Relationship between the Japanese-style diet, gut microbiota, and dementia: a cross-sectional study

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Research

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Abstract

Background

Previous studies have shown associations between the gut microbiota, microbial metabolites, and cognitive decline. However, the effect of the dietary composition on such associations has not been fully investigated.

Methods

We performed a cross-sectional sub-analysis of data from our prospective hospital-based cohort study (the Gimlet study) to evaluate the relationships between dietary composition, cognitive decline, and the gut microbiota. All the participants of the Gimlet study had been provided with information regarding this sub-study in 2018. Patients were excluded if they were unable to provide sufficient data in the questionnaire regarding their dietary composition. We assessed their demographics, dietary composition, risk factors, cognitive function, results of brain imaging, gut microbiome, and microbial metabolites. On the basis of previous studies, a nine-component traditional Japanese diet index (JDI_9), a 12-component modern JDI (JDI_{12}), and a 12-component revised JDI ($rJDI_{12}$), were defined. Higher JDI scores indicated greater conformity to the traditional Japanese diet. We then evaluated the relationships between the JDI scores, cognitive function, and the gut microbiome and microbial metabolites using multivariable logistic regression analyses.

Results

We analyzed data from 85 eligible patients (61% women; mean age: 74.6 ± 7.4 years; mean Mini-Mental State Examination score: 24 ± 5). Compared with participants with dementia, those without dementia were more likely to consume foods in the JDI_{12}, including fish and shellfish (64.5% *vs.* 39.1%, $P = 0.048$), mushrooms (61.3% *vs.* 30.4%, $P = 0.015$), soybeans and soybean-derived foods (62.9% *vs.* 30.4%, $P = 0.013$), and coffee (71.0% *vs.* 43.5%, $P = 0.024$). There were non-significant trends towards lower fecal concentrations of gut microbial metabolites in participants with a more traditional Japanese diet. Participants with dementia had lower JDI_9, JDI_{12}, and $rJDI_{12}$ scores than participants without dementia (dementia *vs.* non-dementia, median JDI_9 score: 5 *vs.* 7, $P = 0.049$; JDI_{12}: 7 *vs.* 8, $P = 0.017$; and $rJDI_{12}$: 7 *vs.* 9, $P = 0.006$, respectively).

Conclusions

Adherence to a traditional Japanese diet was found to be inversely associated with cognitive decline and tended to be associated with lower concentrations of gut microbial metabolites.

Trial registration:

UMIN000031851.

Background

Dementia is an important healthcare problem because 47 million people were living with dementia in 2015 [1], and the number of patients is increasing. Therefore, a comprehensive strategy for dementia research has been introduced in Japan [2]. The assessment of dementia from various viewpoints is important to improve future healthcare.

Recently, the relationship between the diet and dementia has become an intriguing research focus [3–5]. Dietary patterns such as the Mediterranean diet [3] and the Japanese diet [4, 5] are receiving a lot of attention because these can reduce the risk of dementia. Furthermore, previous studies have shown that both the Mediterranean diet [6] and the Japanese diet [7] are able to alter the gut microbiota. With respect to the Japanese dietary pattern, its characteristics are described using the Japanese diet index (JDI), which has been modified according to the findings of previous studies [8, 9]. The original index (JDI_9) comprises nine components that define the traditional Japanese dietary pattern [8], but a modified index, the JDI_{12}, has been established by the addition of three further components to the JDI_9 [9]. However, recent studies have suggested that the inclusion of one component that is excluded from both the JDI_9 and JDI_{12} may have a positive effect on cognitive function [10]. Therefore, the use of these different versions of the JDI should be compared.

Several researchers have identified associations between the gut microbiota and cognitive decline [11–13]. Previous studies have shown that dysregulation of the gut microbiome, which is characterized in the form of enterotypes, is associated with cognitive decline [12, 13]. Furthermore, bacterial products, such as gut microbial metabolites, can increase systemic inflammation [14] and are also associated with dementia [15]. According to the results of these previous studies, the gut microbiota and the microbial metabolites [16, 17] modulate host brain function *via* a microbiota–gut–brain axis [18]. The diversity of the gut microbiota may be an important mediator of this relationship [12], but knowledge regarding the effects of the gut microbiota and its metabolites on cognitive function remains limited.

The results of these previous studies suggest that the Japanese diet may be associated with a gut microbial composition that inhibits cognitive decline. However, the mechanism of this association has not been identified because the associations between the diet and cognitive decline, and between cognitive decline and the gut microbiota, have been analyzed separately to date. To remedy this deficiency, an analysis of the relationships that underpin the diet–microbiota–gut–brain axis is needed.

We are presently conducting a clinical study that was designed to investigate the relationship between the gut microbiota and cognitive function. In this study, we have shown that gut microbial dysregulation is cross-sectionally associated with cognitive decline [12, 13], vascular risk factors [19], and brain

magnetic resonance imaging (MRI) abnormalities [20]. Furthermore, metabolites of the gut microbiota may play important roles in these associations [15]. Therefore, we hypothesized that the consumption of a Japanese-style diet would be inversely associated with cognitive decline and that there would be an association between this diet and the gut microbiome and/or microbial metabolites.

In the present study, we aimed to evaluate the relationships between adherence to a Japanese-style diet, the gut microbiota, and cognitive decline by means of a sub-analysis of data from the ongoing clinical study. Furthermore, we aimed to evaluate the three forms of the JDI (the conventional (JDI_9), updated (JDI_{12}), and a newly-modified JDI) to determine which would show the closest relationships with cognition and the gut microbiota.

Methods

Study design

We performed a cross-sectional sub-analysis of data from a hospital-based prospective cohort study, the Gerontological Investigation of Microbiome: a Longitudinal Estimation Study (the Gimlet study), which has been conducted at the National Center for Geriatrics and Gerontology (NCGG) in Japan. Detailed information regarding the Gimlet study is provided in our previous reports [12, 13, 15]. Briefly, we enrolled patients visiting the Memory clinic at the NCGG who agreed to undergo both a medical assessment of their cognitive function and a fecal examination. The activities of daily living and cognitive function of the participants were assessed annually after their enrollment.

Participants

Between March 2016 and March 2017, we enrolled consecutive patients who visited the Memory clinic at the NCGG and agreed to undergo both a medical assessment of their cognitive function and a fecal examination. Participants in the Gimlet study were eligible for this sub-study if they met the following criteria: (1) they were able to undergo brain MRI and complete a questionnaire regarding their dietary composition; and (2) they provided their informed consent in writing. Patients were excluded from this sub-study if they: (1) were unable to undergo MRI and/or complete the questionnaire; or (2) they were unable to provide sufficient data in the questionnaire regarding their diet. Patients who had potential confounders and effect modifiers for the variables of interest (for example, the recent use of antibiotics) had been excluded at the time of enrollment in the Gimlet study. All the patients who had enrolled in the Gimlet study and their families had been provided with information regarding this sub-study in 2018, after their enrollment in the Gimlet study.

Baseline assessments

All the participants underwent a comprehensive geriatric assessment [21] that was based on the following: (1) demographic characteristics; (2) risk factors; (3) basic and instrumental activities of daily living (ADL) scales; (4) global cognitive function, assessed using the Mini-Mental State Examination

(MMSE) [22] and Clinical Dementia Rating (CDR) [23] scales; (5) neuropsychological testing; (6) behavioral and psychological symptoms; (7) assessment of the burden for caregivers; (8) depression status; (9) laboratory parameters; (10) arterial stiffness, as an indicator of arteriosclerosis [24], and the 'impact' of pulse [25]; and (11) the results of brain imaging, such as MRI and single-photon emission computed tomography (SPECT). All the clinical samples and data were provided by the NCGG Biobank, which collects clinical data for research.

Dietary assessments

The questionnaire regarding dietary composition consisted of 12 items. All the components of a typical Japanese diet were grouped on the basis of the definitions used in the Japanese National Health and Nutrition Survey of 2011 [26]. As in previous studies [8, 9], we identified the following 12 components of the diet: rice, miso, fish and shellfish, green and yellow vegetables, seaweed, pickles, fruit, soybeans and soybean-derived foods, mushrooms, beef and pork, chicken, green tea, and coffee. The participants and their families answered questions regarding their consumption of these items using the following options: (1) always (on 6–7 days per week), (2) usually (on 3–5 days per week), (3) sometimes (on 1–2 days per week), and (4) rarely (on <1 day per week).

Japanese dietary indices

We evaluated three Japanese dietary indices. The first was the conventional JDI (JDI_9) [8]: (1) for each of the seven beneficial components (rice, miso, fish and shellfish, green and yellow vegetables, seaweed, pickles, and green tea), the participants were assigned one point if their daily intake of the item was equal to or greater than the sex-specific median dietary intake; and (2) for each of the two less beneficial components (beef and pork, and coffee), the participants were assigned one point if their daily intake was below the sex-specific median intake because there are sex differences regarding the dietary intake of these items [27]. Thus, the JDI_9 score ranged from 0 to 9, with higher scores indicating greater conformity to the traditional Japanese diet.

The second index was defined recently [9, 28] and comprises 12 components (the JDI_{12}) because three further beneficial components (soybeans and soybean-derived foods, fruit, and mushrooms) had been added to the JDI_9. Therefore, the JDI_{12} score ranged from 0 to 12, and was indicative of an expanded traditional Japanese diet. However, according to recent reports [29, 30], higher intake of coffee is associated with better health status and contributes to a lower risk of dementia. Therefore, we also defined a 12-component revised JDI ($rJDI_{12}$), in which one less beneficial component (coffee) in the JDI_{12} was changed to be a beneficial component. The score of the $rJDI_{12}$, which is more representative of a modern Japanese diet, also ranged from 0 to 12 points.

Classification of cognitive function

Dementia was defined as an MMSE < 20 and/or a CDR ≥ 1. The participants who did not have dementia were further categorized as having mild cognitive impairment (MCI) or normal cognition (NC). MCI was

defined as an MMSE ≥ 20 and a CDR = 0.5, which implies possible, very mild dementia, and suggests that the patient has a higher risk of developing dementia in the future [31]. In contrast, NC was defined as an MMSE ≥ 20 and a CDR = 0.

Brain imaging

The participants underwent a 1.5-T MRI of their brains (Philips Ingenia, Eindhoven, the Netherlands). MRI scans were obtained, including diffusion-weighted images, fluid-attenuated inversion recovery images, T2-weighted images, $T2^*$-weighted gradient-echo images, three-dimensional T1-weighted sagittal and axial coronal views, and 3D time-of-flight magnetic resonance angiography scans. The presence and components of cerebral small vessel disease (SVD), such as silent lacunar infarct (SLI), white matter hyperintensity (WMH), cerebral microbleeds (CMB), and enlarged periventricular space (EPVS), were categorized using previously published standards for reporting vascular changes on neuroimaging [32]. The voxel-based specific regional analysis system for Alzheimer's Disease (VSRAD) software (Eisai Co., Ltd., Tokyo, Japan) was used to quantify cortical and hippocampal atrophy, using standardized z-scores [33]. A high VSRAD score suggests the presence of Alzheimer's disease (AD) because this score reflects hippocampal atrophy, which is one of the characteristics of the brain of a patient with AD. The participants also underwent N-isopropyl-p-[^{123}I]-iodoamphetamine-SPECT, in which the presence of low blood flow in the area of the posterior cingulate gyrus and/or the precuneus was regarded as a surrogate marker of AD [34].

Total SVD score

As in a previous study [35], we rated the MRI burden of SVD on an ordinal scale from 0 to 4 by recording the presence of each of four features of cerebral SVD. This score consisted of the following: (1) SLI (1 point if present); (2) CMB (1 point if present); (3) EPVS (1 point if moderate-to-severe EPVSs are present); and (4) WMH (1 point if present).

Gut microbiome

Fecal samples were collected at the participants' homes, and the samples were then frozen and stored at −81°C at the NCGG Biobank. After all the samples had been collected, the gut microbiome of each participant was analyzed by the TechnoSuruga Laboratory (Shizuoka, Japan) using terminal restriction fragment-length polymorphism (T-RFLP) analysis [36]. The T-RFLP analysis was used to classify gut microbes into the following 10 groups: *Prevotella*, *Bacteroides*, Lactobacillales, *Bifidobacterium*, *Clostridium* cluster IV, *Clostridium* subcluster XIVa, *Clostridium* cluster IX, *Clostridium* cluster XI, *Clostridium* cluster XVIII, and 'others'. By referencing the Human Fecal Microbiome T-RFLP profile [37, 38], each gut microbiome was categorized as representing one of three enterotypes: enterotype I, which included *Bacteroides* at > 30%; enterotype II, which included *Prevotella* at > 15%; and enterotype III, which comprised other combinations of microorganisms. The Firmicutes/Bacteroidetes (F/B) ratio was also calculated because a high ratio is indicative of dysbiosis [39].

Analysis of microbial metabolites in feces

In previous studies, the concentrations of gut microbial metabolites, including short-chain fatty acids (SCFAs) [6, 17] and lipopolysaccharide [17], have been quantified. In the present study, we measured the fecal concentrations of organic acids, SCFAs, ammonium ions, indoles, phenol, skatole, and p-cresol, as previously described [15]. The concentrations of organic acids and SCFAs (acetic acid, propionic acid, butyric acid, iso-butyric acid, succinic acid, lactic acid, formic acid, valeric acid, and iso-valeric acid) were measured using high-performance liquid chromatography. Ammonium ion concentrations were quantified using ion chromatography; and the fecal concentrations of indoles, phenol, skatole, and p-cresol were quantified using gas chromatography/mass spectrometry. Detailed information regarding the analysis of the fecal metabolites is provided in our previous report [15] and the Supplementary file.

Statistical analysis

Continuous, ordinal, and categorical variables are expressed as the mean ± standard deviation, median and interquartile range, or frequency or proportion (percentage), respectively. Data were compared using the unpaired Student's *t*-test, Wilcoxon rank-sum test, and χ^2 test, respectively. First, the participants were allocated to groups according to the presence or absence of dementia, the presence or absence of enterotype I, and those with MCI or NC, among the participants who did not have dementia, and their clinical characteristics were compared using the Wilcoxon rank-sum test. In addition, their gut microbiomes and gut microbial metabolites were compared using the χ^2 test or the Wilcoxon rank-sum test. Second, we evaluated the relationships between the gut microbiome, microbial metabolites, and dietary composition. Third, the participants were allocated to two groups according to their JDI_{12}: a high JDI_{12} group (above the median value) and a low JDI_{12} group (below the median value), and we compared their clinical characteristics. We also compared the differences between participants with high $rJDI_{12}$ scores and those with low $rJDI_{12}$ scores. Finally, multivariable logistic regression models were used to identify independent associations between the presence of dementia, JDI score (JDI_{12} or $rJDI_{12}$), and the gut microbiome. Odds ratios (ORs) and 95% confidence intervals (CIs) are presented. All the comparisons were two-tailed, and $P < 0.05$ was considered to represent statistical significance. Data were analyzed using the JMP 12.0 software package and SAS v9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Participant characteristics

We previously enrolled 128 participants in the Gimlet study, but of these, 43 were excluded from this sub-analysis because of incomplete data and/or refusal to participate. We therefore analyzed data from the remaining 85 eligible participants (61.1% women; mean age: 74.6 ± 7.4 years; mean MMSE score: 24 ± 5). These participants were classified according to their level of cognitive function and their enterotype: 23 participants (27.1%) were classified as having dementia, 42 (49.4%) were classified as having MCI, and

20 (23.5%) were classified as having NC; 28 (32.9%) were classified as having enterotype I, 4 (4.7%) enterotype II, and 53 (62.4%) enterotype III.

Participants with dementia vs. those without

Compared with participants with dementia, those without were more likely to consume fish and shellfish (non-dementia *vs.* dementia, 64.5% *vs.* 39.1%, $P = 0.048$), mushrooms (61.3% *vs.* 30.4%, $P = 0.015$), soybeans and soybean-derived foods (62.9% *vs.* 30.4%, $P = 0.013$), and coffee (71.0% *vs.* 43.5%, $P = 0.024$; Table 1). Although there were no significant differences, participants without dementia tended to have higher intakes of rice, noodles, miso, seaweed, fruits, beef and pork, chicken, and green tea. Participants with dementia had lower JDI scores (JDI_9, JDI_{12}, and $rJDI_{12}$) than those without (dementia *vs.* non-dementia, median scores for JDI_9: 5 *vs.* 7, $P = 0.049$; JDI_{12}: 7 *vs.* 8, $P = 0.017$; and $rJDI_{12}$: 7 *vs.* 9, $P = 0.006$, respectively; Fig. 1). The $rJDI_{12}$ score showed clearer differences in the prevalence of dementia among the participants when they were classified according to the tertile of JDI score than the JDI_9 and JDI_{12} scores (low *vs.* middle *vs.* high JDI score, according to tertile: JDI_9: 38.7% *vs.* 17.5% *vs.* 28.6%, $P = 0.135$; JDI_{12}: 40.9% *vs.* 33.3% *vs.* 12.1%, $P = 0.039$; and $rJDI_{12}$: 48.3% *vs.* 16.7% *vs.* 15.4%, $P = 0.007$, respectively; Fig. 2). With regard to the methods of food preparation, participants without dementia were more likely to use soup stocks than those with dementia (93.6% *vs.* 60.9%, $P = 0.001$; Table 1).

Table 1
Comparison of dietary composition between participants with dementia and those without

	Dementia (+)	Dementia (−)	*P*
	(*n* = 23)	(*n* = 62)	
Food			
Rice, *n* (%)	19 (82.6)	57 (91.9)	0.245
Bread, *n* (%)	13 (56.5)	33 (53.2)	0.812
Noodles, *n* (%)	6 (26.1)	23 (37.1)	0.443
Miso, *n* (%)	12 (52.2)	39 (62.9)	0.457
Fish and shellfish, *n* (%)	9 (39.1)	40 (64.5)	0.048
Vegetables, *n* (%)	21 (91.3)	58 (93.6)	0.660
Seaweed, *n* (%)	10 (43.5)	32 (51.6)	0.627
Pickles, *n* (%)	11 (47.8)	33 (53.2)	0.808
Mushrooms, *n* (%)	7 (30.4)	38 (61.3)	0.015
Fruit, *n* (%)	14 (60.9)	43 (69.4)	0.604
Beef and pork, *n* (%)	13 (56.5)	46 (74.2)	0.184
Chicken, *n* (%)	10 (43.5)	39 (62.9)	0.140
Soybeans and soybean-derived foods, *n* (%)	7 (30.4)	39 (62.9)	0.013
Milk and dairy products, *n* (%)	14 (60.9)	41 (66.1)	0.799
Green tea, *n* (%)	11 (47.8)	41 (66.1)	0.140
Coffee, *n* (%)	10 (43.5)	44 (71.0)	0.024
Cooking method			
Boiling, *n* (%)	18 (78.3)	35 (56.5)	0.081
Steaming, *n* (%)	7 (30.4)	22 (35.5)	0.799
Raw, *n* (%)	12 (52.2)	41 (66.1)	0.314
Deep-frying, *n* (%)	10 (43.5)	21 (33.9)	0.454
Frying, *n* (%)	12 (52.2)	41 (66.1)	0.314

The Wilcoxon rank-sum test and the χ^2 test were used.

	Dementia (+)	Dementia (−)	*P*
	(*n* = 23)	(*n* = 62)	
Use of soup stock, *n* (%)	14 (60.9)	58 (93.6)	0.001
Use of fermented seasoning, *n* (%)	18 (78.3)	57 (91.9)	0.125
The Wilcoxon rank-sum test and the χ^2 test were used.			

Enterotype I vs. other enterotypes

Compared with participants with the other enterotypes, those with enterotype I tended to consume less seaweed, fruit, and milk and dairy products, although these differences were not significant (Table S1).

MCI vs. NC patients

Among the participants who did not have dementia, the participants with NC tended to consume more fish, shellfish, and coffee than those with MCI, although these differences were not statistically significant (Table S2). In addition, participants with enterotype I tended to consume less miso, fish and shellfish, seaweed, fruit, chicken, and milk and dairy products, but again the differences were not statistically significant (Table S3).

Microbial metabolites

Participants who consumed more mushrooms (eg. higher *vs.* lower intake; median concentration of iso-butyric acid: 0.03 *vs.* 0.11 mg/g, $P = 0.017$; Table S4), soybeans and soybean-derived foods (Table S5), or coffee (Table S6) had lower fecal concentrations of several gut microbial metabolites than those who consumed smaller amounts of these items.

High vs. Low JDI_{12} score

Participants with high JDI_{12} scores were less likely to be female (High *vs.* Low JDI_{12}: 46.8% *vs.* 79.0%, $P = 0.004$), less likely to have dementia (14.9% *vs.* 42.1%, $P = 0.007$) and WMH (17.0% *vs.* 36.8%, $P = 0.048$), had lower GDS, ZBI, and VSRAD scores, and were more likely to have good neuropsychological test results (Table 2). The concentrations of the majority of the gut microbial metabolites in participants with high JDI_{12} scores were lower than in those with low JDI_{12} scores (Table 3).

Table 2
Comparison of the characteristics of participants with JDI12 scores above or below the median value

	High JDI_{12}	Low JDI_{12}	*P*
	(*n* = 47)	(*n* = 38)	
Demographic factor			
Age, years	75, 68–80	77, 72–81	0.428
Female sex, *n* (%)	22 (46.8)	30 (79.0)	0.004
Education, years	12, 9–13	12, 9–12	0.300
Body mass index, kg/m^2	22.4, 20.6–24.5	22.8, 20.6–24.8	0.630
Systolic BP, mmHg	151, 128–1,632	143, 123–162	0.221
Diastolic BP, mmHg	83, 72–90	77, 70–86	0.128
Risk factor			
Hypertension, *n* (%)	28 (59.6)	25 (65.8)	0.654
Diabetes mellitus, *n* (%)	6 (12.8)	5 (13.2)	1.000
Dyslipidemia, *n* (%)	21 (44.7)	23 (60.5)	0.191
IHD, *n* (%)	5 (10.6)	6 (15.8)	0.530
Stroke, *n* (%)	5 (10.6)	3 (7.9)	0.726
CKD, *n* (%)	15 (31.9)	14 (36.8)	0.653
Smoking habit, *n* (%)	13 (27.7)	7 (18.4)	0.441
Alcohol consumption, *n* (%)	21 (44.7)	13 (34.2)	0.378

Continuous, ordinal, and categorical variables are expressed as the mean ± standard deviation, median and interquartile range, or frequency or proportion (percentage), respectively. The Wilcoxon rank-sum test and the χ^2 test were used.

*Low blood flow in the area of the posterior cingulate gyrus and/or the precuneus.

Abbreviations: JDI, Japanese dietary index; BP, blood pressure; IHD, ischemic heart disease; CKD, chronic kidney disease; ApoE, apolipoprotein E; IADL, instrumental activities of daily living; DBDS, Dementia Behavior Disturbance Scale; GDS, Geriatric Depression Scale; ZBI, Zarit Caregiver Burden Interview; MNA-SF, Mini-Nutritional Assessment-Short Form; MMSE, Mini-Mental State Examination; CDR-GB, Clinical Dementia Rating Global Score; CDR-SB, Clinical Dementia Rating-Sum of Boxes; ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; RCPM, Raven's Colored Progressive Matrices; FAB, Frontal Assessment Battery; LM-WMSR, Logical Memory subtests I and II of the Wechsler Memory Scale-Revised; SLI, silent lacunar infarct; WMH, white matter hyperintensity; CMB, cerebral microbleeds; EPVS, enlarged perivascular space; SVD, small vessel disease; VSRAD, voxel-based specific regional analysis system for Alzheimer's disease; SPECT, single-photon emission computed tomography; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate.

	High JDI_{12}	Low JDI_{12}	*P*
	(*n* = 47)	(*n* = 38)	
APOE ε4 carrier, *n* (%)	10 (21.3)	11 (29.0)	0.456
Dementia, *n* (%)	7 (14.9)	16 (42.1)	0.007
Frailty, *n* (%)	5 (10.6)	8 (21.1)	0.232
Comprehensive geriatric assessment			
Barthel index	100, 100–100	100, 99–100	0.059
IADL impairment, *n* (%)	15 (31.9)	18 (47.4)	0.182
DBDS	5, 3–11	9, 4–16	0.225
GDS	2, 1–4	4, 2–5	0.057
ZBI	6, 3–16	12, 5–22	0.085
MNA-SF	13, 11–14	12, 11–13	0.269
Cognitive function			
MMSE	26, 22–29	24, 19–28	0.066
CDR-GB			0.025
0, *n* (%)	12 (25.5)	8 (21.1)	
0.5, *n* (%)	33 (68.1)	17 (44.7)	
≥1, *n* (%)	3 (6.4)	13 (34.2)	
CDR-SB	1.0, 0.5–3.0	2.0, 0.9–5.1	0.036

Continuous, ordinal, and categorical variables are expressed as the mean ± standard deviation, median and interquartile range, or frequency or proportion (percentage), respectively. The Wilcoxon rank-sum test and the χ^2 test were used.

*Low blood flow in the area of the posterior cingulate gyrus and/or the precuneus.

Abbreviations: JDI, Japanese dietary index; BP, blood pressure; IHD, ischemic heart disease; CKD, chronic kidney disease; ApoE, apolipoprotein E; IADL, instrumental activities of daily living; DBDS, Dementia Behavior Disturbance Scale; GDS, Geriatric Depression Scale; ZBI, Zarit Caregiver Burden Interview; MNA-SF, Mini-Nutritional Assessment-Short Form; MMSE, Mini-Mental State Examination; CDR-GB, Clinical Dementia Rating Global Score; CDR-SB, Clinical Dementia Rating-Sum of Boxes; ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; RCPM, Raven's Colored Progressive Matrices; FAB, Frontal Assessment Battery; LM-WMSR, Logical Memory subtests I and II of the Wechsler Memory Scale-Revised; SLI, silent lacunar infarct; WMH, white matter hyperintensity; CMB, cerebral microbleeds; EPVS, enlarged perivascular space; SVD, small vessel disease; VSRAD, voxel-based specific regional analysis system for Alzheimer's disease; SPECT, single-photon emission computed tomography; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate.

	High JDI_{12}	Low JDI_{12}	*P*
	(*n* = 47)	(*n* = 38)	
ADAS-cog	8.0, 5.0–14.0	11.3, 6.9–16.7	0.085
RCPM	29, 24–32	28, 24–30	0.431
FAB	11, 9–14	11, 9–13	0.984
LM-WMSR I	11, 5–18	7, 3–13	0.048
LM-WMSR II	5, 0–12	1, 0–6	0.033
Brain MRI finding			
SLI, *n* (%)	6 (12.8)	3 (7.9)	0.725
WMH, *n* (%)	8 (17.0)	14 (36.8)	0.048
CMB, *n* (%)	9 (19.2)	6 (15.8)	0.779
EPVS, *n* (%)	8 (17.0)	10 (26.3)	0.424
SVD score	1, 0–1	0, 0–2	0.506
VSRAD	0.80, 0.57–1.30	1.09, 0.78–2.08	0.087
SPECT			
Low blood flow*	30 (65.2)	23 (62.2)	0.821
Arterial stiffness			
Ankle brachial index	1.11, 1.04–1.14	1.12, 1.05–1.16	0.553
Pulse wave velocity, m/s	18.6, 15.8–21.9	17.2, 14.6–19.8	0.159

Continuous, ordinal, and categorical variables are expressed as the mean ± standard deviation, median and interquartile range, or frequency or proportion (percentage), respectively. The Wilcoxon rank-sum test and the χ^2 test were used.

*Low blood flow in the area of the posterior cingulate gyrus and/or the precuneus.

Abbreviations: JDI, Japanese dietary index; BP, blood pressure; IHD, ischemic heart disease; CKD, chronic kidney disease; ApoE, apolipoprotein E; IADL, instrumental activities of daily living; DBDS, Dementia Behavior Disturbance Scale; GDS, Geriatric Depression Scale; ZBI, Zarit Caregiver Burden Interview; MNA-SF, Mini-Nutritional Assessment-Short Form; MMSE, Mini-Mental State Examination; CDR-GB, Clinical Dementia Rating Global Score; CDR-SB, Clinical Dementia Rating-Sum of Boxes; ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; RCPM, Raven's Colored Progressive Matrices; FAB, Frontal Assessment Battery; LM-WMSR, Logical Memory subtests I and II of the Wechsler Memory Scale-Revised; SLI, silent lacunar infarct; WMH, white matter hyperintensity; CMB, cerebral microbleeds; EPVS, enlarged perivascular space; SVD, small vessel disease; VSRAD, voxel-based specific regional analysis system for Alzheimer's disease; SPECT, single-photon emission computed tomography; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate.

	High JDI_{12}	Low JDI_{12}	*P*
	(*n* = 47)	(*n* = 38)	
Laboratory finding			
Total protein, g/dL	7.2, 6.9–7.6	7.3, 6.9–7.6	0.814
Albumin, g/dL	4.3, 4.0–4.5	4.3, 4.0–4.4	0.552
CRP, mg/dL	0.06, 0.02–0.18	0.05, 0.02–0.13	0.505
eGFR, mL/min/1.73 m^2	70.4, 55.8–74.1	61.2, 53.1–73.3	0.340
HbA1c, %	5.8, 5.6–6.2	5.7, 5.6–6.0	0.550

Continuous, ordinal, and categorical variables are expressed as the mean ± standard deviation, median and interquartile range, or frequency or proportion (percentage), respectively. The Wilcoxon rank-sum test and the χ^2 test were used.

*Low blood flow in the area of the posterior cingulate gyrus and/or the precuneus.

Abbreviations: JDI, Japanese dietary index; BP, blood pressure; IHD, ischemic heart disease; CKD, chronic kidney disease; ApoE, apolipoprotein E; IADL, instrumental activities of daily living; DBDS, Dementia Behavior Disturbance Scale; GDS, Geriatric Depression Scale; ZBI, Zarit Caregiver Burden Interview; MNA-SF, Mini-Nutritional Assessment-Short Form; MMSE, Mini-Mental State Examination; CDR-GB, Clinical Dementia Rating Global Score; CDR-SB, Clinical Dementia Rating-Sum of Boxes; ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; RCPM, Raven's Colored Progressive Matrices; FAB, Frontal Assessment Battery; LM-WMSR, Logical Memory subtests I and II of the Wechsler Memory Scale-Revised; SLI, silent lacunar infarct; WMH, white matter hyperintensity; CMB, cerebral microbleeds; EPVS, enlarged perivascular space; SVD, small vessel disease; VSRAD, voxel-based specific regional analysis system for Alzheimer's disease; SPECT, single-photon emission computed tomography; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate.

Table 3
Comparison of the gut microbiome and fecal microbial metabolite concentrations of participants with JDI12 scores above or below the median value

	High JDI_{12}	Low JDI_{12}	*P*
	(*n* = 47)	(*n* = 38)	
Gut microbiome			0.716
Enterotype I, *n* (%)	15 (34.2)	13 (34.1)	
Enterotype II, *n* (%)	3 (6.4)	1 (2.6)	
Enterotype III, *n* (%)	29 (61.7)	24 (63.2)	
F/B ratio	1.50, 0.82–2.70	1.84, 1.11–3.12	0.147
Metabolite			
Ammonia, mg/g	0.64, 0.37–0.98	0.58, 0.24–0.94	0.431
Succinic acid, mg/g	0.03, 0.03–0.10	0.03, 0.03–0.44	0.622
Lactic acid, mg/g	0.03, 0.03–0.10	0.03, 0.03–0.58	0.398
Formic acid, mg/g	0.05, 0.05–0.05	0.05, 0.05–0.05	0.282
Acetic acid, mg/g	2.27, 0.03–6.09	2.91, 0.03–6.84	0.741
Propionic acid, mg/g	0.23, 0.03–1.51	0.84, 0.03–2.46	0.206
Iso-butyric acid, mg/g	0.06, 0.03–0.19	0.07, 0.03–0.15	0.669
n-butyric acid, mg/g	0.13, 0.03–0.86	0.29, 0.03–0.88	0.863
Iso-valeric acid, mg/g	0.03, 0.03–0.38	0.03, 0.03–0.25	0.347
n-valeric acid, mg/g	0.24, 0.03–1.95	0.17, 0.03–2.61	0.639
Phenol, μg/g	1.02, 0.0003–1.93	1.16, 0.0003–2.12	0.495
P-cresol, μg/g	0.32, 0.0003–118.07	0.24, 0.0003–15.27	0.213
4-Ethylphenol, μg/g	0.26, 0.0003–0.91	0.0003, 0.0003–0.66	0.110
Indoles, μg/g	1.79, 0.14–25.57	1.06, 0.0003–22.53	0.728
Skatole, μg/g	0.11, 0.0003–5.79	0.0003, 0.0003–0.17	0.033

The Wilcoxon rank-sum test and the χ^2 test were used.

High vs. Low $rJDI_{12}$ score

Participants with high $rJDI_{12}$ scores were less likely to be female, less likely to have dementia (High *vs.* Low $rJDI_{12}$: 15.0% *vs.* 37.8%, $P = 0.027$) and WMH (12.5% *vs.* 37.8%, $P = 0.012$), had lower ZBI (5 *vs.* 14 points, $P = 0.010$) and VSRAD (median score; 0.74 *vs.* 1.15, $P = 0.031$) scores, and were more likely to have good neuropsychological test results (Table S7). In addition, the fecal concentrations of the majority of the gut microbial metabolites in participants with high $rJDI_{12}$ scores were lower than in those with low $rJDI_{12}$ scores (Table S8).

Results of multivariate analyses

In univariable analyses, greater intakes of fish and shellfish (OR, 95% CI; 0.35, 0.13–0.93, $P = 0.036$), mushrooms (0.28, 0.09–0.75, $P = 0.011$), soybeans and soybean-derived foods (0.26, 0.09–0.70, $P = 0.007$), and coffee (0.31, 0.11–0.84, $P = 0.021$) were associated with significantly lower ORs for dementia (Table S9), as was the use of soup stock (0.32. 0.03–0.38, $P = 0.001$). However, there were no significant differences in univariable analyses for the presence of enterotype I (Table S10).

In multivariable analyses, participants with high JDI_{12} scores were inversely associated with the presence of dementia and were significantly associated with lower ORs (Table 4). The increment in both JDI_{12} and $rJDI_{12}$ scores (per one point increment) were also inversely associated with the presence of dementia and were associated with lower ORs; however, there were no significant differences in the stepwise multivariable logistic regression analyses (Table S11). The area under the receiver operating curve (AUC) of $rJDI_{12}$ for the presence of dementia was the highest among those of the three JDI indices (AUC for JDI_9: 0.637; JDI_{12}: 0.668; and $rJDI_{12}$: 0.693).

Table 4
Multivariable logistic regression analyses for the presence of dementia

	OR	95% CI	*P*
High JDI_9score (vs.**Low score**) *			
Model 1	0.41	0.15–1.08	0.070
Model 2	0.48	0.17–1.38	0.175
Model 3	0.59	0.18–1.94	0.384
Model 4	0.36	0.12–1.03	0.057
High JDI_{12}score (vs.**Low score**) *			
Model 1	0.24	0.08–0.65	0.005
Model 2	0.33	0.11–0.97	0.043
Model 3	0.22	0.07–0.66	0.006
Model 4	0.10	0.01–0.45	0.002
High rJDI_{12}score (vs.**Low score**) *			
Model 1	0.29	0.09–0.80	0.016
Model 2	0.36	0.11–1.06	0.064
Model 3	0.34	0.10–1.10	0.072
Model 4	0.34	0.07–1.32	0.120

*Allocated to two groups according to their JDI: a high JDI_{12} group (above the median value) and a low JDI group (below the median value).

Abbreviations: OR, odds ratio; CI, confidence interval; JDI, Japanese dietary index. The dependent variable was the presence of dementia. JDI_9: conventional JDI score, which comprised seven beneficial components (“rice”, “miso”, “fish and shellfish”, “green and yellow vegetables”, “seaweed”, “pickles”, and “green tea”), and two less beneficial components (“beef and pork” and “coffee”); 0–9 points. JDI_{12}: modified JDI score, comprising the JDI_9 components and three additional beneficial components (“soybeans and soybean-derived foods”, “fruit”, and “mushrooms”); 0–12 points. r-JDI_{12}: revised JDI_{12} score, in which one less beneficial component (“coffee”) in the JDI_{12} was changed to a beneficial component, such that these became “rice”, “miso”, “fish and shellfish”, “green and yellow vegetables”, “seaweed”, “pickles”, “green tea” and “coffee”; and there was just one less beneficial component (“beef and pork”), making it more consistent with the modern Japanese diet; 0–12 points.

	OR	95% CI	*P*
Model 1: univariate analyses. Model 2: adjusted for age, sex. Model 3: backward stepwise multivariable logistic regression analyses, which were adjusted for the model 2 factors, years of education, and risk factors (hypertension, dyslipidemia, diabetes mellitus, ischemic heart disease, chronic kidney disease, smoking, alcohol consumption, and ApoE). Model 4: backward stepwise multivariable logistic regression analyses adjusted for the factors in model 3, plus enterotype I, silent lacunar infarct, white matter hyperintensity, cerebral microbleeds, enlarged perivascular space, score of the voxel-based specific regional analysis system for Alzheimer's disease, single-photon emission-computed tomography findings (presence or absence of low blood flow in the area of the posterior cingulate gyrus and/or precuneus), ankle brachial index, and pulse wave velocity.			

Discussion

The main finding of the present study is that adherence to a traditional Japanese diet was inversely associated with cognitive decline and tended to be associated with low concentrations of several gut microbial metabolites. Associations between adherence to a traditional Japanese diet and cognitive decline have previously been reported in community-dwelling older people [4, 5, 40] and in younger adults [41]. However, this relationship had not previously been evaluated in older adults in a hospital-based cohort. Therefore, our findings are novel in this respect. Such associations among diet, clinical data, the gut microbiome, and microbial metabolites had not been previously reported.

Traditional Japanese diets include large amounts of fish and shellfish, miso, seaweed, vegetables, soy products, fruit, and green tea [40, 42], and some of these (fish, vegetables, soy products, and fruit) are associated with beneficial effects on cognitive function [40, 42–44]. In the present study, we found that greater intake of these foods was inversely associated with cognitive decline in univariate analyses and tended to be associated with lower fecal concentrations of specific gut microbial metabolites. These findings are consistent with those of previous studies.

The assessment of dietary patterns using the JDI_{12} and $rJDI_{12}$ yielded similar results in the present study. However, the $rJDI_{12}$ showed more clearly that the consumption of larger amounts of four foods (soybeans and soybean-derived foods, fruit, mushrooms, and coffee) was associated with a lower OR for the presence of dementia. Therefore, these foods likely make the largest contribution to the association between diet and dementia.

The Japanese dietary pattern shares characteristics with the Mediterranean diet; for instance, the high intake of vegetables, legumes, and fish, and the low consumption of meat [42]. Therefore, the mechanism underlying the association between adherence to a Japanese-style diet and the lower risk of dementia may be similar to that reported following studies of the Mediterranean diet. Specifically, the Mediterranean diet affects the composition of the gut microbiota and the concentrations of the derived metabolites, and is associated with improvements in biomarkers of AD [6].

In particular, we found that mushroom and soybean consumption was associated with lower ORs for the presence of dementia. Mushrooms and soybeans contain many useful nutrients, such as dietary fiber,

minerals, B vitamins, vitamin D, and vitamin E [44, 45]. Furthermore, mushroom consumption alters lipid metabolism, and has anti-obesity, anti-atherosclerotic, and anti-diabetic effects [45]. In addition, soybeans contain phytoestrogens (isoflavones), which have beneficial effects on cognitive function [44]. This is consistent with both JDI_{12} and $rJDI_{12}$ being inversely associated with the presence of dementia.

Milk and dairy products are considered to be beneficial for health. Previous studies have shown that the consumption of milk and dairy products is associated with better mental health [46] and a lower risk of dementia [5, 47] in older adults, but there was insufficient evidence regarding its relationship with cognitive function to draw a conclusion in a previous meta-analysis [48]. In the present study, a significant relationship between dementia and the consumption of milk and dairy products was also not identified.

The relationships between the consumption of green tea and coffee and cognitive function are also unclear. One previous study showed that the consumption of green tea prevents oxidative stress, but may not significantly affect cognitive function in older adults [49], and another showed that green tea, but not coffee, reduces the risk of cognitive decline in older adults [50]. It has also been reported that caffeine consumption, and especially the moderate quantities consumed in coffee or green tea, reduces the risk of dementia [10], probably because caffeine affects neural and vascular activity, including vasoconstriction and cerebral blood flow [10]. In the present study, there was no significant association between green tea consumption and dementia, but greater intake of coffee tended to be associated with lower concentrations of microbial metabolites that are associated with dementia. This trend will be investigated further in the future.

Polyunsaturated fatty acid [51] and probiotic [52] consumption have been shown to ameliorate or preserve cognitive function. Previous studies have suggested that intake of the probiotics *Bifidobacterium* [52] or *Lactobacillus* [53] inhibits cognitive decline. Dietary diversity is also protective against cognitive decline [54], and nutritional education [55] is essential for patients and their family members. In the present study, the effects of soup stock on the gut microbiota and cognitive function were unclear, and these relationships will be investigated in more detail in the future.

The present study had several strengths. First, we have provided evidence for novel relationships between the Japanese dietary indices, the gut microbiota, and cognitive decline, which are consistent with the existence of a diet–microbiome–gut–brain axis. Specifically, adherence to a traditional Japanese diet is associated with low fecal concentrations of specific gut microbial metabolites. Moreover, increments in the JDI scores are associated with decreases in the prevalence of dementia. Second, we systematically assessed the cognitive function of patients using a comprehensive geriatric assessment and a range of neuro-psychological tests. Last, our findings may lead to greater attention being paid to the relationships between the composition of the diet and cognitive function, through assessment of the gut microbiome.

Th present study also had several limitations. A causal relationship between the gut microbiome and dietary pattern could not be identified because of the cross-sectional nature of the study. We are currently

conducting a longitudinal observational study that will help us identify causality in these relationships in the near future. In addition, other research groups are conducting randomized, placebo controlled, double-blind clinical studies regarding the links between the gut microbiota and cognition using antioxidant or probiotic supplements [56, 57]. The small number of participants and large number of potential variables in the present study mean that it may have been statistically underpowered; a larger-scale study might have yielded significant findings where we only identified trends. In addition, selection bias may also exist because we studied a single, hospital-based cohort. We could not quantitatively evaluate dietary intake, and frequency evaluation is unable to determine the dose-dependency of the relationships. The specific effects of each microbial metabolite have not been determined. However, there have been recent studies of the associations between metabolites and cognitive function [16, 17, 58], and those findings will be complemented by others in the future that will clarify the nature of such relationships. Measurement of the concentration of amyloid-β precursor protein may be also useful because it is associated with the risk of cognitive impairment [59].

Although the present sub-study was of a small number of patients, which renders the analysis preliminary, our findings provide evidence for relationships between the Japanese dietary pattern, the gut microbiota, and cognitive function. Longitudinal assessments of these relationships should be made in future studies to determine the underlying mechanisms involved.

Conclusions

Adherence to a traditional Japanese diet was inversely associated with cognitive decline and tended to be associated with lower concentrations of several microbial metabolites in an older Japanese population.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the NCGG (no. 1191-3). Written informed consent was obtained from all the patients and their families before their participation in this study. The Gimlet study is registered with the UMIN Clinical Trials Registry (UMIN000031851).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

Dr Saji has received a Grant-in-Aid for Scientific Research (C), JSPS KAKENHI (20k07861), the NARO Bio-oriented Technology Research Advancement Institution Project (Advanced Integration Research for Agriculture and Interdisciplinary Fields), the Danone Institute of Japan Foundation, the Honjo International Scholarship Foundation, and the BMS/Pfizer Japan Thrombosis Investigator-initiated Research Program. Dr Saji, Dr Niida, and Dr Sakurai have received research grants from the Research Funding of Longevity Sciences from the National Center for Geriatrics and Gerontology. Dr Saji, Dr Toba, Dr Niida, and Dr Sakurai have received research funding for Comprehensive Research on Aging and Health from the Japan Agency for Medical Research and Development (AMED). Dr Tsuduki has received grants from the NARO Bio-oriented Technology Research Advancement Institution Project (Advanced Integrative Research for Agriculture and Interdisciplinary Fields).

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Author's contributions

NS was the principal investigator and contributed to the concept, design of the protocol, analyzed the data, and wrote the manuscript. TT analyzed the data and reviewed the manuscript. KM, TH, TS, AK, SN, KT, and TS reviewed the manuscript and made constructive suggestions. All the authors read and approved the final version of the manuscript.

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Abbreviations

JDI: Japanese diet index.

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Tables

Table 1. Comparison of dietary composition between participants with dementia and those without

	Dementia (+) (n = 23)	Dementia (−) (n = 62)	P
Food			
Rice, n (%)	19 (82.6)	57 (91.9)	0.245
Bread, n (%)	13 (56.5)	33 (53.2)	0.812
Noodles, n (%)	6 (26.1)	23 (37.1)	0.443
Miso, n (%)	12 (52.2)	39 (62.9)	0.457
Fish and shellfish, n (%)	9 (39.1)	40 (64.5)	0.048
Vegetables, n (%)	21 (91.3)	58 (93.6)	0.660
Seaweed, n (%)	10 (43.5)	32 (51.6)	0.627
Pickles, n (%)	11 (47.8)	33 (53.2)	0.808
Mushrooms, n (%)	7 (30.4)	38 (61.3)	0.015
Fruit, n (%)	14 (60.9)	43 (69.4)	0.604
Beef and pork, n (%)	13 (56.5)	46 (74.2)	0.184
Chicken, n (%)	10 (43.5)	39 (62.9)	0.140
Soybeans and soybean-derived foods, n (%)	7 (30.4)	39 (62.9)	0.013
Milk and dairy products, n (%)	14 (60.9)	41 (66.1)	0.799
Green tea, n (%)	11 (47.8)	41 (66.1)	0.140
Coffee, n (%)	10 (43.5)	44 (71.0)	0.024
Cooking method			
Boiling, n (%)	18 (78.3)	35 (56.5)	0.081
Steaming, n (%)	7 (30.4)	22 (35.5)	0.799
Raw, n (%)	12 (52.2)	41 (66.1)	0.314
Deep-frying, n (%)	10 (43.5)	21 (33.9)	0.454
Frying, n (%)	12 (52.2)	41 (66.1)	0.314
Use of soup stock, n (%)	14 (60.9)	58 (93.6)	0.001

Use of fermented seasoning, *n* (%)	18 (78.3)	57 (91.9)	0.125

The Wilcoxon rank-sum test and the χ^2 test were used.

Table 2. Comparison of the characteristics of participants with JDI_{12} scores above or below the median value

	High JDI_{12} (n = 47)	Low JDI_{12} (n = 38)	P
Demographic factor			
Age, years	75, 68–80	77, 72–81	0.428
Female sex, *n* (%)	22 (46.8)	30 (79.0)	0.004
Education, years	12, 9–13	12, 9–12	0.300
Body mass index, kg/m^2	22.4, 20.6–24.5	22.8, 20.6–24.8	0.630
Systolic BP, mmHg	151, 128–1,632	143, 123–162	0.221
Diastolic BP, mmHg	83, 72–90	77, 70–86	0.128
Risk factor			
Hypertension, *n* (%)	28 (59.6)	25 (65.8)	0.654
Diabetes mellitus, *n* (%)	6 (12.8)	5 (13.2)	1.000
Dyslipidemia, *n* (%)	21 (44.7)	23 (60.5)	0.191
IHD, *n* (%)	5 (10.6)	6 (15.8)	0.530
Stroke, *n* (%)	5 (10.6)	3 (7.9)	0.726
CKD, *n* (%)	15 (31.9)	14 (36.8)	0.653
Smoking habit, *n* (%)	13 (27.7)	7 (18.4)	0.441
Alcohol consumption, *n* (%)	21 (44.7)	13 (34.2)	0.378
APOE ε4 carrier, *n* (%)	10 (21.3)	11 (29.0)	0.456
Dementia, *n* (%)	7 (14.9)	16 (42.1)	0.007
Frailty, *n* (%)	5 (10.6)	8 (21.1)	0.232
Comprehensive geriatric assessment			
Barthel index	100, 100–100	100, 99–100	0.059
IADL impairment, *n* (%)	15 (31.9)	18 (47.4)	0.182
DBDS	5, 3–11	9, 4–16	0.225
GDS	2, 1–4	4, 2–5	0.057

ZBI	6, 3–16	12, 5–22	0.085
MNA-SF	13, 11–14	12, 11–13	0.269
Cognitive function			
MMSE	26, 22–29	24, 19–28	0.066
CDR-GB			0.025
0, *n* (%)	12 (25.5)	8 (21.1)	
0.5, *n* (%)	33 (68.1)	17 (44.7)	
≥1, *n* (%)	3 (6.4)	13 (34.2)	
CDR-SB	1.0, 0.5–3.0	2.0, 0.9–5.1	0.036
ADAS-cog	8.0, 5.0–14.0	11.3, 6.9–16.7	0.085
RCPM	29, 24–32	28, 24–30	0.431
FAB	11, 9–14	11, 9–13	0.984
LM-WMSR I	11, 5–18	7, 3–13	0.048
LM-WMSR II	5, 0–12	1, 0–6	0.033
Brain MRI finding			
SLI, *n* (%)	6 (12.8)	3 (7.9)	0.725
WMH, *n* (%)	8 (17.0)	14 (36.8)	0.048
CMB, *n* (%)	9 (19.2)	6 (15.8)	0.779
EPVS, *n* (%)	8 (17.0)	10 (26.3)	0.424
SVD score	1, 0–1	0, 0–2	0.506
VSRAD	0.80, 0.57–1.30	1.09, 0.78–2.08	0.087
SPECT			
Low blood flow*	30 (65.2)	23 (62.2)	0.821
Arterial stiffness			
Ankle brachial index	1.11, 1.04–1.14	1.12, 1.05–1.16	0.553
Pulse wave velocity, m/s	18.6, 15.8–21.9	17.2, 14.6–19.8	0.159
Laboratory finding			
Total protein, g/dL	7.2, 6.9–7.6	7.3, 6.9–7.6	0.814
Albumin, g/dL	4.3, 4.0–4.5	4.3, 4.0–4.4	0.552

CRP, mg/dL	0.06, 0.02–0.18	0.05, 0.02–0.13	0.505
eGFR, mL/min/1.73 m^2	70.4, 55.8–74.1	61.2, 53.1–73.3	0.340
HbA1c, %	5.8, 5.6–6.2	5.7, 5.6–6.0	0.550

Continuous, ordinal, and categorical variables are expressed as the mean ± standard deviation, median and interquartile range, or frequency or proportion (percentage), respectively. The Wilcoxon rank-sum test and the χ^2 test were used.

*Low blood flow in the area of the posterior cingulate gyrus and/or the precuneus.

Abbreviations: JDI, Japanese dietary index; BP, blood pressure; IHD, ischemic heart disease; CKD, chronic kidney disease; ApoE, apolipoprotein E; IADL, instrumental activities of daily living; DBDS, Dementia Behavior Disturbance Scale; GDS, Geriatric Depression Scale; ZBI, Zarit Caregiver Burden Interview; MNA-SF, Mini-Nutritional Assessment-Short Form; MMSE, Mini-Mental State Examination; CDR-GB, Clinical Dementia Rating Global Score; CDR-SB, Clinical Dementia Rating-Sum of Boxes; ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; RCPM, Raven's Colored Progressive Matrices; FAB, Frontal Assessment Battery; LM-WMSR, Logical Memory subtests I and II of the Wechsler Memory Scale-Revised; SLI, silent lacunar infarct; WMH, white matter hyperintensity; CMB, cerebral microbleeds; EPVS, enlarged perivascular space; SVD, small vessel disease; VSRAD, voxel-based specific regional analysis system for Alzheimer's disease; SPECT, single-photon emission computed tomography; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate.

Table 3. Comparison of the gut microbiome and fecal microbial metabolite concentrations of participants with JDI_{12} scores above or below the median value

	High JDI_{12} (n = 47)	Low JDI_{12} (n = 38)	P
Gut microbiome			0.716
Enterotype I, *n* (%)	15 (34.2)	13 (34.1)	
Enterotype II, *n* (%)	3 (6.4)	1 (2.6)	
Enterotype III, *n* (%)	29 (61.7)	24 (63.2)	
F/B ratio	1.50, 0.82–2.70	1.84, 1.11–3.12	0.147
Metabolite			
Ammonia, mg/g	0.64, 0.37–0.98	0.58, 0.24–0.94	0.431
Succinic acid, mg/g	0.03, 0.03–0.10	0.03, 0.03–0.44	0.622
Lactic acid, mg/g	0.03, 0.03–0.10	0.03, 0.03–0.58	0.398
Formic acid, mg/g	0.05, 0.05–0.05	0.05, 0.05–0.05	0.282
Acetic acid, mg/g	2.27, 0.03–6.09	2.91, 0.03–6.84	0.741
Propionic acid, mg/g	0.23, 0.03–1.51	0.84, 0.03–2.46	0.206
Iso-butyric acid, mg/g	0.06, 0.03–0.19	0.07, 0.03–0.15	0.669
n-butyric acid, mg/g	0.13, 0.03–0.86	0.29, 0.03–0.88	0.863
Iso-valeric acid, mg/g	0.03, 0.03–0.38	0.03, 0.03–0.25	0.347
n-valeric acid, mg/g	0.24, 0.03–1.95	0.17, 0.03–2.61	0.639
Phenol, μg/g	1.02, 0.0003–1.93	1.16, 0.0003–2.12	0.495
P-cresol, μg/g	0.32, 0.0003–118.07	0.24, 0.0003–15.27	0.213
4-Ethylphenol, μg/g	0.26, 0.0003–0.91	0.0003, 0.0003–0.66	0.110
Indoles, μg/g	1.79, 0.14–25.57	1.06, 0.0003–22.53	0.728
Skatole, μg/g	0.11, 0.0003–5.79	0.0003, 0.0003–0.17	0.033

The Wilcoxon rank-sum test and the χ^2 test were used.

Table 4. Multivariable logistic regression analyses for the presence of dementia

	OR	95% CI	*P*
High JDI_9 score (*vs.* Low score) *			
Model 1	0.41	0.15-1.08	0.070
Model 2	0.48	0.17-1.38	0.175
Model 3	0.59	0.18-1.94	0.384
Model 4	0.36	0.12-1.03	0.057
High JDI_{12} score (*vs.* Low score) *			
Model 1	0.24	0.08-0.65	0.005
Model 2	0.33	0.11-0.97	0.043
Model 3	0.22	0.07-0.66	0.006
Model 4	0.10	0.01-0.45	0.002
High rJDI_{12} score (*vs.* Low score) *			
Model 1	0.29	0.09–0.80	0.016
Model 2	0.36	0.11-1.06	0.064
Model 3	0.34	0.10-1.10	0.072
Model 4	0.34	0.07-1.32	0.120

*Allocated to two groups according to their JDI: a high JDI_{12} group (above the median value) and a low JDI group (below the median value).

Abbreviations: OR, odds ratio; CI, confidence interval; JDI, Japanese dietary index. The dependent variable was the presence of dementia. JDI_9: conventional JDI score, which comprised seven beneficial components (“rice”, “miso”, “fish and shellfish”, “green and yellow vegetables”, “seaweed”, “pickles”, and “green tea”), and two less beneficial components (“beef and pork” and “coffee”); 0–9 points. JDI_{12}: modified JDI score, comprising the JDI_9 components and three additional beneficial components (“soybeans and soybean-derived foods”, “fruit”, and “mushrooms”); 0–12 points. r-JDI_{12}: revised JDI_{12} score, in which one less beneficial component (“coffee”) in the JDI_{12} was changed to a

beneficial component, such that these became “rice”, “miso”, “fish and shellfish”, “green and yellow vegetables”, “seaweed”, “pickles”, “green tea” and “coffee”; and there was just one less beneficial component (“beef and pork”), making it more consistent with the modern Japanese diet; 0–12 points.

Model 1: univariate analyses. Model 2: adjusted for age, sex. Model 3: backward stepwise multivariable logistic regression analyses, which were adjusted for the model 2 factors, years of education, and risk factors (hypertension, dyslipidemia, diabetes mellitus, ischemic heart disease, chronic kidney disease, smoking, alcohol consumption, and ApoE). Model 4: backward stepwise multivariable logistic regression analyses adjusted for the factors in model 3, plus enterotype I, silent lacunar infarct, white matter hyperintensity, cerebral microbleeds, enlarged perivascular space, score of the voxel-based specific regional analysis system for Alzheimer’s disease, single-photon emission-computed tomography findings (presence or absence of low blood flow in the area of the posterior cingulate gyrus and/or precuneus), ankle brachial index, and pulse wave velocity.

Figures

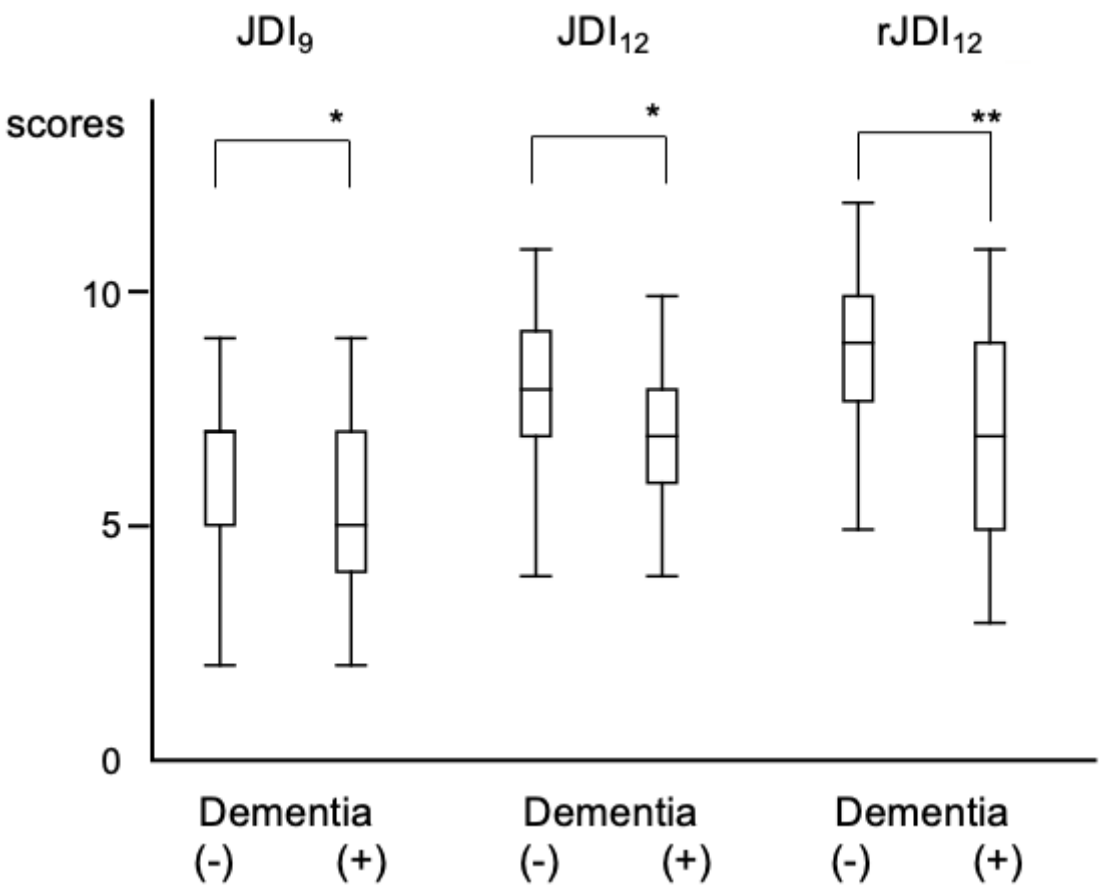

Figure 1

Comparison of the Japanese diet indices (JDI9, JDI12, and rJDI12) in participants with and without dementia The x-axis shows the presence or absence of dementia and the y-axis the JDI score. * $P < 0.05$ and ** $P < 0.01$, according to the Wilcoxon rank-sum test. JDI9: conventional JDI score; JDI12: modified JDI score, including three additional components (soybeans and soybean-derived foods, fruit, and mushrooms); rJDI12: revised JDI12 score, in which one less beneficial component (coffee) in the JDI12 was redefined as a beneficial component. The rJDI12 score more clearly shows the difference between participants with and without dementia than the JDI9 and JDI12 scores.

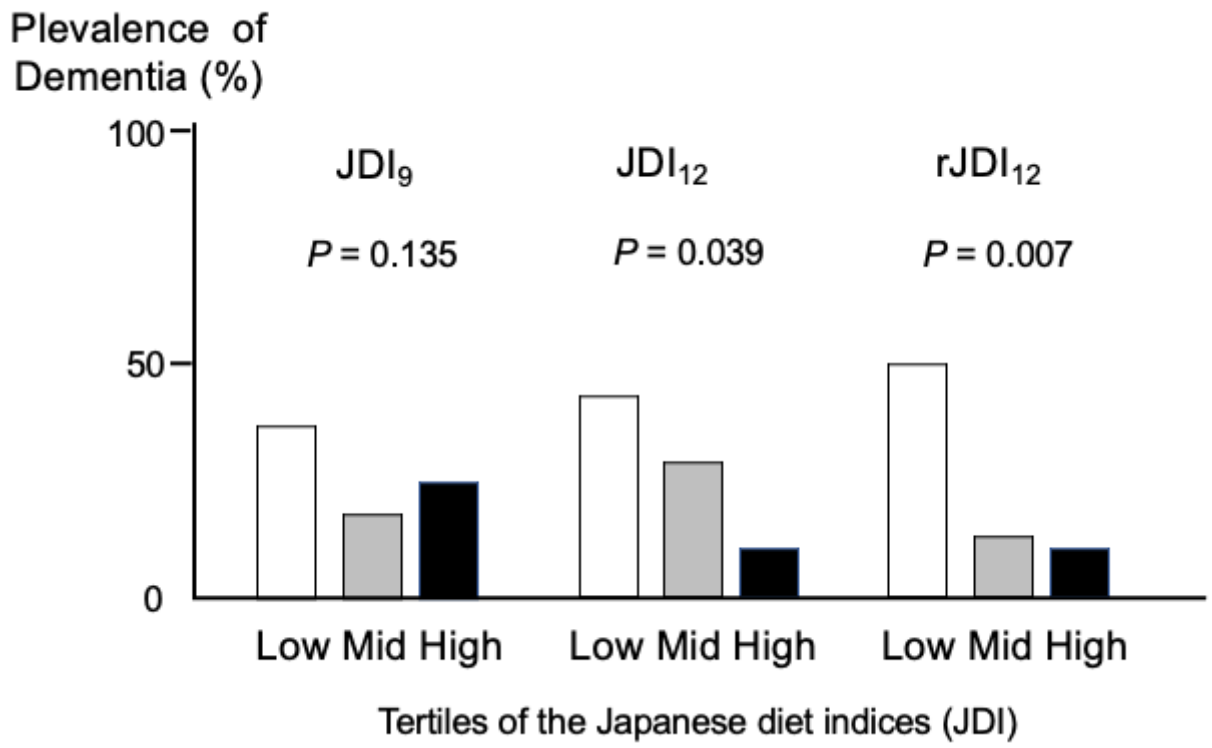

Figure 2

Prevalences of dementia, according to the tertiles of Japanese dietary index scores (JDI9, JDI12, and rJDI12) The x-axis shows the tertiles of the Japanese diet indices (JDI) and the y-axis the prevalence of dementia (%). rJDI12 more clearly shows the difference among participants categorized according to the tertiles of the JDI score than JDI9 and JDI12.

Supplementary Files

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