npj | science of food

Article

Published in partnership with Beijing Technology and Business University

https://doi.org/10.1038/s41538-024-00364-w

Green tea consumption and cerebral white matter lesions in community-dwelling older adults without dementia

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This study investigated the association between green tea or coffee consumption with cerebral white matter lesions and hippocampal and total brain volumes among 8766 community-dwelling participants recruited from the Japan Prospective Studies Collaboration for Aging and Dementia between 2016 and 2018. A Food Frequency Questionnaire was used to assess green tea and coffee consumption, whereas brain magnetic resonance imaging was performed to assess cerebral white matter lesions, hippocampal volume, and total brain volume. Multivariable-adjusted analysis revealed significant correlations between fewer cerebral white matter lesions and higher green tea consumption, whereas no significant differences were found between green tea consumption and hippocampal or total brain volume. Regarding coffee consumption, no significant differences were observed in cerebral white matter lesions or hippocampal or total brain volumes. Hence, higher green tea consumption was associated with fewer cerebral white matter lesions, suggesting that it may be useful in preventing dementia.

Tea and coffee are widely consumed beverages that contain caffeine, polyphenols, and vitamins, which possess neuroprotective effects. Several epidemiological studies have shown that tea and coffee consumption are associated with cognitive benefits in older adults[1–6]. In some studies did not classified types of tea such as black tea and green tea strictly[5,6]. Neuroprotective ingredients containing beverages are known to be epigallocatechin gallate for green tea, theaflavins for black tea, and chlorogenic acid and caffeic acid for coffee, those ingredients have antioxidant and anti-inflammatory effects[7–15].

The Japan Prospective Studies Collaboration for Aging and Dementia (JPSC-AD), a multisite, ongoing community-based observational study of dementia conducted at eight research sites in Japan, comprises data from approximately 10,000 older participants who underwent brain magnetic resonance imaging (MRI) examinations and dietary surveys at baseline. A detailed description of this survey has been published previously[16–18].

Aging is a major risk factor for dementia and causes brain changes, such as brain atrophy, hippocampal atrophy, and an increase in cerebral white matter lesions. Although green tea and coffee are expected to have positive effects on mitigating cognitive decline, the link between tea or coffee consumption and brain changes in older adults remains poorly understood. Nonetheless, increased green tea consumption has been linked to reduced annual hippocampal atrophy at the population level[19] and regular coffee consumption has been linked to higher cortical thickness[20].

Therefore, the present study aimed to investigate the associations of green tea, black tea, and coffee intake with cerebral white matter lesion, hippocampal, and total brain volumes using brain MRI data in an older Japanese population without dementia.

Results

Study population and baseline characteristics

In the JPSC-AD, a baseline survey was conducted from 2016 to 2018. In total, 11,410 individuals aged ≥ 65 years from eight research sites participated in the study. Among them, 9646 underwent MRI with three-dimensional T1-weighted images. After excluding 167 participants for whom the FreeSurfer analysis did not pass quality control, 341 participants without available data on green tea, black tea, and/or coffee intake, and 372

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participants with dementia at baseline, the remaining 8766 participants were deemed eligible for inclusion in the present study (Fig. 1).

The percentages of participants with a habit of drinking green tea, coffee, and black tea were 91.6%, 82.0%, and 19.2%, respectively. Due to the low number of black tea consumers, we did not analyze the association between black tea consumption and brain volume on head MRI. The median (interquartile range) green tea and coffee intake for the entire cohort was 450.0 (150.0–750.0) ml and 150.0 (42.9–300.0) ml, respectively.

The clinical characteristics of the study population according to daily green tea intake are shown in Table 1. The frequency of female sex, median age, regular exercise and Mini-Mental State Examination (MMSE) scores increased significantly with higher daily green tea intake, whereas smoking and drinking habits and Geriatric Depression Scale (GDS) scores decreased significantly with higher daily green tea intake. According to daily coffee intake levels, the frequencies of diabetes mellitus, smoking habits, and electrocardiogram abnormalities significantly increased with higher daily coffee intake (Table 2). Conversely, the mean values of age, hypertension, low education, and serum high-density lipoprotein (HDL) cholesterol levels significantly decreased with higher daily coffee intake (Table 2).

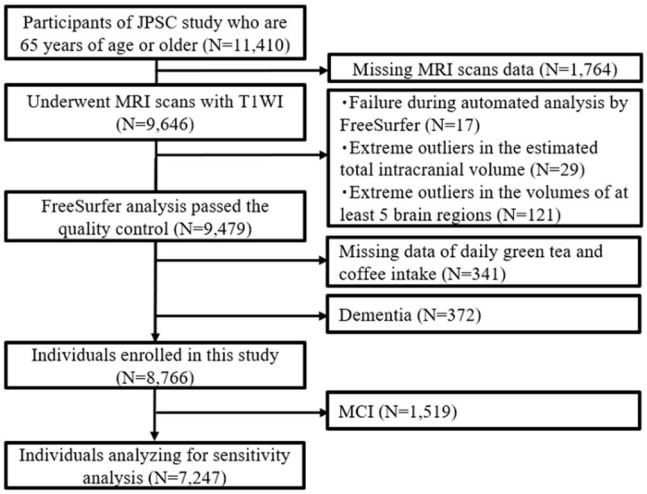

Fig. 1 | Selection process of the study population. JPSC-AD Japan Prospective Studies Collaboration for Aging and Dementia, MRI magnetic resonance imaging, T1WI T1-weighted imaging, MCI mild cognitive impairment.

Table 1 | Clinical characteristics according to the daily green tea consumption levels in older adults without dementia

Variables	Green tea consumption (ml/day)			
	0–200	201–400	401–600	601–
N	2723	1187	1639	3217
Age, y, median, IQR	70 (67–75)	71 (68–76)	72 (68–78)	72 (68–77)*
Women, %	46.5	55.3	59.3	66.8*
Hypertension, %	73.7	73.5	73.2	71.7
DM, %	18.3	13.7	16.6	16.1
Serum LDL-chol, mg/dL, median, IQR	116 (97–136)	116 (99–138)	114 (95–136)	116 (97–136)
Serum HDL-chol, mg/dL, median, IQR	60 (50–72)	62 (51–74)	59 (49–71)	61 (51–73)
Education≦12 y, %	29.4	27.6	31.9	29.5
Smoking habit, %	11.3	8.5	7.3	6.0*
Drinking habit, %	51.3	48.7	40.8	36.0*
ApoE ε4, present, %	18.6	18.3	17.9	17.7
BMI, kg/m^2, median, IQR	23.3 (21.3–25.4)	23.3 (21.1–25.4)	23.0 (21.1–25.2)	23.2 (21.1–25.3)
Regular exercise, %	41.4	43.1	43.8	44.5*
History of stroke, %	5.3	4.9	4.7	4.7
Electrocardiogram abnormalities, %	13.3	12.5	12.5	13.5
GDS, score, median, IQR	2 (1–4)	2 (1–4)	2 (1–4)	2 (1–4)*
MMSE, score, median, IQR	28 (26–29)	28 (26–29)	28 (26–29)	28 (26–30)*

APOE Apolipoprotein E, *BMI* body mass index, *DM* diabetes mellitus, *GDS* geriatric depression scale, *HDL-chol* High-density lipoprotein cholesterol, *IQR* interquartile range, *LDL-chol* low-density lipoprotein cholesterol, *MMSE* Mini-Mental State Examination *p for trend < 0.05.

Influence on brain volumes

Significant associations were observed between daily green tea consumption and white matter lesion volume (WMLV)/estimated total intracranial volume (eTIV), hippocampal volume (HV)/eTIV ratios after adjusting for age, sex, research site, and educational level (Model 1). The association between higher daily intake of green tea and lower WMLV/eTIV ratio remained unchanged even after adjusting for age, sex, research site, educational levels, presence of apolipoprotein E (*ApoE*) ε4, hypertension, body mass index (BMI) levels, serum low-density lipoprotein (LDL) and HDL cholesterol levels, regular exercise, and smoking and drinking habits (Model 2) (p for trend = 0.007). However, the associations between green tea intake and total brain volume (TBV)/eTIV and HV/eTIV ratios did not reach significant levels in Model 2 (Table 3) (p for trend = 0.959 and 0.240, respectively).

Table 2 | Clinical characteristics according to the daily coffee consumption levels in older adults without dementia

Variables	Coffee consumption (ml/day)			
	0–200	201–400	401–600	601–
N	5246	2057	1151	312
Age, y, median, IQR	73 (68–78)	70 (67–75)	70 (67–75)	71 (67–75)*
Women, %	56.8	60.1	58.9	46.8*
Hypertension, %	74.3	71.7	68.4	72.9*
DM, %	15.7	16.3	18.5	25.2*
Serum LDL-chol, mg/dL, median, IQR	115 (96–136)	117 (98–137)	117 (99–137)	116 (98–138) *
Serum HDL-chol, mg/dL, median, IQR	60 (50–72)	62 (51–74)	62 (51–75)	59 (50–72) *
Education≦12 y, %	31.7	23.7	26.3	25.7*
Smoking habit, %	7.2	7.9	11.1	16.7*
Drinking habit, %	42.9	44.8	43.0	43.7
ApoE ε4, present, %	18.1	17.2	18.5	18.5
BMI, kg/m^2, median, IQR	23.2 (21.1–25.4)	23.2 (21.2–25.3)	23.1 (21.2-25.2)	23.5 (21.6-26.2)
Regular exercise, %	42.7	43.5	46.2	39.7
History of stroke, %	5.4	3.3	5.2	7.1
Electrocardiogram abnormalities, %	14.4	10.3	11.6	15.3*
GDS, score, median, IQR	2 (1–4)	2 (1–4)	2 (1–4)	2 (1–4)*
MMSE, score, median, IQR	28 (26–29)	28 (26–30)	28 (26–30)	29 (26–30)*

APOE Apolipoprotein E, *BMI* body mass index, *DM* diabetes mellitus *GDS* geriatric depression scale, *HDL-chol* high-density lipoprotein cholesterol, *IQR* interquartile range, *LDL-chol* low-density lipoprotein cholesterol, *MMSE* Mini-Mental State Examination *p for trend < 0.05.

Table 3 | Association of daily consumption of green tea and coffee with total brain volume, total hippocampal volume and white matter lesion volume in older adults without dementia

Daily consumption (ml)	No. of Participants	Model 1			Model 2		
		TBV/eTIV (%)	HV/eTIV (%)	WMLV/eTIV (%)	TBV/eTIV (%)	HV/eTIV (%)	WMLV/eTIV (%)
Green tea							
0 ~ 200	2498	59.00 (58.87–59.12)	0.4951 (0.4927–0.4974)	0.3978 (0.3826–0.4130)	58.38 (58.15–58.61)	0.4915 (0.4870–0.4961)	0.4939 (0.4652–0.5226)
201 ~ 400	1114	59.07 (58.90–59.25)	0.4980 (0.4947–0.5014)	0.3967 (0.3751–0.4182)	58.39 (58.12–58.65)	0.4934 (0.4882–0.4986)	0.5039 (0.4711–0.5367)
401 ~ 600	1536	59.09 (58.95–59.24)	0.4967 (0.4938–0.4995)	0.3762 (0.3579–0.3944)	58.43 (58.18–58.68)	0.4925 (0.4876–0.4974)	0.4830 (0.4522–0.5138)
601~	3054	59.09 (58.98–59.21)	0.4998 (0.4976–0.5021)	0.3641 (0.3495–0.3786)	58.41 (58.18–58.64)	0.4949 (0.4904–0.4995)	0.4781 (0.4494–0.5067)
p for trend		0.654	0.032*	< 0.001*	0.959	0.240	0.007*
Coffee							
0 ~ 200	4921	59.05 (58.96–59.14)	0.4967 (0.4949–0.4984)	0.3832 (0.3720–0.3944)	58.39 (58.17–58.61)	0.4922 (0.4878–0.4965)	0.4914 (0.4643–0.5186)
201 ~ 400	1908	59.05 (58.92–59.19)	0.4986 (0.4960–0.5012)	0.3706 (0.3540–0.3872)	58.35 (58.10–58.59)	0.4940 (0.4892–0.4988)	0.4818 (0.4517–0.5119)
401 ~ 600	1083	59.19 (59.02–59.37)	0.4992 (0.4958–0.5026)	0.3957 (0.3740–0.4175)	58.58 (58.32–58.84)	0.4957 (0.4905–0.5008)	0.4945 (0.4623–0.5267)
601~	290	58.76 (58.43–59.08)	0.4963 (0.4900–0.5027)	0.3735 (0.3326–0.4144)	58.16 (57.77–58.54)	0.4917 (0.4841–0.4992)	0.4571 (0.4098–0.5043)
p for trend		0.126	0.407	0.170	0.072	0.262	0.171

eTIV estimated total intracranial volume, *HV* hippocampal volume, *IQR* interquartile range, *TBV* total brain volume, *WMLV* white matter lesions volume.

Values were shown as a mean (95% confidence interval).

Model 1 was adjusted for age, sex, research site, and educational levels.

Model 2 was further adjusted for the presence of Apolipoprotein E ε4 allele, hypertension, diabetes mellitus, history of stroke, electrocardiogram abnormalities, smoking habit, alcohol intake, regular exercise, body mass index levels, serum low-density lipoprotein and high-density lipoprotein cholesterol levels, regular exercise, and smoking and drinking habits.

* *p* for trend < 0.05.

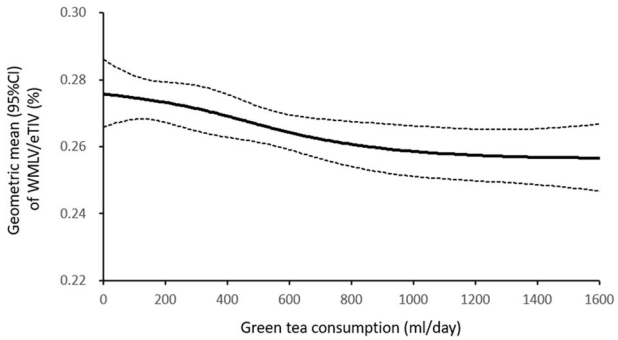

Fig. 2 | The association between daily green tea consumption levels and the geometric mean of WMLV/eTIV in older adults without dementia using a general linear model with restricted cubic splines. Solid lines represent the hazard ratio, while dashed lines represent their corresponding 95% confidence intervals (CIs). Knots were positioned at the 5th, 35th, 65th, and 95th percentiles (0, 300, 600, and 1500 ml/day) of daily green tea consumption. The same percentiles of geometric mean of WMLV/eTIV (0.276, 95%CI 0.266–0.286; 0.271, 95%CI: 0.265–0.278; 0.264, 95%CI: 0.259–0.270; and 0.257, 95%CI 0.248–0.266). eTIV estimated total intracranial volume, WMLV white matter lesion volume. Adjusted for age, sex, research site, educational levels, the presence of the Apolipoprotein E ε4 allele, hypertension, diabetes mellitus, history of stroke, electrocardiogram abnormalities, smoking and drinking habits, regular exercise, body mass index levels, and serum low- and high-density lipoprotein cholesterol levels.

We also addressed the shape of the association between daily green tea consumption levels and the geometric mean of WMLV/eTIV using restricted cubic spline analyses. As shown in Fig. 2, the geometric mean of WMLV/eTIV decreased gradually with higher daily green tea consumption in older adults without dementia after adjusting for confounding factors. Supplementary Fig. 1 demonstrates the ratio of WMLV/eTIV for each daily green tea consumption to WMLV/eTIV for 200 ml of daily green tea consumption (= reference), estimated using restricted cubic spline analyses. Cerebral white matter lesion volumes were significantly lower by 0.97 times (95% confidence interval 0.94–0.99) and 0.94 times (0.90–0.98) at daily green tea consumption levels of 600 ml (approximately 3 glasses per day) and 1500 ml (approximately 7–8 glasses per day), respectively, as compared to a consumption level of 200 ml.

No significant associations were observed between coffee intake and the TBV/eTIV, HV/eTIV, or WMLV/eTIV ratios (Table 3) (p for trend = 0.072, 0.262, and 0.171, respectively).

Sensitivity analysis

A sensitivity analysis was performed on those with normal cognitive function, excluding those with mild cognitive impairment (MCI) (Fig. 1). The clinical characteristics of the study population according to the daily intakes of green tea and coffee are shown in Supplementary Tables 1 and 2. The trends observed for the clinical characteristics of the sensitivity analysis were similar to those of the overall trends that included participants with MCI.

Significant associations were observed between the daily intake of green tea and WMLV/eTIV ratios in Model 1. The association between higher daily green tea intake and lower WMLV/eTIV ratio remained unchanged in Model 2 (p for trend = 0.021). The associations between green tea intake and the TBV/eTIV and HV/eTIV ratios did not reach statistical significance in Model 2 (Supplementary Table 3) (p for trend = 0.976, and 0.202, respectively). No significant associations were observed between coffee intake and the TBV/eTIV, HV/eTIV, or WMLV/eTIV ratios (Supplementary Table 3) (p for trend = 0.119, 0.327, and 0.215, respectively).

Green tea intake, depression, and *ApoE* ε4 carrier status

Upon examining the link between green tea intake and cerebral white matter lesions in the presence or absence of depression and the *ApoE* ε4 allele, we found a significant relationship between increased green tea consumption and decreased white matter lesions in individuals without depression, whereas no significant difference was found in individuals with depression (Supplementary Table 4) (p for trend = 0.007 and 0.457, respectively). Similarly, we observed a significant relationship between increased green tea intake and decreased white matter lesions in individuals without the *ApoE* ε4 allele, but not in individuals with the *ApoE* ε4 allele (p for trend = 0.008 and 0.491, respectively) (Supplementary Table 5).

Discussion

This cross-sectional study found a significant association between lower cerebral white matter lesions and higher green tea consumption, but not coffee consumption, in older adults without dementia, even after adjusting for confounding factors. Similar significant associations were observed when analyses were limited to older adults with normal cognitive function, excluding individuals with MCI.

Epidemiological studies suggest the association between green tea consumption and slowing cognitive decline[1,2]. White matter lesions, indicative of cerebral small vessel disease, are associated with vascular dementia and Alzheimer's disease (AD)[21]. Habes et al. reported that larger white matter lesions were associated with more severe brain atrophy in patients with AD[22,23]. Recently, a longitudinal study also identified white matter lesions as an independent risk factor for cognitive decline, even after accounting for traditional AD risk factors and MRI biomarkers, such as *ApoE* ε4 carrier status, total brain volume, and HV[24].

Hypertension is considered the most important risk factor for white matter lesions, and green tea consumption has been reported to reduce blood pressure[25,26]. A recent meta-analysis reported that regular green tea consumption lowered systolic and diastolic blood pressure by −6.22 mmHg and −2.36 mmHg, respectively[25]. The study also reported that longer periods of green or black tea consumption (> 3 months) positively affected blood pressure, with green tea having a stronger antihypertensive effect than black tea[25]. Another meta-analysis found that green tea consumption reduced systolic and diastolic blood pressure by −1.98 mmHg and −1.92 mmHg, respectively[26]. Therefore, green tea consumption may contribute to white matter lesion reduction by improving blood pressure. Moreover, green tea contains less caffeine than coffee, which negatively affects blood pressure[27], thus suggesting that green tea may have a more beneficial impact on white matter lesions.

Unlike our findings, Zhang et al. reported a significant association between higher HV and higher green tea consumption[6]. This discrepancy in findings may be attributed to the inclusion of community-dwelling older adults aged ≥ 65 years in our study, whereas Zhang et al. targeted adults aged 40–89 years. In addition, we evaluated each participant's cognitive function to exclude individuals with dementia, whereas Zhang et al. excluded individuals with dementia through self-reporting. Sun et al. examined the association between tea intake and cerebral white matter hyperintensity volumes using the UK Biobank data and they did not find the causal association[28]. They analyzed all types of tea, so it is unclear what proportion of green tea was included, but since the study was conducted in the UK, it can be assumed that there was more black tea than green tea[28]. Because our study performed with older Japanese participants, it is necessary to clarify the association between green tea intake and cerebral white matter lesions in people with different ethnicities, genetics, and lifestyles.

In our study, the associations between green tea consumption and white matter lesions were observed only in the groups without depression and the *ApoE* ε4 allele. We can infer that, since depression and *ApoE* ε4 are strong risk factors for dementia, green tea may not be effective in reducing white matter lesions in individuals with depression and *ApoE* ε4. Alternatively, the sample sizes of the groups with depression and *ApoE* ε4 might have been too small for adequate evaluation. In addition, the prevalence of hypertension ($p = 0.018$) and diabetes ($p = 0.005$) was significantly higher and exercise habits ($p < 0.001$) were lower in the group with depression compared to the group without it. Even though we controlled for these factors, there may be other residual confounding factors.

Green tea catechins have been shown to exert antioxidant effects through free radical scavenging[13]. They also exhibit anti-inflammatory

properties through inhibition of nuclear factor kappa B activation[14,15], anti-platelet aggregation effects[29], and nitric oxide regulation in the vascular endothelium[30], and theanine has an antihypertensive effect[31]. Additionally, epigallocatechin gallate has been reported to confer neuroprotective effects by inhibiting amyloid β aggregation and production[32–34]. In this study, black tea was excluded from the analysis because there were few participants who consumed black tea. Theaflavins are the main neuroprotective ingredients containing in black tea and it has been reported that theaflavins are similar in mechanism and at least equal in efficacy to epigallocatechin gallate which is the main neuroprotective ingredients containing in green tea in weaking formation of protofibrils and fibrils of amyloid β and α synuclein[11]. Further studies are needed to clarify the association between black tea consumption with cerebral white matter lesion and brain volumes. There are many reports that coffee has a positive effect on cognitive function and brain volumes, but most of the reports are from Europe and the United States[6,34–36], and few from Asia[37]. Differences in ethnicity and lifestyle (foods to eat with coffee and meal times, etc.) may have led to differences from previous reports.

This study has some limitations. First, we only investigated green tea and coffee intake when consumed as beverages and did not account for the amount contained in snacks. Importantly, there was also no information on how green tea was brewed, leading to potential variations in the content of bioactive substances. Second, we could not investigate the association between black tea consumption and brain volume changes due to the limited sample size of black tea consumers within the study population.

Third, being a cross-sectional study, it was difficult to determine the causal relationship between green tea consumption and cerebral white matter lesions. Finally, this study focused only on data from Japanese individuals; therefore, it is unclear whether similar trends are observed in other ethnicities and races. Despite these limitations, our study had notable strengths. It included a large sample size and was able to adjust for many confounding factors, exclusively targeted individuals without dementia to minimize the impact of cognitive decline on tea and coffee consumption behaviors, and accurately recorded intake habits using a Food Frequency Questionnaire (FFQ).

In conclusion, this study revealed that increased green tea consumption was associated with reduced cerebral white matter lesions. Given that cerebral white matter lesions are closely related to vascular dementia and AD, our findings indicate that drinking green tea, especially three or more glasses per day, may help prevent dementia. Nevertheless, further prospective longitudinal studies and basic research are needed to validate our results.

Methods

Study population

Among the 11,410 participants in the JPSC-AD study aged ≥ 65 years, 9646 underwent three-dimensional T1-weighted MRI. After excluding 167 participants who did not pass the quality control of the FreeSurfer analysis; 103 participants who did not have hippocampal measurement data; 341 participants without available data on green tea, black tea, and/or coffee intake; and 372 participants with dementia at baseline, 8766 participants were enrolled in the study (Fig. 1).

Ethical approvals and patient consents

This study was approved by the Kyushu University Institutional Review Board for clinical research (approval number 686-10) and by each of the local ethics committee of the eight research institutes: Kanazawa University (approval numbers 2185 and 437), Hirosaki University (approval number 2019-064-3), Iwate Medical University (approval number HG2020-017), Keio University School of Medicine (approval number 20160214), Matsue Medical Center (approval number H28-14), Ehime University (approval numbers 1610004 and 2210016), Kumamoto University (approval number 333), and Tohoku University (approval number 2021-1-245). This study complied with the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants.

Brain MRI analysis

The MRI equipment was set to T1-weighted imaging parameters according to the brain MRI protocol for the Alzheimer Disease Neuroimaging Initiative study[38]. Segmentation and volume measurements of cortical and subcortical brain structures, including WMLV, HV, and eTIV, were performed automatically using FreeSurfer (version 7.0; http://surfer.nmr.mgh.harvard.edu). TBV was calculated from brain segmentation volumes without ventricles. Cortical parcellation was performed using the Desikan-Killiany atlas[39].

To adjust for head size, TBV, HV, and WMLV were calculated as percentages of eTIV (i.e., TBV-to-eTIV ratio (TBV/eTIV) [%], HV-to-eTIV ratio (HV/eTIV) [%], and WMLV-to-eTIV ratio (WMLV/eTIV) [%]).

Dietary survey

The daily intake of green tea and coffee was calculated based on FFQ. Dietary surveys, using a weighing and dietary recording method to measure the average intake of each food and nutrient, were performed for 4 consecutive days (three weekdays and one weekend day) over 16 days across all four seasons. The participants completed FFQ at a health center or at home and were provided with a dietary recording form, recording manual, digital weighing scale, measuring spoons, camera photography scale (standard graphic tool used in the National Health and Nutrition Survey), instant camera (for those unable to take pictures with mobiles or smartphones), and instructions on usage. Nutritional values were calculated according to the Japanese Standard Tables of Food Composition, 2015 (7th revision). The validity of the intake data was evaluated using Pearson's correlation coefficients. The daily intake of green tea and coffee was classified into four groups: 0–200, 201–400, 401–600 and ≥ 601 ml, with one glass being approximately 200 ml.

Other risk factor measurements

Each participant completed a self-administered questionnaire collecting sociodemographic data (age, sex, and educational level), medical history (diabetes mellitus, hypertension, and past history of stroke), smoking and drinking habits, and regular exercise (defined as physical activity specifically undertaken for at least 30 min twice per week over the most recent year or longer). Completed questionnaires were reviewed by trained researchers to identify inconsistent or unanswered items. Depressive symptoms were evaluated using GDS (short form)[40] cognitive function was evaluated using MMSE. The details have been previously described[16]. Blood pressure was measured thrice using a sphygmomanometer with intervals of at least 5 min, and the average of the three measurements was used for the analysis. Electrocardiographic abnormalities were defined as one or more of the following: left ventricular hypertrophy (Minnesota Code, 3-1), atrial flutter/fibrillation (8-3), and ST-segment depression (4-1, 2, 3). Hypertension was defined as blood pressure levels of ≥ 140/90 mmHg or the current use of antihypertensive agents. BMI (kg/m^2) was used as an indicator of obesity. Serum HDL and LDL cholesterol levels were enzymatically measured[17]. *Apo*E polymorphisms were identified using a multiplex PCR-based targeted sequencing method, with two single-nucleotide polymorphisms (rs429358 and rs7412) genotyping, as previously reported[41].

Statistical analyses

Clinical characteristics were evaluated using the t-test, Jonckheere-Terpstra test, chi-square test, or Mantel-Haenszel test for continuous and categorical variables. Analysis of covariance was performed to estimate and compare the multivariate-adjusted values and 95% confidence intervals (CIs) for the TBV/eTIV, HV/eTIV, and WMLV/eTIV ratios. The WMLV/eTIV ratio was transformed using a common logarithm due to its skewed distribution. The shape of the associations of daily green tea consumption levels with the geometric mean of WMLV/eTIV among older adults without dementia in the multivariable-adjusted model was examined using a general linear model with restricted cubic splines, in which knots were positioned at the 5th, 35th, 65th, and 95th percentiles (0, 300, 600, and 1500 ml/day) of daily green tea consumption.

The association between daily green tea consumption and the WMLV/eTIV ratio relative to the reference value in older adults without dementia was also analyzed using multivariate-adjusted models. The reference value was set at 200 ml/day, which corresponds to one cup of green tea.

Model 1 was adjusted for age, sex, research site, and education level. Model 2 was further adjusted for hypertension, diabetes mellitus, *ApoE* ε4 allele, BMI, serum LDL and HDL cholesterol levels, smoking and drinking habits, electrocardiogram abnormalities, history of stroke, depressive symptoms (GDS score), cognitive function (MMSE score), and regular exercise. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using the SPSS software package (version 29; SPSS Inc., Chicago, IL, USA) and SAS version 9.4 (SAS Institute, Cary, NC).

After excluding 1519 participants with MCI at baseline, a sensitivity analysis was conducted for all participants. The relationship between green tea consumption and cerebral white matter lesions was also analyzed based on the presence or absence of the *ApoE* ε4 allele and depression.

Data availability

The datasets used in the present study are not publicly available, because they contain confidential clinical data on the study participants. However, the data are available on reasonable request and with the permission of the Principal Investigator of this study, Toshiharu Ninomiya.

Code availability

No custom code or mathematical algorithm was developed for this study. Details regarding the specific codes used can be found in the references cited. Any access restrictions or licensing information associated with the codes used can be obtained from the respective sources as indicated in the references.

Received: 3 August 2024; Accepted: 18 December 2024;
Published online: 07 January 2025

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Acknowledgements

We would like to thank the participants for the contribution of their time to the JPSC-AD study. We would like to gratefully acknowledge the diligent work and contributions of all researchers and investigators in the JPSC-AD Study Group. Funding: This study was supported by the Japan Agency for Medical Research and Development (JP23dk0207053) and Suntory Holdings Limited (Osaka, Japan). The sponsor had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

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Competing interests

Toshiharu Ninomiya reports receiving grants from Suntory Holdings Limited. The remaining authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41538-024-00364-w.

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