



Applied nutritional investigation

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

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ABSTRACT

Objective: 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. The aims of this study were to evaluate the relationships between adherence to a Japanese-style diet, the gut microbiota, and cognitive decline. Furthermore, we aimed to evaluate the three forms of the Japanese diet index (JDI; the conventional [JDI₉], updated [JDI₁₂], and a newly modified JDI) to determine which would show the closest relationships with cognition and the gut microbiota.

Methods: We performed a cross-sectional subanalysis of data from a prospective hospital-based cohort study. We assessed the patients' demographic characteristics, dietary composition, risk factors, cognitive function, brain imaging, gut microbiome, and microbial metabolites. On the basis of previous studies, a nine-component traditional JDI (JDI₉), a 12-component modern JDI (JDI₁₂), and a 12-component revised JDI (rJDI₁₂), were defined. We 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 participants (61% women; mean age: 74.6 ± 7.4 y). Compared with participants who had dementia, those without dementia were more likely to consume foods in the JDI₁₂, including fish and shellfish (64.5 versus 39.1%, $P = 0.048$), mushrooms (61.3 versus 30.4%, $P = 0.015$), soybeans and soybean-derived foods (62.9 versus 30.4%, $P = 0.013$), and coffee (71 versus 43.5%, $P = 0.024$). There were non-significant trends toward lower fecal concentrations of gut microbial metabolites in participants with a more traditional Japanese diet. Participants with dementia had lower JDI scores than those without dementia (dementia versus non-dementia, median JDI₉ score: 5 versus 7, $P = 0.049$; JDI₁₂: 7 versus 8, $P = 0.017$; and rJDI₁₂: 7 versus 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.

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Introduction

Dementia is an important health care problem. It affects many individuals worldwide and it imposes burdens on the patients,

caregivers, and health care systems. Globally, 47 million individuals worldwide were living with dementia in 2015 [1]. Because the number of patients in Japan is increasing, a comprehensive strategy for dementia research has been introduced [2]. The assessment of dementia from various viewpoints is important to improve future health care because a multifactorial assessment of cognitive function can be useful for preventing dementia.

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Dementia also may expose the individual to an increased risk for nutritional problems. Indeed, reversible risk factors such as decreased dietary intake, poor quality of foods, and social isolation should be carefully evaluated and corrected for preventing the risk for nutritional issues [3]. Recently, the relationship between diet and dementia has become an intriguing research focus [4–6]. Dietary patterns such as the Mediterranean diet (MedDiet) [4] and the Japanese diet (JD) [5,6] are receiving a lot of attention because they can reduce the risk for dementia. Furthermore, previous studies have shown that both the MedDiet [7] and the JD [8] are able to alter the gut microbiota. With respect to the JD pattern, its characteristics are described using the Japanese diet index (JDI), which has been modified according to the findings of previous studies [9,10]. The original index (JDI₉) comprises nine components (rice, miso, fish and shellfish, green and yellow vegetables, seaweed, pickles, green tea, beef and pork, and coffee) that define the traditional Japanese dietary pattern [9], but a modified index, the JDI₁₂, has been established by the addition of three beneficial components (soybeans and soybean-derived foods, fruit, and mushrooms) to the JDI₉ [10]. However, recent studies have suggested that the inclusion of one component (coffee) that was defined as a less beneficial component in both the JDI₉ and JDI₁₂ may have a positive effect on cognitive function [11]. 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 [12–14]. Previous studies have shown that dysregulation of the gut microbiome is associated with cognitive decline [13,14]. Furthermore, bacterial products, such as gut microbial metabolites, can increase systemic inflammation [15] and are also associated with dementia [16]. According to the results of these previous studies, the gut microbiota and the microbial metabolites [17,18] modulate host brain function via a microbiota–gut–brain axis [19]. The diversity of the gut microbiota may be an important mediator of this relationship [13], 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 JD 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 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 an observational 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 associated with cognitive decline [13,14], vascular risk factors [20], and brain magnetic resonance imaging (MRI) abnormalities [21]. Furthermore, metabolites of the gut microbiota may play important roles in these associations [16]. 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. Furthermore, we aimed to evaluate the three forms of the JDI (the conventional [JDI₉], the updated [JDI₁₂], 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 subanalysis of data from a hospital-based prospective cohort study, the Gimlet (Gerontological Investigation of Microbiome: A Longitudinal Estimation Study) study, which was conducted at the National Center for Geriatrics and Gerontology (NCGG) in Japan. Detailed information regarding the Gimlet study is provided in previous reports [13,14,16]. 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 participants' activities of daily living (ADLs) and cognitive function were assessed annually after enrollment. 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. 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.

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 substudy if they were able to undergo brain MRI and complete a questionnaire regarding their dietary composition; and if they provided their informed consent in writing. Patients were excluded from this substudy if they were unable to undergo MRI and/or complete the questionnaire. Patients with potential confounders and effect modifiers for the variables of interest (e.g., the recent use of antibiotics) had been excluded at the time of enrollment in the Gimlet study.

Baseline assessments

All participants underwent a comprehensive geriatric assessment that was based on the following:

- Demographic characteristics;
- Risk factors;
- ADL scales;
- Global cognitive function, assessed using the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR) scales;
- Neuropsychological testing;
- Behavioral and psychological symptoms;
- Burden for caregivers, assessed by the Zarit Caregiver Burden Interview (ZBI);
- Depression status, assessed by the Geriatric Depression Scale (GDS);
- Laboratory parameters;
- Arterial stiffness, as an indicator of arteriosclerosis [22], and the effects of pulse [23]; and
- 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 JD were grouped on the basis of the definitions used in the Japanese National Health and Nutrition Survey and the previous studies [9,10]. 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 d/wk), [2] *usually* (on 3–5 d/wk), [3] *sometimes* (on 1–2 d/wk), and [4] *rarely* (on <1 d/wk).

Japanese dietary indices

We evaluated three JDIs. The first was the conventional JDI (JDI₉) [9]:

- 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 1 point if their daily intake of the item was equal to or greater than the sex-specific median dietary intake; and
- For each of the two less beneficial components (beef and pork, and coffee), the participants were assigned 1 point if their daily intake was below the sex-specific median intake.

Thus, the JDI₉ score ranged from 0 to 9, with higher scores indicating greater conformity to the traditional JD.

The second index was defined recently [10,24] and comprises 12 components (the JDI₁₂) because three further beneficial components (soybeans and soybean-derived foods, fruit, and mushrooms) had been added to the JDI₉. Therefore, the JDI₁₂ score ranged from 0 to 12, and was indicative of an expanded traditional JD. However, according to recent reports [25,26], higher intake of coffee is associated with better health status and contributes to a lower risk for dementia. Therefore, we also defined a 12-component revised JDI (rJDI₁₂), in which one less beneficial component (coffee) in the JDI₁₂ was changed to be a beneficial component. The score of the rJDI₁₂, which is more representative of a modern JD, also ranged from 0 to 12 points.

Classification of cognitive function

Dementia was defined as an MMSE <20 and/or a CDR ≥1. Participants who did not have dementia were further categorized as having mild cognitive impairment (MCI) or normal cognition. MCI was defined as an MMSE ≥20 and a CDR of 0.5, which implies possible, very mild dementia, and suggests that the patient has a higher risk for developing dementia in the future. In contrast, normal cognition was defined as an MMSE ≥20 and a CDR of 0.

Brain imaging

The participants underwent a 1.5-T MRI of their brains (Philips Ingenia, Eindhoven, the Netherlands). The presence and components of cerebral small vessel disease, such as silent lacunar infarct, white matter hyperintensity (WMH), cerebral microbleeds, and enlarged periventricular space were assessed. 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. A high VSRAD score suggests the presence of Alzheimer's disease. The participants also underwent N-isopropyl-p-[¹²³I]-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 Alzheimer's disease. Detailed information regarding the analysis of the brain imaging is provided in the Supplementary data.

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. The gut microbiome of each participant was then analyzed by the TechnoSuruga Laboratory (Shizuoka, Japan) using terminal restriction fragment-length polymorphism (T-RFLP) analysis [27]. The T-RFLP analysis was used to classify gut microbes. By referencing the Human Fecal Microbiome T-RFLP profile [28], 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- to-Bacteroidetes (F/B) ratio was also calculated because a high ratio is indicative of dysbiosis [29].

Analysis of microbial metabolites in feces

In previous studies, the concentrations of gut microbial metabolites, including short-chain fatty acids (SCFAs) [7,18] and lipopolysaccharide [18], 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 [16]. 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 [16] and the Supplementary data.

Statistical analysis

Continuous, ordinal, and categorical variables are expressed as the mean ± SD, median and interquartile range (IQR), 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. Additionally, 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 JDI₁₂: a high JDI₁₂ group (above the median value) and a low JDI₁₂ group (below the median value), and we compared their clinical characteristics. We also compared the differences between participants with high rJDI₁₂ scores and those with low rJDI₁₂ scores. Finally, multivariable logistic regression models were used to identify independent associations between the presence of dementia, JDI score (JDI₁₂ or rJDI₁₂), and the gut microbiome. Odds ratios (ORs) and 95% confidence intervals (CIs) are presented. All comparisons were two-tailed, and *P* < 0.05 was considered statistically significant. 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. Of these, 43 were excluded from this subanalysis 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 y; 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 versus those without

Compared with participants with dementia, those without were more likely to consume fish and shellfish (non-dementia versus dementia, 64.5 versus 39.1%, *P* = 0.048), mushrooms (61.3 versus 30.4%, *P* = 0.015), soybeans and soybean-derived foods (62.9 versus 30.4%, *P* = 0.013), and coffee (71 versus 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.

Table 1

Comparison of dietary composition between participants with and without dementia

	Dementia (+) (n = 23)	Dementia (−) (n = 62)	<i>P</i> -value
Food, n (%)			
Rice	19 (82.6)	57 (91.9)	0.245
Bread	13 (56.5)	33 (53.2)	0.812
Noodles	6 (26.1)	23 (37.1)	0.443
Miso	12 (52.2)	39 (62.9)	0.457
Fish and shellfish	9 (39.1)	40 (64.5)	0.048
Vegetables	21 (91.3)	58 (93.6)	0.660
Seaweed	10 (43.5)	32 (51.6)	0.627
Pickles	11 (47.8)	33 (53.2)	0.808
Mushrooms	7 (30.4)	38 (61.3)	0.015
Fruit	14 (60.9)	43 (69.4)	0.604
Beef and pork	13 (56.5)	46 (74.2)	0.184
Chicken	10 (43.5)	39 (62.9)	0.140
Soybeans and soybean-derived foods	7 (30.4)	39 (62.9)	0.013
Milk and dairy products	14 (60.9)	41 (66.1)	0.799
Green tea	11 (47.8)	41 (66.1)	0.140
Coffee	10 (43.5)	44 (71)	0.024
Cooking method, n (%)			
Boiling	18 (78.3)	35 (56.5)	0.081
Steaming	7 (30.4)	22 (35.5)	0.799
Raw	12 (52.2)	41 (66.1)	0.314
Deep-frying	10 (43.5)	21 (33.9)	0.454
Frying	12 (52.2)	41 (66.1)	0.314
Use of soup stock	14 (60.9)	58 (93.6)	0.001
Use of fermented seasoning	18 (78.3)	57 (91.9)	0.125

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

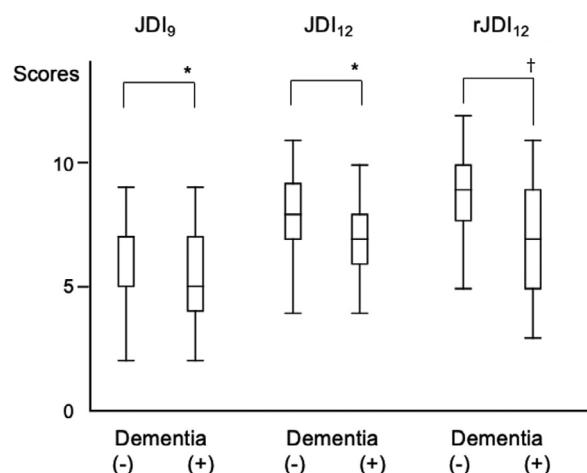


Fig. 1. Comparison of the Japanese diet indices (JDI₉, JDI₁₂, and rJDI₁₂) in participants with and without dementia. The x axis shows the presence or absence of dementia and the y axis the JDI score. * $P < 0.05$ and † $P < 0.01$, according to the Wilcoxon rank-sum test. JDI₉: conventional JDI score; 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.

Participants with dementia had lower JDI scores (JDI₉, JDI₁₂, and rJDI₁₂) than those without (dementia versus non-dementia, median scores for JDI₉: 5 versus 7, $P = 0.049$; JDI₁₂: 7 versus 8, $P = 0.017$; and rJDI₁₂: 7 versus 9, $P = 0.006$, respectively; Fig. 1). The rJDI₁₂ 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 JDI₉ and JDI₁₂ scores (low versus middle versus high JDI score, according to tertile: JDI₉: 38.7 versus 17.5 versus 28.6%, $P = 0.135$; JDI₁₂: 40.9 versus 33.3 versus 12.1%, $P = 0.039$; and rJDI₁₂: 48.3 versus 16.7 versus 15.4%, $P = 0.007$, respectively; Fig. 2). Regarding the methods of food preparation, participants without dementia were more likely to use soup stocks than those with dementia (93.6 versus 60.9%, $P = 0.001$; Table 1).

Enterotype I versus other enterotypes

Compared with participants with the other enterotypes, those with enterotype I tended to consume less seaweed, fruit, and milk

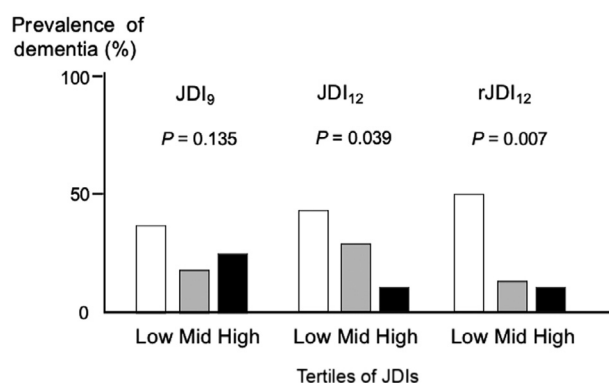


Fig. 2. Prevalences of dementia, according to the tertiles of Japanese dietary index scores (JDI₉, JDI₁₂, and rJDI₁₂). The x axis shows the tertiles of the Japanese diet indices (JDI) and the y axis the prevalence of dementia (%). rJDI₁₂ more clearly shows the difference among participants categorized according to the tertiles of the JDI score than JDI₉ and JDI₁₂.

and dairy products, although these differences were not significant (Supplementary Table 1).

MCI versus NC patients

Among the participants who did not have dementia, those with NC tended to consume more fish, shellfish, and coffee than those with MCI, although these differences were not statistically significant (Supplementary Table 2). Additionally, 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 (Supplementary Table 3).

Microbial metabolites

Participants who consumed more mushrooms (e.g., higher versus lower intake; median concentration of iso-butyric acid: 0.03 versus 0.11 mg/g, $P = 0.017$; Supplementary Table 4), soybeans and soybean-derived foods (Supplementary Table 5), or coffee (Supplementary Table 6) had lower fecal concentrations of several gut microbial metabolites than those who consumed smaller amounts of these items.

High versus low JDI₁₂ score

Participants with high JDI₁₂ scores were less likely to be female (high versus low JDI₁₂: 46.8 versus 79.0%, $P = 0.004$), less likely to have dementia (14.9 versus 42.1%, $P = 0.007$) and WMH (17 versus 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 JDI₁₂ scores were lower than in those with low JDI₁₂ scores (Table 3).

High versus low rJDI₁₂ score

Participants with high rJDI₁₂ scores were less likely to be female, less likely to have dementia (high versus low rJDI₁₂: 15 versus 37.8%, $P = 0.027$) and WMH (12.5 versus 37.8%, $P = 0.012$), had lower ZBI (5 versus 14 points, $P = 0.010$) and VSRAD (median score; 0.74 versus 1.15, $P = 0.031$) scores, and were more likely to have good neuropsychological test results (Supplementary Table 7). Additionally, the fecal concentrations of the majority of the gut microbial metabolites in participants with high rJDI₁₂ scores were lower than in those with low rJDI₁₂ scores (Supplementary Table 8).

Results of multivariate analyses

In univariable analyses, greater intakes of fish and shellfish (OR, 0.35; 95% CI, 0.13–0.93; $P = 0.036$), mushrooms (OR, 0.28; 95% CI, 0.09–0.75; $P = 0.011$), soybeans and soybean-derived foods (OR, 0.26; 95% CI, 0.09–0.70; $P = 0.007$), and coffee (OR, 0.31; 95% CI, 0.11–0.84; $P = 0.021$) were associated with significantly lower ORs for dementia (Supplementary Table 9), as was the use of soup stock (OR, 0.32; 95% CI, 0.03–0.38; $P = 0.001$). However, there were no significant differences in univariable analyses for the presence of enterotype I (Supplementary Table 10).

Multivariable analyses showed that high JDI₁₂ score was inversely associated with the presence of dementia and was significantly associated with lower OR (Table 4). The increments in both the JDI₁₂ and rJDI₁₂ scores (per 1 point increment) were also inversely associated with the presence of dementia and were associated with lower OR. However, no significant differences were

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

	High JDI ₁₂ (n = 47)	Low JDI ₁₂ (n = 38)	P-value
Demographic factor			
Age, y	75, 68–80	77, 72–81	0.428
Female sex, n (%)	22 (46.8)	30 (79)	0.004
Education, y	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, 128–163.2	143, 123–162	0.221
Diastolic BP, mmHg	83, 72–90	77, 70–86	0.128
Risk factor, n (%)			
Hypertension	28 (59.6)	25 (65.8)	0.654
Diabetes mellitus	6 (12.8)	5 (13.2)	1.000
Dyslipidemia	21 (44.7)	23 (60.5)	0.191
IHD	5 (10.6)	6 (15.8)	0.530
Stroke	5 (10.6)	3 (7.9)	0.726
CKD	15 (31.9)	14 (36.8)	0.653
Smoking habit	13 (27.7)	7 (18.4)	0.441
Alcohol consumption	21 (44.7)	13 (34.2)	0.378
APOE ε4 carrier	10 (21.3)	11 (29.0)	0.456
Dementia	7 (14.9)	16 (42.1)	0.007
Frailty	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	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)	14 (36.8)	0.048
CMB, n (%)	9 (19.2)	6 (15.8)	0.779
EPVS, n (%)	8 (17)	10 (26.3)	0.424
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, 4–4.5	4.3, 4–4.4	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	0.550

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

Continuous, ordinal, and categorical variables are expressed as the mean ± SD, median and IQR, or frequency or proportion (percentage), respectively. 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.

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

	High JDI ₁₂ (n = 47)	Low JDI ₁₂ (n = 38)	P-value
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

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

identified in the stepwise multivariable logistic regression analyses (Supplementary Table 11). The area under the receiver operating curve (AUC) of rJDI₁₂ for the presence of dementia was the highest among those of the three JDI indices (AUC for JDI₉: 0.637; JDI₁₂: 0.668; and rJDI₁₂: 0.693).

Discussion

The main finding of the present study was that adherence to a traditional JD 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 JD and cognitive decline have previously been reported in community-dwelling older people [5,6] and in younger adults [30]. 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 JDs include large amounts of fish and shellfish, miso, seaweed, vegetables, soy products, fruit, and green tea [31], and some of these (fish, vegetables, soy products, and fruit) are associated with beneficial effects on cognitive function [31–33]. 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 JDI₁₂ and rJDI₁₂ yielded similar results in the present study. However, the rJDI₁₂ 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 MedDiet; for instance, the high intake of vegetables, legumes, and fish, and the low consumption of meat [33]. Therefore, the

Table 4
Multivariable logistic regression analyses for the presence of dementia

	OR	95% CI	P-value
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

ApoE, apolipoprotein E; JDI, Japanese dietary index; SPECT, single-photon emission-computed tomography

The dependent variable was the presence of dementia. JDI₉: 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. JDI₁₂: modified JDI score, comprising the JDI₉ components and three additional beneficial components (soybeans and soybean-derived foods, fruit, and mushrooms); 0–12 points. r-JDI₁₂: revised JDI₁₂ score, in which one less beneficial component (coffee) in the JDI₁₂ 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, SPECT 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

*Participants were allocated to two groups, according to their JDI: a high JDI₁₂ group, if their score was above the median value; and a low JDI group, if their score was below the median value.

mechanism underlying the association between adherence to a Japanese-style diet and the lower risk for dementia may be similar to that reported following studies of the MedDiet. Specifically, the MedDiet affects the composition of the gut microbiota and the concentrations of the derived metabolites, and is associated with both improvements in biomarkers of Alzheimer's disease [7] and reductions of mortality and relevant financial costs in older adults [34].

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 [33,35]. Furthermore, mushroom consumption alters lipid metabolism, and has antiobesity, antiatherosclerotic, and antidiabetic effects [35]. Some dietary fiber can be classified as prebiotics and beneficial [36]. Additionally, soybeans contain phytoestrogens (isoflavones), which have beneficial effects on cognitive function [33]. This is consistent with both JDI₁₂ and rJDI₁₂ being inversely associated with the presence of dementia.

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 [37], and another showed that green tea, but not coffee,

reduces the risk for cognitive decline in older adults [38]. It has also been reported that caffeine consumption, and especially the moderate quantities consumed in coffee or green tea, reduces the risk for dementia [11], probably because caffeine affects neural and vascular activity, including vasoconstriction and cerebral blood flow [11]. 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.

Probiotic consumption has been shown to ameliorate or preserve cognitive function [38]. Previous studies have suggested that intake of the probiotics *Bifidobacterium* [39] or *Lactobacillus* [40] inhibits cognitive decline. Dietary diversity is also protective against cognitive decline [41]. Comprehensive clinical nutritional strategies including appropriate diet and intake of probiotics may help maintain the growth of commensal bacteria in the gut [42]. 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 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 JD 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 neuropsychological 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.

The 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 identify causality in these relationships in the near future. Additionally, 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 [17,18,43], neurodegenerative diseases [44], 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 for cognitive impairment [45].

Although the present substudy was of a small number of patients, which renders the analysis preliminary, our findings provide evidence for relationships between the JD 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 JD was inversely associated with cognitive decline and tended to be associated with lower concentrations of several microbial metabolites in an older Japanese population.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.nut.2021.111524](https://doi.org/10.1016/j.nut.2021.111524).

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