners and cognitive decline during eight years of follow-up stratified by diabetes status (n = 12,772).

	Without diabetes (n = 11,363)		**With diabetes (1,409)**	
	β (95% CI)	**p**	**β (95% CI)**	**p**
Memory				
Tertile 1*Time	Reference		Reference	
Tertile 2*Time	-0.002 (-0.023; 0.024)	0.826	-0.069 (-0.093; -0.006)	0.030
Tertile 3*Time	-0.011 (-0.033; 0.010)	0.304	-0.088 (-0.148; -0.028)	0.004
Verbal fluency				
Tertile 1*Time	Reference		Reference	
Tertile 2*Time	-0.021 (-0.042; -0.001)	0.040	-0.047 (-0.102; 0.006)	0.086
Tertile 3*Time	-0.036 (-0.057; -0.014)	<0.001	-0.047 (-0.099; 0.005)	0.076
Executive function				
Tertile 1*Time	Reference		Reference	
Tertile 2*Time	-0.002 (-0.025; 0.020)	0.850	0.023 (-0.056; 0.104)	0.560
Tertile 3*Time	0.000 (-0.022; 0.023)	0.963	0.022 (-0.055; 0.098)	0.583
Global cognition				
Tertile 1*Time	reference		Reference	
Tertile 2*Time	-0.008 (-0.023; 0.006)	0.255	-0.052 (-0.096; -0.008)	0.025
Tertile 3*Time	-0.018 (-0.034; -0.002)	0.019	-0.063 (-0.105; -0.021)	0.005

β: estimate, CI: confidence interval
Diabetes was self-reported or defined as glycated Hb ≥ 6.5%.
Tertiles of low and no-caloric sweeteners: 1st tertile: 0.02mg to 37.2mg; 2nd tertile: 37.3mg to 102.3mg; 3rd tertile: 102.4mg to 856.5mg
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.

eTable 9. Association of individual low and no-caloric sweeteners* at the study baseline and cognitive decline during eight years of follow-up stratified by diabetes status. (n = 12,772).

	Without diabetes (n = 11,363)		With diabetes (1,409)	
	β (95% CI)	**p for trend**	**β (95% CI)**	**p for trend**
Memory				
Aspartame	0.000 (-0.002; 0.000)	0.323	-0.004 (-0.007; -0.002)	0.002
Saccharin	-0.004 (-0.012; 0.002)	0.234	-0.024 (-0.038; -0.009)	0.001
Acesulfame-k	-0.001 (-0.004; 0.001)	0.368	-0.009 (-0.015; -0.004)	<0.001
Erythritol	-0.038 (-0.070; -0.004)	0.025	-0.030 (-0.107; 0.045)	0.427
Sorbitol	-0.0007 (-0.001; 0.000)	0.033	0.000 (-0.002; 0.001)	0.376
Xylitol	-0.029 (-0.049; -0.007)	0.007	-0.069 (-0.122; -0.014)	0.012
Tagatose	0.030 (-0.016; 0.077)	0.203	0.035 (0.104; 0.176)	0.616
Verbal fluency				
Aspartame	0.001 (-0.002; 0.000)	0.353	-0.003 (-0.006; 0.000)	0.020
Saccharin	-0.001 (-0.008; 0.006)	0.691	-0.009 (-0.022; 0.002)	0.134
Acesulfame-k	0.000 (-0.002; 0.002)	0.845	-0.007 (-0.012; -0.002)	0.005
Erythritol	-0.021 (-0.054; 0.010)	0.180	-0.033 (-0.100; 0.034)	0.329
Sorbitol	-0.0007 (-0.001; 0.000)	0.018	-0.001 (-0.002; 0.000)	0.080
Xylitol	-0.010 (-0.031; 0.009)	0.299	-0.044 (-0.091; 0.002)	0.060
Tagatose	0.028 (-0.018; 0.074)	0.232	0.098 (-0.222; 0.026)	0.120
Executive function				
Aspartame	0.001 (0.000; 0.002)	0.185	0.001 (-0.002; 0.005)	0.623
Saccharin	0.000 (-0.007; 0.007)	0.996	0.010 (-0.008; 0.029)	0.265
Acesulfame-k	0.002 (0.000; 0.004)	0.136	0.001 (-0.006; 0.008)	0.800
Erythritol	-0.017 (-0.053; 0.018)	0.346	-0.072 (-0.172; 0.028)	0.160
Sorbitol	0.000 (-0.001; 0.000)	0.604	0.000 (-0.002; 0.002)	0.916
Xylitol	-0.004 (-0.027; 0.018)	0.693	0.012 (-0.057; 0.083)	0.716
Tagatose	0.018 (-0.031; 0.068)	0.476	-0.216 (-0.404; -0.029)	0.023
Global cognition				
Aspartame	0.001 (-0.001; 0.000)	0.303	-0.003 (-0.005; -0.001)	0.002
Saccharin	-0.003 (-0.009; 0.001)	0.177	-0.014 (-0.024; -0.003)	0.009
Acesulfame-k	0.000 (-0.003; 0.001)	0.539	-0.006 (-0.010; -0.002)	<0.001
Erythritol	-0.024 (-0.047; -0.001)	0.039	-0.036 (-0.090; 0.018)	0.196
Sorbitol	-0.0005 (-0.001; 0.000)	0.011	0.000 (-0.002; 0.000)	0.203
Xylitol	-0.016 (-0.031; -0.001)	0.030	-0.051 (-0.089; -0.013)	0.009
Tagatose	0.033 (0.000; 0.066)	0.050	-0.043 (-0.144; 0.057)	0.395

β: estimate, CI: confidence interval

Diabetes was self-reported or defined as glycated Hb ≥ 6.5%.

* Apartame, Saccharin, Acesulfame-k, Sorbitol, Xylitol, and Tagatose consumption ranged from 0 to 550 mg and were categorized in intervals of 5 mg each and analyzed as a continuous variable. Erythritol consumption raged from 0 to 1.8 mg and was categorized in intervals of 0.5 mg and analyzed as a continuous variable

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.