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Dietary Prebiotic Consumption is Associated with Reduced Risk of Alzheimer's Disease in a Multiethnic Population

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Abstract

Objective: To investigate the association between dietary prebiotic intake and risk for Alzheimer's disease (AD).

Methods: This longitudinal study includes 1,837 elderly (≥65 years) participants of a multi-ethnic community-based cohort study who were dementia-free at baseline and had provided dietary information from food frequency questionnaires. Total daily intake of fructan, one of the best-known prebiotics, was calculated based on consumption frequency and fructan content per serving of 8 food items. The associations of daily fructan intake with AD risk were examined using a Cox proportional hazards model, adjusted for cohort recruitment wave, age, gender, race/ethnicity, education, daily caloric intake, and *APOE* genotype. Effect modification by race/ethnicity, *APOE* genotype, and gender was tested by including an interaction term into the Cox models, as well as by stratified analyses.

Results: Among 1,837 participants (1,263 women [69%]; mean [SD] age= 76 [6.3] years), there were 391 incident AD cases during a mean follow-up of 7.5 years (13736 person-years). Each additional gram of fructan intake was associated with 24% lower risk for AD ((95% CI)=0.60–0.97; P=0.03). Additional adjusting for smoking, alcohol consumption, and comorbidity index

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Statistical analysis and interpretation of data: Nishikawa and Gu.

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did not change results materially. The associations were not modified by race/ethnicity, gender, and *APOE* genotype, although stratified analyses showed that fructan intake was significantly associated with reduced AD risk in Hispanics but not in non-Hispanic Blacks or Whites.

Conclusions: Higher dietary fructan intake is associated with reduced risk of clinical Alzheimer's disease among older adults.

Introduction

Recent data support a bidirectional influence of the gut microbiome on the central nervous system (CNS) via the "gut-brain axis"[1]. Alterations in the gut microbiome are with neurological conditions including autism spectrum disorder[2], multiple sclerosis[3], and Parkinson's disease[4]. Studies of fecal samples from patients with Alzheimer's Disease (AD) suggest broad-scale differences in gut microbiome composition, such as decreased microbial diversity, compared with individuals without AD[5].

Diet is one of the key modifiable factors that is involved in shaping the gut microbiome[6]. There is increased recognition of the role of diet in modulating gut microbiome diversity and metabolic activity[7]. Within our diet, we may consume foods that contain probiotic and prebiotic ingredients. Probiotics are live microbial organisms such as *bifidobacteria* that confer health benefits to the host when consumed in adequate quantities[8], whereas prebiotics are non-digestible substances that act as substrates for our autochthonous probiotic bacteria[9]. Fructans, or fructose-derived oligo- and polysaccharides, are one of the best-known prebiotics that stimulates probiotic growth and important modulators of gut microbiota ecology[10]. Fructans are found naturally in many foods; they increase numbers of "protective" gut microbiota that inhibit pathogens and enhance gut defenses, such as *lactobacilli* and *bifidobacteria*[11]. Fructans also possibly play a role in improving verbal episodic memory[12], anxiety[13], affect[14], and mood[14] and reduce the risk of developing metabolic disorders[15].

Cumulative evidence from epidemiological studies suggests that high adherence to a healthy diet, such as Mediterranean-type diets[16] and other dietary patterns[17–19], may help prevent AD. The mechanisms for the beneficial roles of these healthy dietary patterns on AD remain unclear, although emerging evidence suggests the potential involvement of inflammatory pathway[18]. Thus, potential factors related to underlying mechanisms of dietary effects, such as microbiome-influencing prebiotics, may provide unique insights into the association between diet and AD. To our knowledge, no studies have examined the relationship between fructan consumption and risk for AD. Furthermore, *APOE* genotype and females are known to be associated with AD. However, the relationship between these factors in the context of fructan consumption is unknown. Additionally, while there is well-documented racial/ethnic disparity in AD [20], which may suggest differential effects of the social and behavioral determinants of health across groups, few studies have examined the association of diet and risk of AD among a racially/ethnically diverse population.

In the current study, we examined the association between daily fructan intake and risk for clinically diagnosed AD dementia using data from the Washington Heights-Inwood Columbia Aging Project (WHICAP), a longitudinal study of community-based, multiethnic

cohort of older adults. We also examined the associations separately in three main racial/ethnic groups.

Methods

Study Population:

This study included elderly (≥65 years) participants from the longitudinal WHICAP study. Participants were selected from a probability sample of Medicare-eligible northern Manhattan residents[20,21]. Participants were followed approximately every 1.5–2 years, repeating baseline examination and consensus diagnosis. Dietary data were not available to and not considered by the consensus panel during the diagnostic process. The current study included participants of the WHICAP cohort recruited in the 1992 and 1999 waves. Among 3,356 WHICAP participants, 2,836 were dementia-free at baseline (Figure 1). Among them, 339 subjects were excluded due to missing dietary information, 442 subjects were excluded due to lack of follow up, 197 subjects were excluded due to missing information on key covariates, and 21 subjects were excluded due to extreme caloric intake (beyond 500–3500 kcal/day). The study's final analytical sample included a total of 1,837 subjects. This study was approved by the institutional review board of the Columbia University Irving Medical Center. All participants provided written informed consent.

Alzheimer's Disease Diagnosis:

At baseline and at each follow-up visit, research staff elicited each subject's medical and neurological history and conducted a standardized physical and neurological examination. Structured in-person interviews were conducted for each participant, including an assessment of cognition using a neuropsychological battery[22]. Standard DMS-III-R criteria[23] were used for diagnosis of dementia at a consensus conference. Consensus diagnoses of probable and possible AD were based on NINCDS-ADRDA criteria[23,24] at each visit, taking into consideration all available neuropsychological and medical information at the current visit but not prior visits. The diagnosis of mild cognitive impairment (MCI) used Petersen criteria[25] as described elsewhere[27].

Diet data:

Trained interviewers administered the 61-item version of the Willett semiquantitative food frequency questionnaire (SFFQ) (Channing Laboratory, Cambridge, Massachusetts) in English or Spanish in order to obtain each participant's average food consumption over one year prior to their baseline assessment. The SFFQs had been previously used and validated for determination of dietary intake in WHICAP populations[26]. A total of eight food items were identified to have fructan content reported in the literature (bananas, white bread, dark bread, potato chips or corn chips, peas or lima beans, beans or lentils, rice or pasta, and cold breakfast cereal). Average fructan content of each food item (grams per serving) was estimated based on published data[28–31], presented as follows: Beans or Lentils (0.20 g/0.5 cup, Potato Chips or Corn Chips (0.29 g/cup), White Bread (0.30 g/slice), Dark Bread (0.30 g/slice), Bananas (0.45 g/medium-sized banana), Peas or Lima Beans (0.47 g/0.5 cup), Rice or Pasta (0.54 g/cup), Cold Breakfast Cereal (0.69 g/cup). Total daily fructan intake was calculated for each participant based on daily consumption frequency and fructan content

per serving of the 8 food items. Total daily fructan intake was then adjusted for total daily caloric intake, and residuals, which are referred to as fructan diet residuals, were used in the analyses.[32] Participants were also divided into three groups based on tertiles of fructan diet residuals.

Covariates evaluation:

Information about recruitment cohort (1992 cohort as reference), age (years), gender (female as reference), education (years), body mass index (BMI, kg/m^2), and smoking status at baseline (no smoking as reference) was obtained from baseline interviews. Self-reported race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or others) was classified based on the 1990 US Census guidelines. Caloric intake (kcal) and alcohol consumption (no alcohol as reference) were calculated from the baseline SFFQ. Apolipoprotein ε4 (*APOE*) genotype was used as a dichotomous variable: absence vs presence (of either 1 or 2) of ε4 alleles. The presence or absence of heart disease (myocardial infarction, congestive heart failure, peripheral vascular disease), hypertension, diabetes mellitus, insulin use, major depressive disorder, psychiatric medication use, and history of head injury, were based on self-report during baseline interviews. A composite comorbidity index was calculated by summing all 7 dichotomous comorbidity scores, ranging from 0–7.

Statistical analysis:

Characteristics of participants by fructan diet residual tertiles were compared using ANOVA for continuous variables and chi-square test for categorical variables. To evaluate the association between daily fructan intake and AD risk, we conducted Cox proportional hazards models, with incident AD as the dichotomous outcome and fructan diet residual (both continuous and tertiles) as the main predicting variable. Time-to-event variable was defined as the time from recording of baseline diet to first visit of AD diagnosis for incident AD cases or to the last follow-up visit for non-incident AD cases. The models were adjusted for recruitment cohort, age, gender, race/ethnicity, education, and caloric intake. In a fully adjusted model, we additionally adjusted for alcohol intake, *APOE* genotype, smoking status, and comorbidity index. All variables were used as time-constant covariates. The proportional hazards assumption was met ($p > 0.10$).

We performed supplementary analyses using the continuous fructan diet residual variable. We performed post-hoc analyses to see which of the eight fructan-containing food items was associated with AD risk by including individual items simultaneously in the model. Effect modification by race/ethnicity, *APOE* genotype, or gender, was tested by including an interaction term (fructan diet continuous score X potential effect modifier) into Cox models, followed by exploratory stratified analyses by race/ethnic groups (non-Hispanic black, non-Hispanic white, or Hispanic), *APOE* genotype, and gender. Sensitivity analyses were also done by limiting analysis to subjects without cognitive impairment (i.e. excluding MCI) at baseline or subjects with fewer than 2 years of follow-up. In addition to all covariates in Model 2, we also adjusted for key AD-related foods or nutrients[19]. Finally, as most fructan-containing foods were cereals and legumes, we examined whether total cereals and total legumes were associated with AD risk in order to test specificity. Tests were considered

statistically significant at $P < 0.05$. All statistical analyses were performed using IBM SPSS software version 26.0 (IBM, Armonk, NY, USA).

Results

Missing Data Analysis:

Compared with participants in the final analytical sample (n=1,837; mean [SD] age, 76 [6.3] years), participants with missing follow-up data, missing dietary information, missing covariate information, or extreme caloric intake (n=999) were slightly older (76.9 vs 75.6; $P < .001$), less likely to be female (64.5% vs 68.8%, $P = .02$), more likely to be Black (35.7% vs 31.55%, $P = .02$), less likely to have smoking history (38.0% vs. 42.5%, $P = .02$), and had fewer comorbidities (1.8 vs. 2.4, $P < .001$). However they were similar in terms of education and BMI.

Clinical-Demographic-Dietary Characteristics:

The participants were on average 75.6 years old at baseline, 68.8% female, with an average BMI of 28.0 kg/m^2, average education of 10.1 years, and mean follow-up duration of 7.5 years. Daily energy intake averaged 1,426 kcal, and the subjects consumed on average 1.00 grams of fructan daily. Compared to non-Hispanic Whites, Hispanic subjects were more likely to be in the middle or highest fructan intake tertiles and non-Hispanic Blacks were more likely to be in the lowest fructan intake tertile. The middle fructan intake tertile had the lowest caloric intake, while subjects with highest fructan intake tended to have lower BMI compared to the lowest or middle tertiles. There was no difference among fructan intake tertiles in age, female gender, education, medical comorbidity index, *APOE* genotype, or smoking status (Table 1).

Three hundred ninety-one incident cases of AD were identified during an average follow-up of 7.5 years (standard deviation [SD], 4.9 years; range, 0–25.6 years, total 13736 person-years). Compared with 1,446 subjects who remained without AD diagnosis, participants with AD diagnosis at follow-up were older, had fewer years of education, had a higher mean comorbidity index, were more likely to be women, had shorter follow-up duration, were more likely to possess the *APOE* ε4 allele, consumed more daily calories, and were more likely to be Hispanic and less likely to be White. Participants who did and did not acquire AD did not differ in daily caloric intake, smoking status, or mean daily fructan intake. (Table 2).

Fructan Consumption and Risk for AD:

Higher daily fructan intake was associated with lower risk for development of AD (Table 3; Figure 2). Using a Cox proportional hazards model adjusted for cohort, age, gender, ethnicity, education, caloric intake, and *APOE* genotype, each additional gram of fructan intake was associated with 24% lower risk for AD development. Compared with subjects in the lowest tertile of daily fructan intake, subjects in the highest tertile had 27% lower risk for development of AD. Results were similar in fully adjusted model (Table 3). Average age at the time of AD diagnosis did not differ among fructan intake tertiles, and no differences

were seen when separately comparing the subjects' APOE allele carrier status and race (Supplemental Table 1).

Supplementary analyses:

Fructan intake from individual food items: Average daily fructan intake from "Bananas", "Rice or Pasta", "Cold Breakfast Cereal", "Dark Bread", "White Bread", "Peas or Lima Beans", "Beans or Lentils", and "Potato Chips or Corn Chips", comprised 24.8%, 23,6%, 21.9%, 15.7%, 10.6%, 7.4%, 5.0%, and 1.3% respectively, of participants' average total daily fructan consumption (1.0 g/day). There was no association between fructan intake from fructan-containing food items and risk of AD (data not shown).

Interactions with fructan intake: The association between fructan intake and AD risk was not modified by race/ethnicity (*P*-interaction = .65 comparing Hispanic to White participants, *P*-interaction = .90 comparing Black to White participants), *APOE* genotype (P-interaction = .12), or gender (*P*-interaction = .61). Stratified analysis showed that fructan intake was associated with reduced AD risk only in Hispanics [HR(95% CI)=0.68 (0.49–0.93), *P* = .01] in adjusted model (Table 4; Figure 2) but not in non-Hispanic Whites or Blacks [HR(95% CI)=0.63 (0.31–1.27), *P* =.20, and 0.99 (0.62–1.60), *P* = .98, respectively]. The association was significant among *APOE* ε4 non-carriers [HR(95% CI)=0.66 (0.49–0.87), *P* = .004] but not among carriers [HR(95% CI)=0.99 (0.67–1.46), *P* = .95], and in women [HR(95%CI)=0.71(0.53–0.95), *P* =.02] but not in men [HR(95%CI)=0.96(0.60–1.53), *P* =.85].

Sensitivity Analysis:

After limiting the analysis to 1,334 cognitively unimpaired participants (excluding 420 subjects with MCI at baseline and 83 subjects without information for MCI diagnosis), we found that results remained significant, with each additional gram of daily fructan intake associated with reduced AD risk HR(95%CI)=0.70 (0.50–0.96), *P* = .03. Similarly, after excluding 157 subjects with fewer than 2 years of follow-up, fructan intake remained associated with reduced AD risk, with HR (95%CI)=0.76(0.59–0.99), *P* = .04. The results remained significant after further additional adjustment for fish, vegetables, antioxidants consumption, or BMI (data not shown). Total legume and cereal intake were not associated with AD risk (data not shown).

Discussion

We found that higher daily fructan consumption was associated with reduced risk of developing clinical AD. We found that the association mainly existed for Hispanics, *APOE* ε4 non-carriers, and women.

With the lack of effective treatment for AD, it is important to identify preventive measures. Accumulating evidence suggests that some dietary patterns[19] are associated with reduced risk of developing AD and MCI, including The DASH diet[33], the Mediterranean diet (MEDI)[16], and the MIND diet[17]. While several mechanisms, including vascular, metabolic, oxidative, and inflammatory mechanisms, have been proposed to explain the beneficial

effect of these dietary patterns on AD risk[34,35], the exact biological pathways have yet to be established. Of note, these diets typically encourage the consumption of foods rich in natural prebiotics (whole grains, fruit, legumes, or vegetables)[17,36], and may support future investigation of gut microbiota modification as one potential pathway for these dietary patterns.

To our knowledge, this is the first study that examines the association of fructan from foods with risk of AD. The association between higher daily fructan consumption and lower risk for AD is consistent with emerging evidence suggesting prebiotic involvement in related clinical effects, such as improved cognition, mood, and recall. Specifically, in two recent studies, direct supplementation with oligofructose or inulin or non-starch polysaccharides improved recall and recognition memory[37] and non-starch polysaccharides improved recall and recognition memory and well-being in middle-aged adults[38].

Although the exact mechanism is unknown, such beneficial neurological and cognitive effects may be explained by fructan involvement in stimulating gut microbiota activity, as clinical trials showed an increase in the number of *lactobacilli* and *bifidobacteria* after fructan supplementation[9]. These gut microbiota influence the “gut-brain-axis” by regulating peripheral and CNS activity through various channels of communication, including neurotransmitter production, vagal nerve activation, and immunomodulation[39]. *Lactobacilli* and *bifidobacter*a produce acetylcholine or short-chain fatty acids such as acetate and butyrate, which could bypass portal circulation and reach the brain through circulation[40] and exert neuroprotection[4].

Another effect of prebiotic supplementation is improved immunoregulation and infection prevention[41]. Prebiotic supplements may activate T lymphocytes and dendritic cells of the gastrointestinal tract[42]. In rodent studies, diet containing fructans increased resistance against infections caused by Salmonella and Listeria[43]. As inflammation is increasingly implicated in AD pathogenesis[44], the immunoregulatory potential of fructans may explain its preventive effect against development of AD.

We found the association between fructan intake and AD risk was significant only in Hispanics, but not in non-Hispanic Blacks or Whites. As Hispanic participants had the highest fructan intake among all three racial/ethnic groups, the results suggest that there may be a possible threshold effect. A certain level of daily fructan consumption may be necessary to see beneficial effects. Another possibility could be that differences in gut microbiota composition exist among racial/ethnic groups, leading to different biological responses to consumed fructans. However, such variations are likely influenced by dietary patterns and medical history[45]. We found an association between fructan intake and AD risk among participants who did not have *APOE* ε4 allele but not in *APOE* ε4 carriers. While it is possible that the sample size of *APOE* ε4 carriers was too small to provide enough statistical power to detect a significant effect, the effect size for carriers does seem to be much smaller compared to that of the non-carriers. Recent rodent studies suggested that *APOE* genotype is associated with different gut microbiome structure[46] and that dietary inulin-type fructans can change gut microbiota and reduce neuro-inflammation in young, asymptomatic *APOE* ε4 positive mice[47]. Thus, future studies with larger number of *APOE* ε4 carriers should test

whether fructan is protective in people with high susceptibility to AD. Finally, we found an association between fructan intake and AD risk in women. Recent studies examined gender differences in both food preferences and the gut microbiome[48], and it would be plausible that dietary and prebiotic effects on gut microbiota differ by gender. Further study of gender differences in gut microbiome response to prebiotics among AD patients would be helpful.

This study has limitations. First, frequencies of daily fructan consumption were based on eight diet constituents, which may underestimate overall fructan consumption. Each of the eight food items as listed on the SFFQ were broad categories that may include several food members with varying fructan contents, which may affect the precision of daily fructan consumption calculations. As such, diet is not a true measurement of prebiotic intake compared to measuring intake by direct prebiotic supplementation. Furthermore, limited accuracy of food exposures estimated from SFFQ is a common limitation of studies of diet and disease. Nevertheless, such potential misclassification bias should be non-differential, leading to attenuation of the associations under investigation. In addition, a single measurement of diet over the course of one year was used, and this may not have captured long-term diet habits of the subjects. However, in the past, we have shown stable diets among the study participants over 8 years[16]. We adjusted for many potential confounders, such as other dietary factors, and thus residual confounding cannot completely be ruled out as an explanation of our findings. However, we found robust results after adjusting for multiple covariates as well as several key foods that are potentially related to AD. Also, the exclusion of subjects from the final analysis due to loss to follow-up or missing data may have introduced selection bias. Finally, despite an average follow-up of 7.2 years, we cannot rule out the possibility of reverse causality. Subtle cognitive changes can antedate the clinical diagnosis of AD by many years[16], so lower fructan consumption could represent a consequence and not a factor preceding AD diagnosis. However, our sensitivity analyses excluding MCI participants and participants with short follow-up time found similar results. Furthermore, it is unlikely that AD patients in the current study would have intentionally reduced their fructan intake or vice versa. Despite a large overall sample size, our study might have limited power for effect modification analyses. Whether prebiotics intake is associated with certain subpopulations needs to be tested further in future larger studies.

This study has many advantages. To our knowledge, this is the first study to examine the association of dietary fructan intake, a key prebiotic, and AD risk in humans. Dietary data were collected with a previously validated instrument widely used in several epidemiological studies[49]. For each food item, fructan content per serving was examined carefully and estimated according to all available published studies[29,50]. The diagnosis of AD was based on comprehensive clinical and neuropsychological assessment and standard research criteria and took place in a university hospital with expertise in dementia. The longitudinal study design and related sensitivity analyses provide strong support for a temporal relationship between fructan intake and the development of AD. The patients were followed up at relatively short intervals. Measures for multiple potential AD risk factors have been carefully recorded and adjusted for in the analyses. Finally, the role of fructan intake in AD risk was examined separately for racial/ethnic group, which may help with design of more precise prevention measures targeting responsive subpopulations.

Conclusion

Our study suggests that higher fructan intake is associated with reduced risk of AD among elderly subjects. Our findings provide support for further exploration of dietary behavior and possible microbiota involvement for the prevention of a global public health concern.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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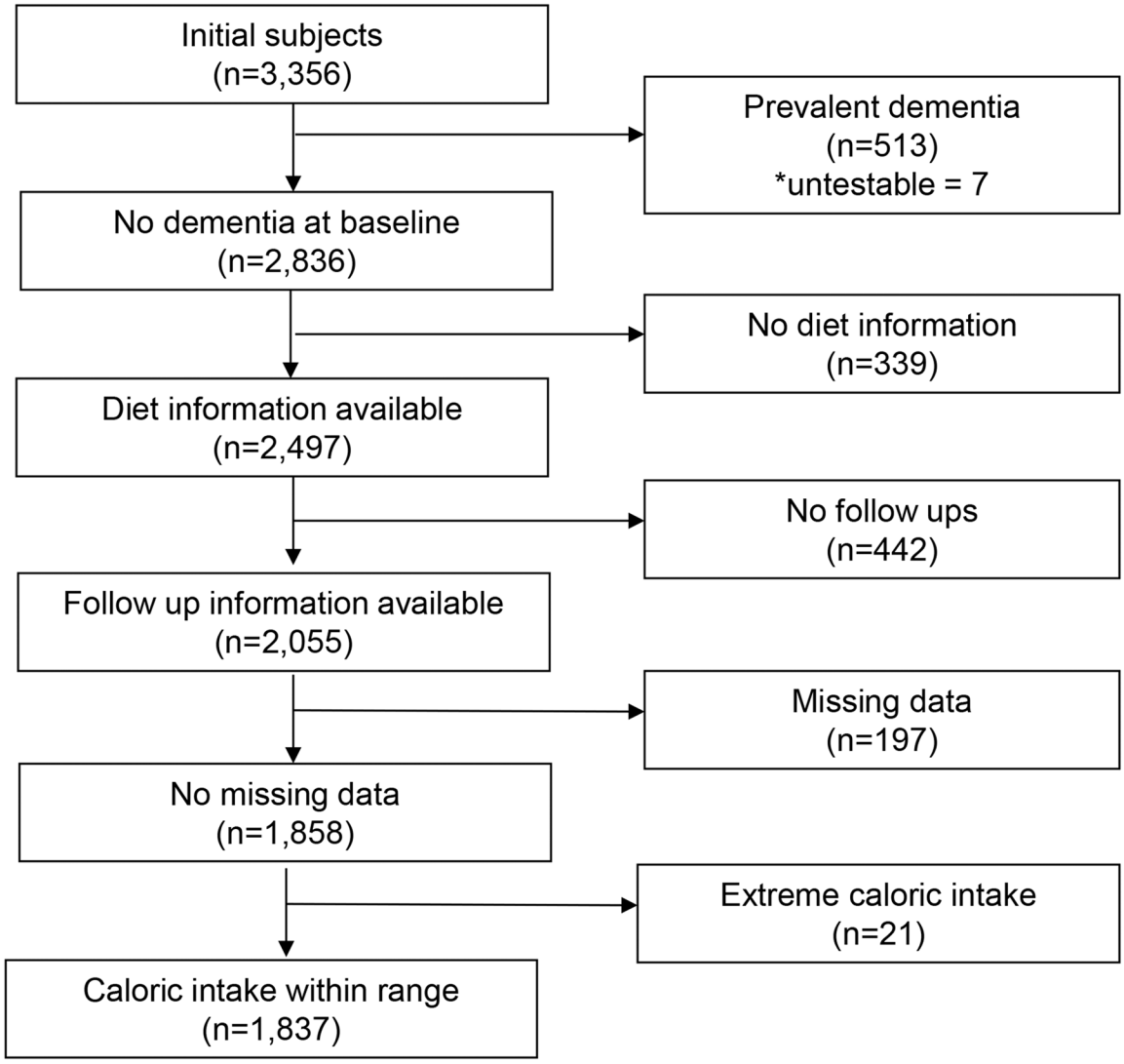
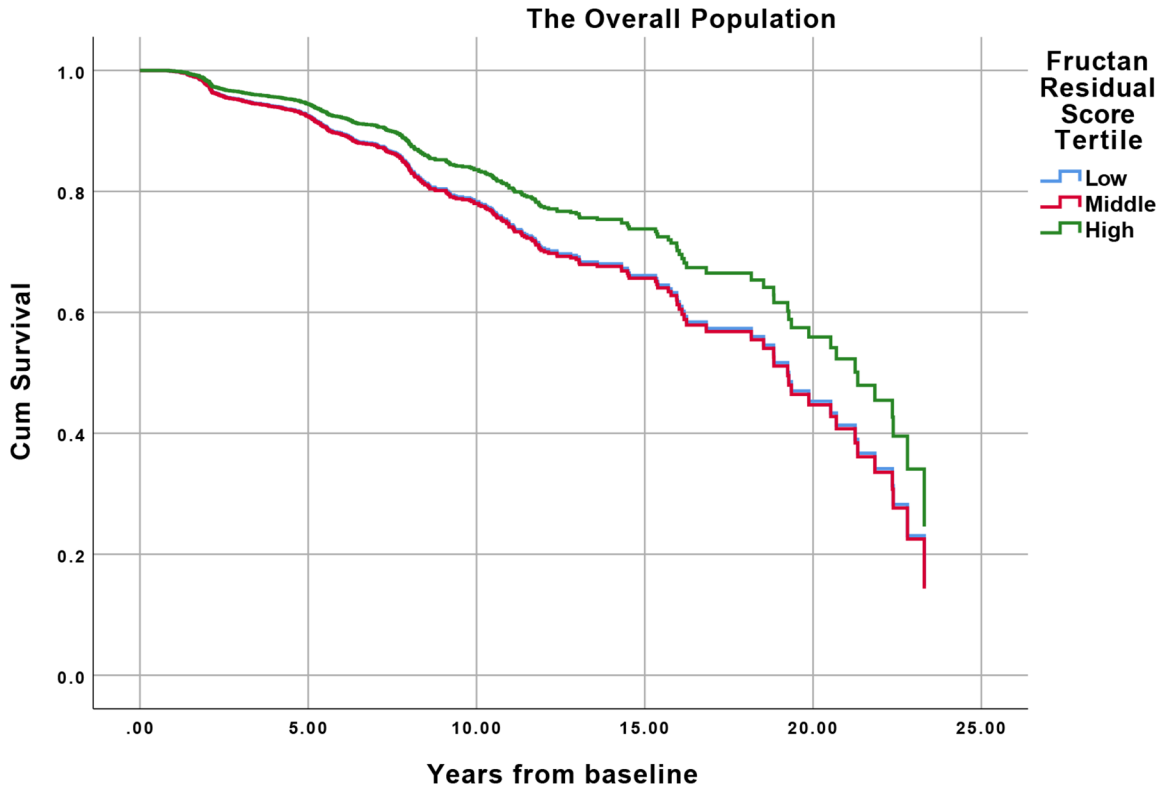


Figure 1.
Flow chart of subject selection.



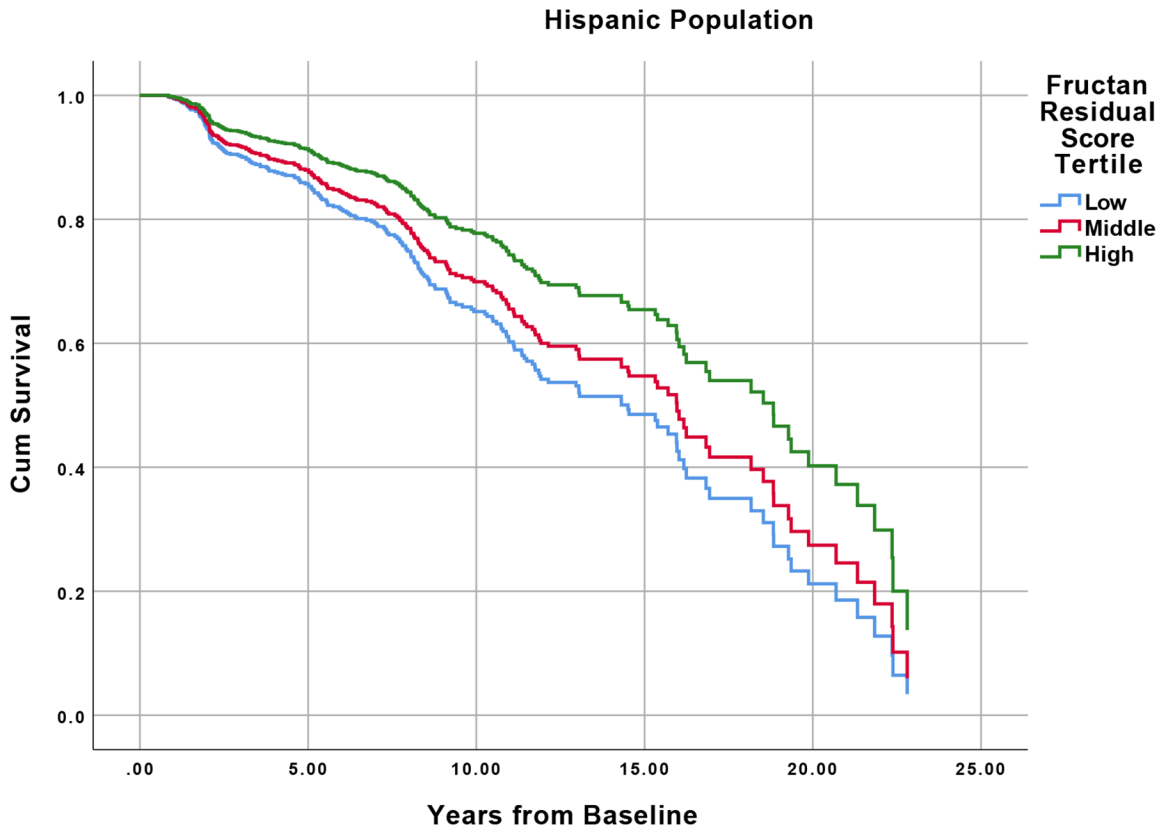


Figure 2.

Survival Curves based on Fructan Residual Score Tertile in the Overall Population and in the Hispanic population.

Table 1.

Demographic and Clinical Characteristics by Fructan Residual Score Tertiles.

Characteristics	Low Fructan Tertile (n = 612)	Middle Fructan Tertile (n = 613)	High Fructan Tertile (n = 612)	All (n = 1,837)	*P* Value
Daily fructan, g/day, mean (SD)	0.60 (0.28)	0.92 (0.27)	1.48 (0.47)	1.00 (0.50)	< .001
Energy-adjusted daily fructan residual, g/day, mean (SD)	−0.43 (0.18)	−0.04 (0.09)	0.46 (0.35)	0.0 (0.43)	< .001
Follow-up duration, years, mean (SD)	7.3 (4.8)	7.4 (5.0)	7.7 (5.0)	7.5 (4.9)	.28
Age, yr, mean (SD)	75.5 (6.4)	75.4 (6.3)	75.9 (6.1)	75.6 (6.3)	.39
Education, yr, mean (SD)	10.4 (4.8)	10.0 (4.9)	10.0 (4.9)	10.1 (4.8)	.29
Comorbidity index, mean (SD)	2.4 (1.5)	2.5 (1.5)	2.5 (1.5)	2.4 (1.5)	.41
Energy intake, kcal, mean (SD)	1473 (535)	1342 (466)	1463 (468)	1426 (494)	< .001
Body mass index (SD)	28.2 (5.9)	28.6 (6.5)	27.0 (5.2)	28.0 (5.9)	< .001
Female gender, n (%)	409 (67)	431 (70)	423 (69)	1263 (69)	.41
Ethnicity, n (%)					.004
White	180 (29)	161 (26)	188 (31)	529 (29)	
Black	220 (36)	193 (32)	167 (27)	580 (32)	
Hispanic	212 (35)	259 (42)	257 (42)	728 (40)	
Presence of *APOE* ε4 allele, n (%)	165 (27)	175 (29)	162 (27)	502 (27)	.70
Smoking, n (%)	273 (45)	261 (43)	247 (40)	781 (43)	.32

Table 2.

Demographic and Dietary Characteristics by AD Status

Characteristics	Non-AD (n = 1,446)	Incident AD (n = 391)	All (n = 1,837)	*P* Value
Daily fructan, g/day, mean (SD)	1.00 (0.51)	1.02 (0.48)	1.0 (0.50)	.35
Energy-adjusted daily fructan residual, g/day, mean (SD)	0.001 (0.430)	−0.002 (0.423)	0.000 (0.43)	.87
Follow-up duration, years, mean (SD)	7.7 (4.9)	6.8 (4.9)	7.5 (4.9)	.002
Age, yr, mean (SD)	75.1 (6.1)	77.6 (6.6)	75.6 (6.3)	<.001
Education, yr, mean (SD)	10.8 (4.6)	7.6 (4.8)	10.1 (4.8)	<.001
Comorbidity index, mean (SD)	2.3 (1.5)	2.9 (1.5)	2.4 (1.5)	<.001
Energy intake, kcal, mean (SD)	1414 (485)	1472 (494)	1426 (494)	.04
Body mass index (SD)	28.1 (6.0)	27.2 (5.9)	28.0 (6.0)	.06
Female gender, n (%)	978 (68)	285 (73)	1283 (69)	.05
Ethnicity, n (%)				<.001
White	479 (33)	50 (13)	529 (29)	
Black	467 (32)	113 (29)	580 (32)	
Hispanic	500 (35)	228 (58)	728 (40)	
Presence of *APOE* ε4 allele, n (%)	372 (26)	130 (33)	502 (27)	.003
Smoking, n (%)	622 (43)	159 (41)	781 (43)	.40
Fructan tertile, n (%)				.71
Low Fructan tertile	487 (34)	125 (32)	612 (33)	
Middle Fructan tertile	476 (33)	137 (35)	613 (33)	
High Fructan tertile	483 (33)	129 (33)	612 (33)	

Table 3.

Cox Proportional Hazard Ratios for Alzheimer's Disease by Fructan Residual Score.

	Fructan Residual Score Continuous		Fructan Residual Score Tertiles		
Model	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* tertile**	***P* for Trend**
Basic model[a]	0.76 (0.60–0.97)	.03			.02
Low			1 (reference)		
Middle			1.02 (0.79–1.30)	0.90	
High			0.73 (0.57–0.95)	0.02	
Full model[b]	0.75 (0.59–0.96)	.02			.01
Low			1 (reference)		
Middle			0.99 (0.77–127)	0.94	
High			0.72 (0.55–0.93)	0.01	

[a]The basic model is adjusted for cohort, age, gender, ethnicity, education, caloric intake, APOE genotype.

[b]The full model is adjusted for cohort, age, gender, ethnicity, education, caloric intake, APOE genotype, smoking, alcohol intake, comorbidity index.

Table 4.

Cox Proportional Hazard Ratios for Alzheimer's Disease by Fructan Residual Score – Hispanic Participants.

	Fructan Residual Score Continuous		Fructan Residual Score Tertiles		
Model	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* tertile**	***P* for Trend**
Basic model[a]	0.68 (0.49–0.93)	.02			.002
Low			1 (reference)		
Middle			0.86 (0.62–1.19)	0.35	
High			0.59 (0.42–0.83)	0.002	
Full model[b]	0.68 (0.50–0.94)	.02			.002
Low			1 (reference)		
Middle			0.83 (0.60–1.15)	0.68	
High			0.59 (0.42–0.83)	0.002	

[a]The basic model is adjusted for cohort, age, gender, ethnicity, education, caloric intake, APOE genotype.

[b]The full model is adjusted for cohort, age, gender, ethnicity, education, caloric intake, APOE genotype, smoking, alcohol intake, comorbidity index.