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Fruit and Vegetable Juices and Alzheimer's Disease: The *Kame* Project

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Abstract

BACKGROUND—Growing evidence suggests that oxidative damage caused by the *β*-amyloid peptide in the pathogenesis of Alzheimer's disease may be hydrogen peroxide mediated. Many polyphenols, the most abundant dietary antioxidants, possess stronger neuroprotection against hydrogen peroxide than antioxidant vitamins.

METHODS—We tested whether consumption of fruit and vegetable juices, containing a high concentration of polyphenols, decreases the risk of incident probable Alzheimer's disease in the *Kame* Project cohort, a population-based prospective study of 1836 Japanese Americans in King County, Washington, who were dementia-free at baseline (1992–1994) and were followed through 2001.

RESULTS—After adjustment for potential confounders, the hazard ratio for probable Alzheimer's disease was 0.24 (95% confidence interval [CI], 0.09–0.61) comparing subjects who drank juices at least 3 times per week with those who drank less often than once per week with a hazard ratio of 0.84 (95% CI, 0.31–2.29) for those drinking juices 1 to 2 times per week (*P* for trend < .01). This inverse association tended to be more pronounced among those with an apolipoprotein E*ε-4* allele and those who were not physically active. Conversely, no association was observed for dietary intake of vitamins E, C, or *β*- carotene or tea consumption.

CONCLUSIONS—Fruit and vegetable juices may play an important role in delaying the onset of Alzheimer's disease, particularly among those who are at high risk for the disease. These results may lead to a new avenue of inquiry in the prevention of Alzheimer's disease.

Keywords

Fruit and vegetable juices; Polyphenols; Antioxidants; Alzheimer's disease; Epidemiology

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In vitro and in vivo data show that chronic accumulation of reactive oxygen species in the brain may exhaust antioxidant capacity, including antioxidant vitamins, and lead to the onset and progression of Alzheimer's disease.[1–3] A recent large clinical trial[4] and several previous prospective epidemiologic studies[5–9] suggest that antioxidant vitamins[9] from dietary fruits and vegetables, but not from supplements, play a role in delaying the onset of Alzheimer's disease.

Other than antioxidant vitamins, the most abundant dietary antioxidants come from nonvitamin polyphenols.[10,11] Several thousand polyphenols have been identified in plants.[10,11] Most polyphenols exist primarily in the outer sections of fruits and vegetables,[10–13] and therefore culinary preparation has a critical impact on the concentrations.[10,11] For example, peeling or boiling can lead to the loss of a majority of the quercetin content in apples, tomatoes, and onions.[10,11] None of the food frequency questionnaires used in current epidemiologic studies are able to collect data on food preparation; therefore it is impossible to accurately measure total intake of polyphenols. Beverages, such as tea, juices, and wine, are major sources of polyphenols, although many fruits and vegetables and herbs possess polyphenols. Several studies have found that consumption of polyphenols from wine,[14] but not tea,[14–17] may be associated with a reduced risk of Alzheimer's disease. A number of studies have reported that commercial fruit and vegetable juices, normally made from frozen concentrates,[12] also possess a high concentration of powerful antioxidant polyphenols.[18–21] Furthermore, under high extracting mechanical pressure, high concentrations of both peel and pulp components from whole fruits or vegetables enter the liquids from which juice concentrates are produced.[12, 13] No epidemiologic study has yet investigated the association between consumption of fruit and vegetable juices and Alzheimer's disease risk. Growing evidence from in vitro,[22–24] in vivo studies,[25] and clinical trials[26] has shown that polyphenols from apple, grape, and citrus fruit juices possess a stronger neuroprotection than antioxidant vitamins. On the basis of these findings, we hypothesized that consumption of fruit and vegetable juices, as a rich source of polyphenols, would be protective and would delay the onset of Alzheimer's disease in a prospective cohort study of Japanese Americans in King County, Washington (the *Kame* Project).

METHODS

The *Kame* Cohort

Data for the current analysis were derived from the *Kame* Project, a large population-based prospective study of Japanese Americans in King County, Washington, who were followed from 1992 to 2001, as part of the Ni-Hon-Sea Project, a cross-cultural study of prevalence and incidence rates of Alzheimer's disease and vascular dementia among Japanese populations living in Hiroshima, Japan; Oahu, Hawaii; and the metropolitan area of Seattle, Washington.[27,28]

A cohort of 3045 eligible individuals aged 65 years and more, 96% of whom were of 100% self-identified Japanese origin, were enumerated in a census of Japanese Americans in King County, Washington, in November 1991. Those identified as eligible by the study census were found to represent 90% of the Japanese American population in King County enumerated by the decennial US Census in 1990. Of those eligible, 1985 (65.2%) participated in the baseline evaluation (1992–1994), of whom 1836, found to be dementia-free at baseline, form the eligible sample for this study. Details of the study census and results from the prevalence study have been described elsewhere.[27]

Clinical Diagnostic Procedures

All participants were interviewed by trained interviewers using highly structured questionnaires. The Cognitive Abilities Screening Instrument (CASI)[29] was administered to assess cognition at baseline and at each of 4 follow-up waves, each 2 years apart for a total of 4 incidence waves. An individual scoring of 87 or less of 100 points at any follow-up was invited for a standardized full clinical and neuropsychologic evaluation, the procedures of which have been described in detail elsewhere.[27] Briefly, the evaluation included protocol-driven physical, neurologic, and laboratory examinations administered by the study physicians[27] and informant interview including the Clinical Dementia Rating Scale.[30]

Neuropsychologic evaluation was conducted by a trained psychometrist using the Consortium to Establish a Registry for Alzheimer's Disease criteria[31,32] and other tests.[32–38] The presence of dementia and its subtypes were determined by consensus committee.[27] The committee filled out the dementia criteria of the *Diagnostic and Statistical Manual, Fourth Edition*,[39] the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria (NINCDS-ADRDA),[40] and a number of criteria for vascular dementia.[41,42] In these analyses, only subjects who developed an incident diagnosis of probable Alzheimer's disease according to NINCDS-ADRDA criteria were considered as cases. Others were censored at the date they were last seen, died, or refused to continue their participation. The study was approved by the University of Washington Human Subjects Committee and supported by a Japanese American Community Advisory Board.

CLINICAL SIGNIFICANCE

- Recent clinical trials have generated disappointing results for several promising agents, including sex hormones, antioxidant vitamins, and anti-inflammatory drugs, in the prevention of Alzheimer's disease.
- In this study, the risk for probable Alzheimer's disease was significantly reduced among people who drank fruit and vegetable juices, a potential source of antioxidant polyphenols, 3 or more times per week, compared with those who drank these juices less than once per week

Dietary Measurement

At baseline interview, we used a self-administered, semi-quantitative food frequency questionnaire developed for Asian populations to obtain usual dietary intake of food, including tea, wine, and fruit and vegetable juices.[43–45] Each food item had eight frequency options and 3 usual portion sizes, which were chosen from provided pictures.[44,45] Of 1836 dementia-free cohort members, 1589 (86.5%) completed the food frequency questionnaire. Usual dietary in-take of nutrients, including total energy, vitamins C and E, and β-carotene, was calculated from an assembled food composition database, which included the US Department of Agriculture's database and other sources that factor in dietary diversity across ethnic groups.[46] A validation study of this food frequency questionnaire was conducted among 262 randomly selected subjects from 5 ethnic groups including Japanese. Japanese men and Chinese women had the highest correlation for major nutrients between intake from 4-week food records throughout 1 year and from the food frequency questionnaire.[45] The intraclass correlation coefficients for Japanese men and women were 0.77 and 0.42 for β-carotene and 0.50 and 0.42 for vitamin C, respectively.[45]

Covariates

Baseline risk factor information was elicited, including smoking and alcohol drinking habits, education, birthplace, place of education before 18 years old, birth date, physical activity, use of antioxidant vitamin supplements in the past month, usual eating preference (Asian or Western), and olfaction diagnostic group (anosmia, microsmia vs normosmia).[47,48] We obtained apolipoprotein E (ApoE) status on 1047 individuals who also completed the food frequency questionnaire (65.9%). For ApoE genotyping, DNA was prepared from buffy coat preparations by a modification of the salting-out procedures.[49] Genotypes were determined using previously described methods.[50,51]

Statistical Analysis

We estimated the main associations using hazard ratios (HRs) in Cox proportional hazard regression models,[52] using age at onset as the time axis and age at entry as the truncation variable;[53] therefore all models are adjusted for age.[54] Intake of antioxidant vitamins was categorized into tertiles based on the distribution of the cohort. Tea, wine, and juice drinking were classified as “less often than once per week,” “once or twice per week,” and “three times or more per week.” Additional models were run adjusting for years of education and other potential confounders. We also adjusted for dietary intake of vitamins C, E, and β-carotene to examine whether the associations between juices, tea, and wine and Alzheimer’s disease may be attributable in part to such intake from food. Other variables, including history of chronic vascular diseases, cancers, self-rated health status, birthplace, place of education, and usual eating preference, did not appreciably alter the risk estimates and were not adjusted for in our final analyses. Stratified analyses by years of education, smoking status, tea-drinking frequency, regular physical activity (yes/no), ApoE *ε-4* (present/absent), and total fat intake (by median) were conducted. Multiplicative interactions also were evaluated in Cox regression models by likelihood ratio tests. *P* values of less than .05 (2-sided probability) were interpreted as being statistically significant.

RESULTS

The sample with dietary information (n = 1589) had a mean age at enrollment of 71.8 years; 54.4% were women; 6.5% of subjects drank sake or wine at least once per week; more than 80% of subjects drank tea at least once per week; 65% drank fruit or vegetable juices at least once per week; and 19.9% of subjects possessed one or more ApoE *ε-4* alleles. Overall, the analyzed sample was comparable to the whole cohort who were dementia-free (n = 1836) by age, gender, baseline CASI scores, education, follow-up time, smoking and alcoholic drinking status, use of antioxidant vitamin supplements, and *ApoE*4* allele (data not shown). Over an average of 6.3 years (standard deviation = 2.6), 81 incident cases were diagnosed with probable Alzheimer’s disease by NINCDS-ADRDA criteria in the dementia-free cohort; 63 of whom (77.8%) completed the food frequency questionnaire at baseline and were included in the analyzed sample.

After adjustment for total energy intake, subjects who drank fruit and vegetable juices more frequently had a lower intake of fat (either saturated or unsaturated fatty acids) and a higher dietary intake of vitamin C, but not vitamin E or β-carotene. They also tended to have a higher educational attainment and more regular physical activity, and were more likely to be nonsmokers, hypertensive, and ApoE *ε-4* allele negative (Table 1).

Table 2 shows the associations between intake frequencies of fruit and vegetable juices, wine and tea, and Alzheimer’s disease. Tea drinking, the most commonly consumed beverage in the study population, was not associated with Alzheimer’s disease risk. Only a small proportion of subjects drank wine, and the association with Alzheimer’s disease was inverse but not

statistically significant. The risk of Alzheimer's disease was substantially decreased with increasing frequency of intake of juices. Risk was even lower after adjustment for other potential confounding factors. The risk was further reduced after taking into account dietary intake of vitamins E and C and β-carotene, with an HR of 0.24 (95% confidence interval [CI], = 0.09–0.61) for subjects who drank juices at least 3 times per week versus those who drank juices less often than once per week (*P* for trend < .01). We also found that dietary consumption of vitamins E, C, and β-carotene was not related to the risk of Alzheimer's disease (data not shown).

The inverse association between fruit and vegetable juices and Alzheimer's disease appeared in all strata of education, smoking status, tea drinking, regular physical activity, ApoE genotype, and total fat intake (Table 3). However, the association tended to be stronger among those who were former or current smokers, drank tea less often, were positive for the ApoE ε-*4* allele, and were less physically active. Although no statistically significant interactions were found, the tests for interactions by ApoE genotype (*P* for interaction, .07) and regular physical activity (*P* for interaction, .06) were of borderline significance. In Table 4, the characteristics at baseline by disease status are presented (Table 1 describes the characteristics with regard to fruit and vegetable juice consumption).

DISCUSSION

In this prospective study conducted among Japanese Americans living in King County, Washington, we found that frequent drinking of fruit and vegetable juices was associated with a substantially decreased risk of Alzheimer's disease. This inverse association was stronger after adjustments for potential confounding factors, and the association was evident in all strata of selected variables. These findings are new and suggest that fruit and vegetable juices may play an important role in delaying the onset of Alzheimer's disease.

We found that subjects with a high intake frequency of fruit and vegetable juices had a higher dietary intake of vitamin C. However, dietary intakes of vitamins C and E and β-carotene were not related to the risk of Alzheimer's disease, and the inverse association between juices and Alzheimer's disease was strengthened after adjustment for antioxidant vitamins. These findings are in accord with those reported in a recent multicenter clinical trial that vitamin E supplementation had no effect on the annual progression rate from mild cognitive impairment to Alzheimer's disease.[4] Our findings also are consistent with those from the Honolulu-Asia Aging Study, a prospective study conducted among Japanese-Americans living in Hawaii whose overall methods were standardized with the *Kame* Project. In that study, which used a single 24-hour dietary recall, midlife intake of vitamins E and C and β-carotene was not related to the risk of Alzheimer's disease.[17] Results from other prospective studies also have been inconsistent.[5–7] In 2 studies, dietary intake of vitamin C,[8] and particularly vitamin E,[8,9] but not antioxidant supplements, was associated with a reduced risk of Alzheimer's disease. These reports, in addition to the findings of antioxidant vitamins in the current study, identify the possibility that other underlying beneficial elements in fruits and vegetables may contribute to Alzheimer's disease risk reduction.[55,56]

Our finding for the consumption of tea concurs with previous studies. Two case-control studies examined whether tea consumption was related to a higher risk of Alzheimer's disease, and neither of them found a significant association.[15,16] Midlife flavonoid intake (from tea only) was not associated with the risk of Alzheimer's disease 25 years later in the Honolulu-Asia Aging Study.[17] It is possible that the reason we did not find a significant inverse association between wine or sake drinking and Alzheimer's disease in the current study is because few subjects in our study drank wine or sake at least once per week. However, the point estimate is consistent with a French study[57,58] in which drinking 3 to 4 standard glasses of wine per

day was associated with more than an 80% reduced risk of dementia and a 75% reduced risk of Alzheimer's disease.[57]

There is growing evidence indicating that oxidative damage caused by the β-amyloid peptide in the pathogenesis of Alzheimer's disease may be hydrogen peroxide (H_2O_2)-mediated.[59–63] Recent studies have shown that polyphenols from apple and citrus juices, such as quercetin, are able to cross the blood-brain barrier[64] and show neuroprotection against H_2O_2.[22,23,65] The effect of polyphenols from citrus is similar to vitamin C, but quercetin from apple juice confers stronger neuroprotection than vitamin C.[22] Early in vitro studies reported that polyphenol flavonols, such as quercetin, protect mammalian and bacterial cells from toxicity induced by H_2O_2, but that α-tocopherol is not effective.[24,66] Recent in vitro studies show that many polyphenols, including flavonols (eg, quercetin and others), protect mouse hippocampal cells from oxidative glutamate and H_2O_2 toxicity, but that the polyphenol catechin, the major polyphenol from tea, was ineffective.[65,67] This may partially explain the null association for tea in the current and previous studies. Additional animal studies showed that chronic administration of flavonols or apple juice protects against aging and cognitive impairment induced by lipopolysaccharide, genetic, and dietary vitamin deficiency in animal models.[25,68] Aside from their antioxidant properties, many polyphenols, such as quercetin, have potent anti-inflammatory properties.[10,11] Recent clinical trials have shown that intake of orange juice significantly reduces plasma concentrations of F2-isoprostanes (a valid biomarker of oxidative stress) and, perhaps, C-reactive protein,[69–71] whereas supplementation of vitamin E did not reduce the concentration of F2-isoprostanes.[72] In addition to antioxidant vitamins and polyphenols, fruit and vegetable juices also may possess other protective components, such as folate and minerals.[73] For example, a high serum level of folate was found to be associated with a decreased risk of Alzheimer's disease.[74]

Selection bias is minimized in the *Kame* Project because this is a population-based cohort study. However, there may still be some errors in reporting of dietary intake associated with incipient dementia or dietary changes related to early changes in olfaction. We therefore adjusted for baseline CASI scores and olfaction diagnostic group in the analyses. Baseline CASI scores were also similarly distributed across exposure groups. Among participants with CASI scores greater than 87, the corresponding HRs (95% CI) were 0.61 (0.15–2.42) for those who drank juices once or twice per week and 0.13 (0.03–0.54) for those who drank at least 3 times per week (P for trend < .01) versus those who drank juices less than once per week. We also conducted analyses using only participants with at least 5 years of follow-up. The corresponding HRs (95% CI) were 0.21 (95% CI, 0.03–1.41) and 0.07 (95% CI, 0.01–0.42). Although we adjusted for many potential confounding factors, we still cannot exclude the possibility that residual confounding may explain our results. Our data are somewhat limited in sample size. Despite this, we still found a highly significant result for juices, even in stratified analyses.

In the present study, the inverse association between intake of fruit and vegetable juices and Alzheimer's disease cannot be solely explained by antioxidant vitamins. Further studies are needed to examine whether components other than antioxidant vitamins, such as polyphenols, may play a protective role. We also did not collect intake information on each specific type of juice and cannot say at present which fruit and vegetable juices might confer protection or for what duration of time they need to be consumed before delay of Alzheimer's disease onset may be realized. Future studies are necessary to confirm our findings and to investigate how intake of different fruit and vegetable juices relate to the risk of Alzheimer's disease.

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Table 1

Baseline Lifestyle Factors and Demographics by Fruit and Vegetable Juice Intake Frequency Among 1589 Subjects 65 Years and Older (the *Kame* Project, 1992–2001)

	Fruit and Vegetable Juices Intake Frequency		
	Less Often Than Weekly	**1–2 Times per Week**	**3 Times or More per Week**
Number free of probable Alzheimer's disease	547	257	785
Mean dietary intake			
Vitamin C, mg/d*	90.7	104.1	160.7
Vitamin E, mg/d*	6.04	6.10	6.07
β-carotene, μg/d*	3631.3	3489.3	3749.1
Total fat, g/d*	34.3	34.8	32.4
Saturated fat, g/d*	10.5	10.8	9.9
Monounsaturated fat, g/d*	11.9	12.3	11.2
Polyunsaturated fat, g/d*	8.1	7.9	7.7
Women (%)	53.9	50.6	55.8
Baseline CASI score ± SD	91.0 ± 5.7	91.2 ± 6.1	90.8 ± 6.0
Age, mean ± SD, y	71.7 ± 5.4	71.6 ± 5.0	72.1 ± 5.2
Education, mean ± SD, y	12.8 ± 3.0	13.3 ± 2.7	13.2 ± 2.7
BMI, mean ± SD	24.1 ± 3.4	24.7 ± 3.1	24.3 ± 3.3
Smokers, former and current (%)	49.6	56.4	47.9
Alcohol drinkers, current and past (%)	37.2	42.2	38.6
Drinking tea weekly (%)	77.9	84.1	80.4
Olfaction diagnostic group (%)			
Normosmia	40.8	46.7	44.1
Microsmia	48.6	44.7	47.1
Anosmia	10.6	8.6	8.8
Regular physical activity (%)	61.3	60.6	68.6
ApoE-ε4 positive (%)	24.6	17.0	17.4
Hypertension (%)	42.5	46.8	49.7
Diabetes mellitus (%)	17.0	17.2	15.6
Vitamin supplementation			
Vitamin C user (%)	24.0	29.4	27.4
Vitamin E user (%)	20.0	19.0	21.0
Multivitamin user (%)	41.0	38.5	42.2

CASI = Cognitive Abilities Screening Instrument; SD = standard deviation; ApoE = apolipoprotein E; BMI = body mass index.

* Total energy-adjusted means.

Table 2

Hazard Ratios for Incident Probable Alzheimer's Disease by Frequency of Intake of Tea, Sake, and Fruit and Vegetable Juices Among 1589 Subjects 65 Years and Older (the *Kame* Project 1992–2001)

	Intake frequency			
	Less Often Than Weekly HR	1–2 Times per Week HR (95% CI)	3 Times or More per Week HR (95% CI)	*P* for Trend
Fruit and vegetable juice				
Cases/unaffected	30/517	11/246	22/763	
Model 1*	1.00	0.89 (0.44–1.79)	0.49 (0.28–0.86)	.01
Model 2†	1.00	0.74 (0.28–1.94)	0.28 (0.13–0.63)	< .01
Model 3‡	1.00	0.84 (0.31–2.29)	0.24 (0.09–0.61)	< .01
Tea drinking				
Cases/unaffected	9/306	8/165	46/1056	
Model 1*	1.00	2.00 (0.76–5.24)	1.29 (0.63–2.64)	.69
Model 2†	1.00	1.24 (0.37–4.22)	1.61 (0.64–4.05)	.29
Model 3‡	1.00	1.49 (0.43–5.16)	1.70 (0.67–4.33)	.27
Wine (sake) drinking§				
Cases/unaffected	60/1412	0/45	2/54	
Model 1*	1.00	0.49 (0.11–2.10)		
Model 2†	1.00	0.10 (0.00–2.28)		
Model 3‡	1.00	0.09 (0.01–1.43)		

HR = hazard ratio; CI = confidence interval.

*Adjusted for years of education in model 1.

†Additionally adjusted for gender, regular physical activity, body mass index, baseline CASI score, olfaction diagnostic group, total energy intake, intake of saturated, monounsaturated, and polyunsaturated fatty acids, ApoE genotype, smoking status, alcohol drinking, supplementation of vitamin C, vitamin E, and multivitamin, and tea drinking, and fruit and vegetable juice drinking in model 2.

‡Further adjusted for dietary intake of vitamin C, vitamin E, and β-carotene in model 3.

§Only two categories were used because the number of cases was too small in one category and alcohol drinking was not adjusted in the model.

Table 3

Numbers of Individuals and Hazard Ratios for Incident Probable Alzheimer's Disease by Frequency of Intake of Fruit and Vegetable Juices Stratified by Potential Modifying Effects Among 1589 Subjects 65 Years and Older (the *Kame* Project, 1992–2001)

	Intake Frequency			
	Less Often Than Weekly HR	**1–2 Times per Week HR (95% CI)**	**3 Times or More per Week HR (95% CI)**	***P* for Trend**
Stratum		Stratified analysis of fruit and vegetable juices*		
Education				
<12 y	9/110	4/25	5/103	
	1.00	0.28 (0.02–3.71)	0.05 (0.00–0.98)	.05
≥12 y	21/407	7/221	17/660	
	1.00	0.51 (0.18–1.41)	0.20 (0.08–0.49)	< .01
		P for interaction, .29		
Smoking status				
Never smokers	17/258	7/105	14/392	
	1.00	0.78 (0.23–2.61)	0.32 (0.12–0.84)	.02
Ever smokers	13/258	4/141	8/365	
	1.00	0.27 (0.06–1.14)	0.04 (0.01–0.24)	< .01
		P for interaction, .98		
Tea drinking				
<3 times/wk	12/168	2/75	3/223	
	1.00	0.04 (0.00–0.46)	0.01 (0.00–0.09)	< .01
≥3 times/wk	17/346	8/166	19/527	
	1.00	0.58 (0.19–1.73)	0.43 (0.17–1.06)	.06
		P for interaction, . 33		
Regular physical activity				
No	16/194	4/95	6/233	
	1.00	0.86 (0.23–3.20)	0.06 (0.01–0.23)	< .01
Yes	14/319	5/147	16/507	
	1.00	0.57 (0.16–1.97)	0.45 (0.16–1.26)	.13
		P for interaction, .06		
ApoE genotype				
ApoE-ε4 negative	12/264	6/145	8/404	
	1.00	0.93 (0.30–2.88)	0.25 (0.07–0.93)	.05
ApoE-ε4 positive	11/79	1/30	7/80	
	1.00	—	0.13 (0.02–0.83)	.02
		P for interaction, .07		
Total fat intake (g/d)				
≤29.9	17/301	7/132	9/334	
	1.00	0.76 (0.26–2.21)	0.23 (0.07–0.78)	.02
>29.9	13/216	4/114	13/429	
	1.00	0.36 (0.07–1.85)	0.14 (0.04–0.46)	<.01
		P for interaction, .28		

HR = hazard ratio; CI = confidence interval; ApoE = apolipoprotein E.

*Adjusted for years of education, gender, regular physical activity, body mass index, baseline CASI score, olfaction diagnostic group, total energy intake, intake of saturated, monounsaturated, and polyunsaturated fatty acids, smoking status, alcoholic drinking, supplementation of vitamin C, vitamin E, and multivitamin, tea drinking, and dietary intake of vitamin C, vitamin E, and β-carotene.

Table 4

Baseline Lifestyle Factors and Demographics by Fruit and Vegetable Juice Intake Frequency and Subsequent Alzheimer's Disease Status Among 1589 Subjects 65 Years and Older (the *Kame* Project, 1992–2001)

		Fruit and Vegetable Juices Intake Frequency		
	AD = 63 Non-AD = 1526	**Less Often Than Weekly**	**1–2 Times per Week**	**≥3 Times per Week**
Mean dietary intake				
Vitamin C, mg/d*	AD	124.8	101.3	172.2
	Non-AD	88.8	104.3	160.3
Vitamin E, mg/d*	AD	8.1	6.6	7.5
	Non-AD	5.9	6.1	6.0
β-carotene, μg/d*	AD	5142.2	3527.1	4182.9
	Non-AD	3546.4	3490.7	3733.4
Total fat, g/d*	AD	33.9	34.1	29.4
	Non-AD	34.3	34.8	32.5
Saturated fat, g/d*	AD	10.5	11.0	8.7
	Non-AD	10.5	10.8	9.9
Monounsaturated fat, g/d*	AD	11.0	11.5	10.2
	Non-AD	12.0	12.3	11.3
Polyunsaturated fat, g/d*	AD	8.7	7.8	7.2
	Non-AD	8.1	7.9	7.7
Women (%)	AD	60.0	54.5	68.2
	Non-AD	53.7	50.2	55.6
Baseline CASI score ± SD	AD	88.0 ± 6.4	80.4 ± 15.3	82.6 ± 7.9
	Non-AD	91.2 ± 5.7	91.7 ± 4.8	91.1 ± 5.8
Age, mean ± SD, y	AD	76.0 ± 5.4	77.5 ± 6.6	77.5 ± 6.5
	Non-AD	71.5 ± 5.3	71.3 ± 4.8	71.9 ± 5.0
Education, mean ± SD, y	AD	12.0 ± 2.5	11.6 ± 2.4	11.4 ± 2.5
	Non-AD	12.8 ± 3.0	13.4 ± 2.7	13.2 ± 2.7
BMI, mean ± SD	AD	23.1 ± 3.5	25.6 ± 3.8	23.7 ± 3.6
	Non-AD	24.1 ± 3.4	24.7 ± 3.0	24.3 ± 3.3
Smokers, former and current (%)	AD	43.3	36.4	36.4
	Non-AD	49.9	57.5	48.1
Alcohol drinkers, current and past (%)	AD	33.3	36.4	36.4
	Non-AD	37.5	42.6	38.7
Drinking tea weekly (%)	AD	75.9	100.0	90.9
	None-AD	78.0	83.4	80.1
Olfaction diagnostic group (%)				
Normosmia	AD	30.0	9.1	27.3
Microsmia	AD	50.0	72.7	59.1
Anosmia	AD	20.0	18.2	13.6
Normosmia	Non-AD	41.4	48.4	44.6
Microsmia	Non-AD	48.5	43.5	46.8
Anosmia	Non-AD	10.1	8.1	8.6
Regular physical activity (%)	AD	46.7	55.6	72.7
	Non-AD	62.2	60.6	68.6
ApoE-ε4 positive (%)	AD	47.8	14.3	46.7
	Non-AD	23.0	17.1	16.7
Hypertension (%)	AD	36.7	90.0	63.6
	Non-AD	42.9	45.3	49.1
Diabetes mellitus (%)	AD	20.0	27.3	14.3
	Non-AD	16.9	16.8	15.6
Vitamin supplementation				
Vitamin C user (%)	AD	30.0	18.2	45.4
	Non-AD	23.7	29.4	26.7

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		Fruit and Vegetable Juices Intake Frequency		
	AD = 63 Non-AD = 1526	**Less Often Than Weekly**	**1–2 Times per Week**	**≥3 Times per Week**
Vitamin E user (%)	AD	23.3	9.1	9.1
	None-AD	19.8	19.6	21.1
Multivitamin user (%)	AD	46.7	9.1	40.9
	Non-AD	40.8	39.6	42.5

AD = Alzheimer's disease; CASI = Cognitive Abilities Screening Instrument; SD = standard deviation; ApoE = apolipoprotein E.

*Total energy-adjusted means. AD stands for subsequently diagnosed cases of Alzheimer's disease. Non-AD stands for subjects without AD after 9 years of follow-up.