

# Associations between healthy Japanese dietary patterns and depression in Japanese women

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## **Abstract**

Objective: Higher quality dietary patterns such as healthy/prudent and Mediterranean dietary patterns have been protectively associated with depression. This study examined whether healthy Japanese dietary patterns, which differ from dietary patterns derived from Western areas, are associated with depressive symptoms among Japanese women.

Design: A cross-sectional study (the Nagano Nutrition and Health Study). Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale. Dietary patterns were derived with a principal component analysis of the consumption of fifty-six food and beverage items, which were assessed by a validated brief diet history questionnaire.

Setting: Nagano, Japan.

Participants: Japanese women (n 1337) aged 20–72 years.

Results: We identified three dietary patterns: 'healthy Japanese', 'sweets-fat' and 'seafood-alcohol'. The highest quality dietary pattern was 'healthy Japanese'. It is characterised by a high intake of vegetables, mushrooms, seaweed, soyabean products, potatoes, fish/shellfish and fruit. The age- and multivariate-adjusted OR (95 % CI) of depressive symptoms for the highest quartiles of the 'healthy Japanese' pattern score were 0.58 (95 % CI 0.41, 0.82) and 0.69 (95 % CI 0.45, 1.06), respectively. Meanwhile, no associations were observed for 'sweets-fat' and 'seafood-alcohol' patterns.

Conclusions: The 'healthy Japanese' pattern may be inversely associated with depressive symptoms with an exposure-response association. The specific Japanese food groups in the 'healthy Japanese' pattern included mushrooms, seaweed, soyabean products and potatoes, as well as vegetables, fish/shellfish and fruit. These seem to create an anti-inflammation-prone dietary pattern, and this factor might be associated with better mental health.

**Keywords** Dietary patterns Depression Japanese dietary patterns Cross-sectional study Japanese women

Depression is a common mental disorder, causing a very high level of disease burden, and is expected to become a rising trend in the next 20 years (1). The WHO has estimated that major depressive disorder will become the second most common contributor to the global burden of disease in worldwide disability-adjusted life-years by the end of 2020. In the global burden of disease 2000 analysis, the prevalence of major depression in a 12-month period was 5.8% in men and 9.5% in women (1.6-fold greater incidence in women). The higher prevalence of major depression in women has been explained by biological factors, such as the variation in ovarian hormone levels and, in particular, decreases in oestrogen<sup>(2,3)</sup>. The World Mental Health Japan 2nd Survey, which was conducted between 2013 and 2015 among the Japanese population, reported that the 12-month prevalence of major depression was 2.7% and this had increased by 0.5% during the past decade. Furthermore, it was also reported that Japan has a lower prevalence rate of major depression compared with Western countries, although the prevalence has been increasing because of social changes, such as economic recessions, natural disasters, and rapidly changing and diversifying social norms and values<sup>(4)</sup>.

Diet has been suggested as a modifiable factor that plays a role in depression<sup>(2)</sup>, and several nutrients or foods have been associated with depressive symptoms. A higher

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intake of n-3 long-chain PUFA, fish, folate and other B vitamins is protectively associated with depression, whereas a higher intake of trans-fatty acids, fast food and commercial baked goods is associated with higher depressive symptoms and higher depression incidence. However, the results have been inconsistent (5-8). Findings from a recent systematic review and meta-analysis have indicated that both fruit and vegetable intake, as well as their combination, were protectively associated with depression in cohort or cross-sectional studies. Fruit and vegetables are rich sources of fibre, vitamins ( $\beta$ -carotenes, vitamin E, vitamin C, vitamin B<sub>6</sub>, vitamin B<sub>12</sub> and folate), minerals and non-nutrient phytochemicals (such as flavonoids and carotenoids) and are also rich sources of antioxidants (5,9,10). Thus, the relationship between single nutrients or foods and depression has been well reported, and some aetiological hypotheses of depression are widely accepted<sup>(7,10,11)</sup>.

However, dietary pattern analysis has become more widely used because it considers the complex combinations of many nutrients and foods(12). In a recent metaanalysis of twenty-one articles, including five Japanese studies, on the associations between dietary patterns and depression risk, it was reported that a healthy/prudent dietary pattern characterised by a high intake of fruit, vegetables, wholegrains, fish, olive oil, low-fat dairy and antioxidants and a low intake of animal-based foods was associated with a decreased risk of depression. In contrast, the Western style/unhealthy dietary pattern characterised by the high consumption of red and/or processed meat, refined grains, high-sugar foods and high-fat dairy products and the low intake of fruits and vegetables was associated with an increased risk of depression<sup>(11)</sup>. Furthermore, a metaanalysis of twenty-nine prospective studies, which included only one Japanese maternal study, reported that a higher quality diet (i.e. a healthy/prudent or Mediterranean diet) was associated with a lower risk of the onset of depressive symptoms<sup>(13)</sup>.

Dietary patterns are likely to vary according to sex, socio-economic status, ethnic group and culture (12). According to the dietary patterns in relation to depressive symptoms found in the Japanese population, higher quality dietary patterns (i.e. healthy/balanced Japanese or healthy Japanese) include not only vegetables, fruits and fish/ shellfish but also mushrooms, seaweed, soyabean products and potatoes (14-18). In relation to other health outcomes, such as all-cause and CVD mortality (19-21), the food components of higher quality dietary patterns found in the prospective Japanese cohort study were almost the same, although green tea was added occasionally. Thus, the higher quality dietary patterns found in the Japanese population that provide better health outcomes involve quite different food components compared with the dietary patterns found in Western populations. In this study, we defined this higher quality dietary patterns found in the Japanese population as the 'healthy Japanese' pattern. Furthermore, the food components of the 'healthy

Japanese' pattern such as vegetables, fruits, fish (n-3 fatty acids), soyabean products, mushrooms and seaweed have higher anti-inflammatory effects (22-25). Thus, a 'healthy Japanese' pattern could have an antidepressant effect, and in this study, we examined whether the 'healthy Japanese' pattern is associated with depressive symptoms among Japanese women. We hypothesised that because of its higher anti-inflammatory properties, the 'healthy Japanese' pattern would be protectively associated with depressive symptoms.

#### Materials and methods

#### **Participants**

The present cross-sectional study was based on data obtained from the Nagano Nutrition and Health Study. The participants were 2112 Japanese women who worked at hospitals, nursery schools and school lunch facilities, living in Nagano prefecture, Japan. Between February and June 2013, we conducted a cross-sectional study. A total of 1346 participants completed the self-administered questionnaire (response rate 63.7%), and the data of nine participants with missing written informed consent were excluded. The final analytic sample included the data from 1337 participants who provided informed consent.

## Assessment of depressive symptoms

Depressive symptoms were assessed using a Japanese version<sup>(26)</sup> of the Center for Epidemiologic Studies Depression (CES-D) Scale<sup>(27)</sup>. The CES-D scale consists of twenty questions that ask participants to rate how often over the past week they experienced symptoms associated with depression, such as restless sleep, poor appetite or feeling lonely. Each question is scored on a four-point scale according to the frequency of the symptom (from 0 to 3), and the total CES-D score ranges from 0 to 60, with high scores indicating greater depression. The CES-D also provides a cut-off score of 16 or higher that aids in identifying individuals at risk of clinical depression, with good sensitivity and specificity and high internal consistency in both Western and Japanese populations (28,29). Therefore, depressive symptoms were defined in the present study when participants had CES-D scores of 16 or greater.

# Dietary assessment

Dietary intake during the preceding 1-month period was assessed using a previously validated brief selfadministered dietary history questionnaire (BDHQ)(30,31) as the FFQ. The BDHQ contains items related to the consumption frequency of fifty-six different foods and beverages and nine dishes commonly consumed in the general Japanese population. The daily dietary intakes for energy and selected nutrients were calculated using an ad boc computer algorithm for the fifty-six foods and beverages



of the BDHQ, which was based on the Standard Table Food Composition in Japan<sup>(32)</sup>. Then, the fifty-six foods were combined into the food groups<sup>(30)</sup>. A validation study of the BDHO was conducted and compared with the gold standard 16-d weighted dietary records. It demonstrated reasonable validity for the food group<sup>(30)</sup> and nutrient<sup>(31)</sup> intakes estimated by the BDHO in both men and women. Spearman's correlation coefficients between energyadjusted food group intakes by density method estimated from the BDHO and dietary records were expressed as median (range: minimum to maximum), which is 0.44 (range: 0.14 to 0.82) in women and 0.48 (range: 0.21 to 0.83) in men<sup>(30)</sup>. Furthermore, the Pearson's correlation coefficients between energy-adjusted nutrient intakes estimated from the BDHQ and dietary records were 0.59 for fat, 0.58 for SFA, 0.19 for *n*-3 PUFA, 0.66 for Ca, 0.59 for Mg, 0.57 for Fe, 0.43 for Zn, 0.42 for  $\beta$ -carotene, 0.47 for  $\alpha$ -tocopherol, 0.48 for vitamin B<sub>6</sub>, 0.40 for vitamin B<sub>12</sub>, 0.54 for folate, 0.61 for vitamin C and 0.69 for total dietary fibre<sup>(31)</sup>. Information on dietary supplements was not used in the calculation of dietary intake because of the lack of reliable composition data for supplements in Japan.

#### Assessment of lifestyle variables and confounders

The self-reported lifestyle questionnaire inquired about age, medical history, family structure, household income, occupation, education, working hours, marriage status, body weight, body height, frequency of eating out, skipping breakfast, time of beginning dinner, family meal at dinner, current smoking, current alcohol intake, rest from sleep, sleeping duration, physical activity and self-reported stress. BMI was calculated as self-reported body weight (kg) divided by the square of self-reported body height (m).

# Statistical analysis

We excluded participants with a past medical history of depression  $(n\,8)$  or psychiatric disorders such as dysautonomia  $(n\,8)$ , anxiety disorders  $(n\,7)$ , Parkinson's disease  $(n\,1)$  and narcolepsy  $(n\,1)$  because patients with mental illness may already be undergoing medical treatment including dietary guidance. Finally, 1312 participants were included in the statistical analysis. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Japan).

Most fundamentally, intake of almost all dietary factors, such as nutrients and foods, tends to be positively correlated with total energy intake<sup>(33)</sup>. Therefore, dietary patterns were derived using a principal component analysis based on the energy-adjusted food intake (g food/4184 kJ/d) using a density method consisting of fifty-two food and beverage items (excluding four items that overlapped with the others) of the BDHQ. The factors were rotated using an orthogonal transformation (varimax rotation function in SPSS) to achieve a simpler structure with

greater interpretability. We considered the components with an eigenvalue greater than 1.0, the scree plot and the interpretability of the factors to determine the number of factors. This served to limit the number of factors as well as to better identify more meaningful factors. After the varimax rotation, three major dietary patterns were identified and these dietary patterns were named according to the food items with high factor loadings (absolute value). The factor scores for each dietary pattern and each individual were determined by summing the intake of each food weighed by the factor loadings<sup>(34)</sup>. A high factor score indicated a high frequency of consuming the foods included in that pattern. The factor scores for each dietary pattern were categorised into quartiles based on the distribution of the study population. We performed a sensitivity analysis on the factor extraction method by using oblique rotation (promax rotation).

Differences in the proportions and means of the covariates according to depressive symptoms were assessed by using  $\chi^2$  and independent t tests, respectively. Regarding the effect size of the nutrient intake, Cohen's d value was used<sup>(35)</sup>. To assess the association between the dietary patterns and anti-/pro-inflammatory nutrients, we selected several nutrients as having higher anti-inflammation effects on depressive symptoms - namely, Ca, Mg, Fe, Zn, vitamin  $B_2$ , vitamin  $B_6$ , vitamin  $B_{12}$ , folate, vitamin C, fibre, n-3 fatty acid and  $\beta$ -carotenes, and several nutrients as having higher pro-inflammation effects on depressive symptoms - namely, total energy, total fat and SFA. These nutrients were selected with consideration for their potential ability to protect against depressive symptoms, as demonstrated in previous studies<sup>(7,10,11)</sup>, and for the lower or higher point of the overall inflammatory effect score (dietary inflammatory index: DII), which indicates a continuum from maximally anti-inflammatory to maximally pro-inflammatory<sup>(36)</sup>. Trend associations across the quartile categories of each dietary pattern were assessed with a Mantel-Haenszel  $\chi^2$  test for categorical variables and linear regression analysis for continuous variables. Meanwhile, ordinal numbers 0-3 were assigned to the quartile categories of each dietary pattern.

To assess the associations between dietary patterns derived from the Japanese population and depressive symptoms, a multiple logistic regression analysis was used to estimate both age- and multivariate-adjusted OR and 95 % CI for depression (dependent variable) for each quartile category of the dietary pattern (independent variables). The first quartile of each dietary pattern was used as a reference category. The first model was adjusted for age, and a multivariate model was calculated by adjusting for potential confounders, including age (years, continuous), family structure (living alone and living with family), household income (less than 5 million yen/year and more than 5 million yen/year), marriage status (not married and married), working hours (8 h/d or less, and more than 8 h/d), frequent eating out (two times/week or less, and more than





two times/week), skipping breakfast (skip more than two times/week and eat almost every day), family meal at dinner (three times/week or less, and more than three times/ week), alcohol consumption (one time/month or less, and quit/never), rest from sleep (not enough and enough), sleeping duration (6 h/d or less and more than 6 h/d) and self-reported stress (moderate or high, and never/ light). The variance inflation factor was used to check for multicollinearity. The association trends were assessed using a logistic regression model and assigning ordinary numbers 0-3 to the quartile categories of each dietary pattern. All reported P values were two-sided, and a P value of < 0.05 was considered statistically significant.

The sample size for the current study was determined through a previous study conducted by the authors, which showed the effect size to be 0.20. We estimated that the prevalence of depressive symptoms (CES-D score ≥16) among Japanese women would be at least 25 %<sup>(15)</sup>. The minimum required sample size was calculated to be 1048 subjects ( $\alpha = 0.05$ ,  $\beta = 0.20$ ). Furthermore, because it was demonstrated that ten individuals per variable are required to estimate regression coefficients in a logistic regression model<sup>(37)</sup>, the required sample size of subjects with depressive symptoms was estimated to be 120 subjects for our logistic regression model (twelve independent variables). Ultimately, a sample size of 1312 participants (including 352 participants with depressive symptoms) was estimated to be sufficient for the current analysis.

## Results

# Participants' characteristics

The characteristics of the study participants according to depressive symptoms are illustrated in Table 1. Threehundred fifty-two participants (26.8%) were identified as having depressive symptoms (CES-D score ≥16). Compared with participants who did not have depressive symptoms, those with depressive symptoms were younger and less likely to be married, have a family meal at dinner, get enough rest from sleep, and get 6 h of sleep or more and more likely to be living alone, earn less than three million yen in household income, eat out frequently, skip breakfast, drink alcohol, and situate their life as stressful. The participants with depressive symptoms had a significantly lower intake of Mg, Zn, vitamin B<sub>6</sub> and vitamin C than the participants without depressive symptoms. These effect sizes were all small.

## Identified dietary pattern

We identified three major dietary patterns that explained 19.4% of the variance in dietary intakes (Table 2). Items in the first dietary pattern represented a high intake of yellow or red vegetables, green leafy vegetables, root vegetables, mushrooms, seaweed, soyabean products (tofu, atsuage and natto), fish, potatoes and fruit. Therefore, this first dietary pattern was labelled the 'healthy Japanese' pattern. Items in the second pattern represented a high intake of Western and Japanese confectioneries, mayonnaise and other dressings, bread, and ice cream and a low intake of rice and miso soup. Therefore, this second dietary pattern was labelled the 'sweets-fat' pattern. Items in the third pattern represented a high intake of pasta (spaghetti and macaroni), fish and fish products, molluscs and shellfish, noodles and alcoholic beverages (beer, wine, sake and shocyu), and a low intake of rice and miso soup. Therefore, this third dietary pattern was labelled the 'seafood-alcohol' pattern. When oblique rotation was used, a factor loading pattern similar to that derived from the orthogonal rotation was obtained.

Table 3 shows the characteristics of study participants according to the quartiles of each dietary pattern. Participants with higher healthy Japanese pattern scores were older and more likely to be married, have a family meal at dinner, and engage in physical activity and less likely to be living alone, earn less than three million yen in household income, work 8 h and more, have more than 15 years of education, eat out frequently, skip breakfast, smoke, and consume alcohol. The nutritional intakes of anti-/pro-inflammatory nutrients selected for the quartiles of each dietary pattern are illustrated in Table 4. Notably, mean values increased for all anti-/pro-inflammatory nutrients with higher quartiles of the healthy Japanese pattern. Meanwhile, mean values of anti-inflammatory nutrients such as Mg, Zn, vitamin D and B<sub>12</sub> decreased and mean values of energy increased with higher quartiles of the sweet-fat pattern. Furthermore, mean food intakes increased for vegetables, fruits, fish, seaweed, soya products and mushrooms, reaching higher quartiles of the healthy Japanese pattern (see online supplementary material, Supplemental Table 1).

# Depressive symptoms and dietary patterns

The age- and multivariate-adjusted OR and 95 % CI for depressive symptoms across the quartiles of all three dietary patterns are illustrated in Table 5. No associations were observed in the 'sweets-fat' and 'seafood-alcohol' patterns according to both the age- and multivariateadjusted models. The age-adjusted OR for depressive symptoms in the first (low), second, third and fourth (high) quartiles of the factor scores for the 'healthy Japanese' pattern was 1.00 (reference); OR = 0.79, 95% CI 0.57, 1.10; OR = 0.61, 95 % CI 0.43, 0.86; and OR = 0.58, 95 % CI 0.41, 0.82, respectively ( $P_{\text{for trend}} = 0.001$ ). Higher 'healthy Japanese' pattern scores were inversely associated with depressive symptoms. However, this significant association disappeared after multivariate adjustment for age, family structure, household income, marriage status, working hours, frequent eating out, skipping breakfast, family meal at dinner, alcohol drinking, rest from sleep, sleeping





Table 1 Characteristics of the study participants with and without depressive symptoms

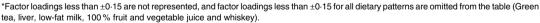
	Participants with symptoms (		Participants withou symptoms (			
Variable	Mean	SD	Mean	SD	P-value*	
Age (years)	36.9	11.3	40.0	11.6	<0.001	
BMI (kg/m²)	21.0	3·2 %	21.2	2.9	0.284	
Family structure	n	70	n	%		
Living alone	62	18-1	114	12.2	<0.001	
Married couple	152	44.3	323	34.7		
Married couple with children	80	23.3	308	33.1		
Married couple with children and grandparents Household income (Japanese yen/year)	49	14.3	186	20.0		
<3 000 000	79	24.2	129	15.1	0.001	
3 000 000–4 990 000	93	28.5	242	28.3		
5 000 000–6 990 000	79	24.2	266	31.1		
7 000 000 Marriage status	75	23.0	217	25.4		
Married	180	51.3	607	65-1	<0.001	
Working hours (h/d)	.00	0.0	00.		10 00 .	
≤8	143	40.9	501	53.8	<0.001	
>8	207	59-1	430	46.2		
Education (year) <13	31	9.0	126	13-6	0.073	
13–14	275	80.2	718	77·4	0.010	
≥15	37	10.8	84	9.1		
Frequent eating out (time/week)						
≥2 <2	125	36·2	250 674	27·1	0.001	
<z Skipping breakfast</z 	220	63.8	0/4	72.9		
Skip more than two times/week	85	24.6	158	17.0	0.002	
Eat almost every day	260	75.4	770	83.0		
Family meal at dinner (time/week)	00	00.0	475	40.4	0.000	
<3 ≥3	92 250	26⋅9 73⋅1	175 739	19⋅1 80⋅9	0.003	
Smoking status	230	73.1	739	00.9		
Former, current	89	25.6	204	21.9	0.158	
Never	258	74.4	727	78-1		
Alcohol consumption	005	50.0	407	50.0	0.004	
≥1 time/month Quit or never	205 143	58⋅9 41⋅1	487 445	52⋅3 47⋅7	0.034	
Rest from sleep	140	71.1	445	77.7		
Not enough	166	47.6	242	25.9	<0.001	
Enough	183	52.4	691	74-1		
Sleeping duration (h/d) <6	104	29.9	194	21.0	0.001	
<0 ≥6	244	70·1	731	79·0	0.001	
Physical activity		701	701	700		
None	244	70⋅5	652	69-8	0.805	
≥1 h/week	102	29.5	282	30.2		
Self-reported stress Moderate or high	342	98-6	765	82.1	<0.001	
Never or light	5	1.4	167	17.9	(0'00')	
	Mean	SD	Mean	SD	<i>P</i> -value*	Effect sizes
Dietary intake						_
Energy (kg/d)	7308 1747	2594	7170	2256	0.378	0.06
Energy (kcal/d) Total fat (% of energy)	26·6	620 5.4	1714 26·8	539 5⋅4	0⋅378 0⋅432	0.06 0.05
SFA (% of energy)	7.4	1.8	7.4	1.8	0.800	0.02
n-3 PUFA (% of energy)	1.2	0.4	1.3	0-4	0.163	0.09
Ca (mg/4184 kJ)	293	105	303	99	0.124	0.10
Mg (mg/4184 kJ) Fe (mg/4184 kJ)	135 4⋅3	35 1·1	139 4.4	31 1.1	0.030 0.178	0·14 0·08
Zn (mg/4184 kJ)	4·3 4·5	0.6	4·4 4·6	0·6	0·178 0·010	0.08 0.16
β-Carotenoids (μg/4184 kJ)	2303	1762	2354	1516	0.609	0.03
Vitamin D (μg/4184 kJ)	7⋅1	4.4	7.5	4.3	0.143	0.09
Vitamin E (mg/4184 kJ)	4.1	1.2	4.2	1.0	0.314	0.07
Vitamin B <sub>6</sub> (mg/4184 kJ)	0.68	0.19	0.71	0.18	0.025	0.14
Vitamin B <sub>12</sub> (μg/4184 kJ) Folate (μg/4184 kJ)	5.0 188	2⋅5 76	5⋅1 195	2·5 73	0⋅265 0⋅146	0·07 0·09
		76 29	70	30	0.146	0.09
Vitamin C (mg/4184 kJ)	66	23	70	30	0.043	0.13

<sup>\*</sup>Independent t test for continuous variables,  $\chi^2$  test for categorical variables.



Table 2 Factor loadings matrix for major dietary patterns identified by principal component analysis\*

Food group Carrots/pumpkin Cabbage/Chinese cabbage Other root vegetables Japanese radish/turnip Green leaves vegetables	0.75 0.72 0.69 0.69 0.66	- - - -	
Carrots/pumpkin Cabbage/Chinese cabbage Other root vegetables Japanese radish/turnip	0.72 0.69 0.69 0.66	- - -	_ _
Other root vegetables Japanese radish/turnip	0.69 0.69 0.66	- -	_
Other root vegetables Japanese radish/turnip	0.69 0.66	_	
	0.66	_	_
		_	_
Green leaves vegetables	0.05	_	_
Mushrooms	0.65	_	_
Seaweeds	0.58	_	_
Lettuces/cabbage (raw)	0.53	0.17	_
Tofu/atsuage†	0.45	_	_
Potatoes	0.40	_	_
Pickled green leaves vegetables	0.34	_	0.18
Other fruit	0.32	0.15	_
Tomatoes	0.32	_	_
Small fish with bones	0.31	_	0.27
Other pickles	0.29	_	0.17
Natto‡	0.27	_	_
Cola drink/soft drink	-0·24	0.21	_
Citrus fruit	0.23	0.16	_
Canned tuna	0.21	_	0.20
Coffee	0.20	_	_
Milk	0.19	_	_
Persimmons/strawberries/kiwifruit	0.17	_	_
Rice	-0.32	-0.77	-0.36
Miso soup	-	-0·64	-0.23
Western-type confectioneries	–0·18	0.54	-0·24
Rice crackers/rice cake/okonomiyaki§	-0·22	0.47	-0.18
Mayonnaise/dressing	_	0.39	_
Bread	_	0.34	_
Ice cream	_	0.28	_
Japanese confectioneries	_	0.27	_
Ham/sausage/bacon	_	0.24	0.24
Pork/beef	_	0.19	-
Black tea/oolong tea	_	0.18	_
Egg	_	0.18	_
Spaghetti and macaroni	_	-	0.43
Oily fish	0.28	_	0.42
Squid/octopus/shrimp/shellfish	0.15	_	0.40
Chinese noodles	-0.29	0.16	0.40
Japanese wheat noodles	_	-	0.36
Beer	_	_	0.36
Low-fat fish	0.34	_	0.34
Dried fish/salted fish	0.24	_	0.32
Buckwheat noodles	- -	_	0.28
Wine	_	_	0.26
Chicken	_	0·17	0.20
Sake	_	U·17	0.22
Shocyu	_	_	0.19
Variation explained (%)	10.6	4.9	3.9



<sup>†</sup>Deep-fried tofu.

duration and self-reported stress. The multivariate OR for depressive symptoms in the first (low), second, third and fourth (high) quartiles of the factor scores for the 'healthy Japanese' pattern were 1.00 (reference); OR = 0.85, 95 % CI 0.57, 1.26; OR = 0.74, 95 % CI 0.48, 1.13; and OR = 0.6995 % CI 0.45, 1.06, respectively ( $P_{\text{for trend}} = 0.076$ ).

# Discussion

The present cross-sectional study identified three dietary patterns among Japanese women. The higher quality dietary pattern was labelled the 'healthy Japanese' pattern, characterised by a high intake of yellow or red vegetables,



<sup>‡</sup>Fermented soyabeans.

<sup>§</sup>Meat/fish and vegetable pancakes.

<sup>||</sup>Japanese distilled alcoholic beverage.



Table 3 Characteristics of the study participants across the three dietary patterns

		Health	ny Japane	se pattern			Sv	veets-fat p	attern			Seafo	od-alcoho	ol pattern	
Variable	Q1	Q2	Q3	Q4	P <sub>for trend</sub> *	Q1	Q2	Q3	Q4	P <sub>for trend</sub> *	Q1	Q2	Q3	Q4	P <sub>for trend</sub>
Number of participants	324	326	325	324		324	326	324	325		325	324	325	325	
Age (years)															
Mean	33.0	38⋅1	41.8	43⋅6	<0.001	40.5	40.2	38.9	37⋅1	<0.001	38.8	40.2	38∙4	39.3	0.950
SD	10.2	10.9	11.2	11.1		11.7	11.1	11.3	11.9		10.9	11.6	11.8	11.9	
BMI (kg/m²)															
Mean	21.0	21.2	21.3	21.3	0.154	21.6	21.4	20.9	20.7	<0.001	20.9	21.3	21.2	21.3	0.111
SD	3.2	3⋅1	2.7	2.9		3.4	2.8	2.9	2.7		2.7	2.9	3.2	3.0	
Family structure (%)															
Living alone	27.0	14.1	7.5	6.3	<0.001	12.5	12.5	14.5	15.6	0.008	15.0	11.9	13.7	14.4	0.739
Married couple	40.1	35.9	37.8	34.9		33.0	33.8	37.4	44.5		36.7	34.7	39.3	38.1	
Married couple with children	23.0	33.1	32.8	33.3		37.7	32.8	28.6	23.1		31.0	34.1	26.8	30.3	
Married couple with children and	9.9	16.9	21.9	25.5		16.8	20.9	19.5	16.8		17.2	19.4	20.2	17.2	
grandparents	0 0			_0 0			_0 0								
<3 000 000	22.4	19.3	12.2	17.1	<0.001	19.5	14.9	18.5	18.3	0.436	19.5	16.2	17.0	18.5	0.307
3 000 000–4 990 000	36.5	26.4	24.3	26.0	νο σοι	30.2	27.5	27.2	28.5	0 100	31.9	28.4	27.2	25.8	0 007
5 000 000–6 990 000	23.1	30.5	34.7	28.6		28.5	32.5	29.5	26.1		25.8	29.4	29.9	31.5	
≥7 000 000	18.1	23.7	28.8	28.3		21.8	25.1	24.8	27.1		22.8	26.0	25.9	24.2	
Marriage status (%)	10-1	20.1	20.0	20.0		21.0	20.1	24.0	21.1		22.0	20.0	20.0	27.2	
Unmarried	55.6	40.3	29.6	29.0	<0.001	35.9	34.8	39.1	44.8	0.011	40.9	36.3	37.3	40.0	0.874
Married	44.4	59.7	70.4	71.0	<b>\0.001</b>	64.1	65.2	60.9	55.2	0.011	59.1	63.7	62.7	60.0	0.07 +
Working hours (h/d, %)	44.4	33.7	70.4	71.0		04.1	03.2	00.9	33.2		33.1	03.7	02.7	00.0	
	34.6	50.0	56.8	60.6	<0.001	52.2	55.6	51.4	42.8	0.010	50.5	54.0	49.1	48.4	0.376
≦8 >8	65·4	50·0 50·0	43.2	39.4	<0.001	52·2 47·8	44.4	48.6	57·2	0.010	49·5	46.0	50·9	51.6	0.376
	65.4	50.0	43.2	39.4		47.0	44.4	40.0	57.2		49.5	46.0	50.9	0.10	
Education (year, %)		10.0	45.4	10.7	.0.001	17.0	10.0	44.0	0.0	0.000	100	10.0	10.0	10.0	0.400
<13	6.2	12.2	15·4	16·7	<0.001	17·0	12.8	11.3	9.3	0.003	10.0	13.8	10.3	16·3	0.123
13–14	81.9	79.6	75.5	74.5		74.2	79.4	78.9	79.1		79.9	76.7	80.3	74.7	
_ ≧15	11.8	8.2	9⋅1	8.8		8.8	7⋅8	9.7	11.5		10.0	9⋅4	9.4	9⋅1	
Frequent eating out (time/week, %)															
≧2	48.8	31.6	23.5	14.9	<0.001	25.8	26.3	29.5	37.3	0.001	21.5	27.4	32.5	37.5	<0.001
<2	51.3	68∙4	76∙5	85⋅1		74.2	73.8	70∙5	62.7		78.5	72.6	67.5	62.5	
Skipping breakfast (%)															
Skip more than two times/week	28.9	20.6	15⋅7	10.4	<0.001	16⋅8	14.1	20.8	23.9	0.004	13.4	12.9	17.4	32.0	<0.001
Eat almost every day	71.1	79.4	84.3	89.6		83.2	85.9	79.2	76⋅1		86.6	87⋅1	82.6	68.0	
Family meal at dinner (time/week, %)															
<3	34.0	25.0	13⋅2	12.5	<0.001	18∙4	22.1	19.0	25.0	0.102	20.1	19.0	22.4	23.1	0.237
<u>≥</u> 3	66.0	75.0	86.8	87.5		81.6	77.9	81.0	75.0		79.9	81.0	77.6	76.9	
Smoking status (%)															
Former, current	30.4	24.6	24.2	12.1	<0.001	21.7	24.5	20.8	24.3	0.698	19.4	21.8	21.3	28.8	0.008
Never	69.6	75.4	75.8	87.9		78.3	75.5	79.2	75.7		80.6	78.2	78.7	71.2	
Alcohol drinking (%)															
≥1 time/month	62.1	58.0	53.0	42.9	<0.001	53.9	56.7	53.5	52.0	0.483	46.3	50.0	53.3	66.7	<0.001
Quit or never	37.9	42.0	47.0	57.1		46.1	43.3	46.5	48.0		53.7	50.0	46.7	33.3	



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Table 3 Continued

		Health	Healthy Japanese	e pattern			Sw	Sweets-fat pattern	attern			Seafoc	Seafood-alcohol pattern	l pattern	
Variable	Q1	<b>Q</b> 2	Q3	Q4	$P_{ m for\ trend}^*$	Ď	Q2	Q3	Φ	$P_{ m for\ trend}^*$	Q1	Q2	<b>Q</b> 3	Q	$P_{ m for\ trend}^*$
Rest from sleep (%)															
Not enough	32.6	35.8	27.9	30.4	0.214	26.3	33.4	35.7	31.4	0.133	28.7	28.0	35.8	34:4	0.032
Enough	67.4	64:2	72·1	9.69		73.7	9.99	64.3	9.89		71.3	72.0	64.2	9-59	
Sleeping duration (h/d, %)															
9>	23.4	23.5	21.7	25.0	0.783	21.9	25.6	23.0	23:1	0.929	21.1	22.4	24.0	26.2	0.110
9	9.92	76.5	78.3	75.0		78·1	74.4	77.0	6.9/		78.9	27.6	0.92	73.8	
Physical activity (%)															
None	74.6	25.6	65.7	63.4	<0.001	20.8	65.3	74.0	69.5	0.686	72.2	72.4	69.4	65.4	0.041
≥1 h/week	25.4	24.4	34.3	36.6		29.2	34.7	26.0	30.5		27.8	27.6	30.6	34.6	
Self-reported stress (%)															
Moderate or high	86.7	89.2	84.9	85.6	0.371	86.7	85.6	87.1	6.98	0.808	87.9	85.1	86.2	87.1	0.879
Never or light	13:3	10.8	15.1	14.4		13.3	14.4	12.9	13.1		12.1	14.9	13.8	12.9	

"Mantel-Haenszel  $\chi^2$  test for categorical variables and linear regression analysis for continuous variables, assigning ordinal numbers 0–3 to quartile categories of each dietary patterns (P < 0.05)

green leafy vegetables, root vegetables, mushrooms, seaweed, soyabean products, potatoes, fish/shellfish and fruit; notably, the higher 'healthy Japanese' pattern score was significantly associated with a higher intake of anti-inflammatory nutrients such as n-3 PUFA, Ca, Mg, Fe, Zn,  $\beta$ -carotenoids, vitamin D, vitamin E, vitamin B<sub>6</sub>, vitamin B<sub>12</sub>, folate, vitamin C and fibre. Higher quartiles of the 'healthy Japanese' pattern scores were inversely associated with depressive symptoms in an age-adjusted model with significant dose-response relationships; however, this significant association disappeared after multivariate adjustment.

Recent studies regarding the relationship between dietary patterns and depressive symptoms among the Japanese population have found that the 'healthy Japanese' or 'balanced Japanese' patterns were associated with a decreased prevalence of depressive symptoms<sup>(15,17,38)</sup>. Furthermore, adherence to a dietary pattern identified using a reduced rank regression, which was based on the six nutrients linked to a decrease in depression - folate, vitamin C, Mg, Ca, Fe and Zn - found in high quantities in vegetables, fruits and typical Japanese foods, including mushrooms, seaweed, soyabean products and green tea, may be associated with a lower prevalence of depressive symptoms<sup>(14)</sup>. Although the relationship was not significant after adjustment in this study, these findings were consistent with our present findings. However, two studies of the Japanese population found no relation between higher quality dietary patterns and depression<sup>(16,18)</sup>. The reason for this inconsistency is not clear; one possible explanation may be that lifestyle, age-sex-related differences in dietary patterns and sample size might have affected these results.

The food components of the 'healthy Japanese' pattern derived from this study have also been observed in previous studies among the Japanese population. The higher factor loadings of the principal component analysis indicate the higher correlations between each food item and the derived factors. The factor score of the 'healthy Japanese' pattern derived from this study involved a diet recognised as higher quality and had higher correlations with vegetables, mushrooms, seaweed, soyabean products, potatoes, fish/shellfish and fruit, in descending order of their related strength (Table 2). In six previous studies regarding the relationship between dietary patterns and depressive symptoms among the Japanese population, the higher quality dietary patterns named 'healthy', 'balanced Japanese' and 'healthy Japanese' had almost identical patterns to those in our study in terms of food groups and their related strength<sup>(14–18,38)</sup>. Although vegetables, fish/shellfish and fruit were common components of a higher quality diet among both Western and Japanese populations<sup>(10)</sup>, mushrooms, seaweed, soyabean products and potatoes from the 'healthy Japanese' pattern were specific food group components of the higher quality diet in the Japanese population<sup>(15)</sup>. The food components of higher quality dietary patterns found in the

Table 4 Nutritional intake for the quartiles of each dietary patterns

				Health	/ Japanese	pattern							Sw	eets-fat pa	ttern				Seafood-alcohol pattern								
		21	C	)2	C	23	(	Q4			Q1	C	Q2	(	Q3	(	Q4			Q1	C	)2	(	23	(	24	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	P <sub>for</sub>	Mean	SD	Mean	SD	Mean	SD	Mean	SD	P <sub>for</sub>	Mean	SD	Mean	SD	Mean	SD	Mean	SD	P <sub>for</sub>
Energy (kJ/d)	6960	2807	7246	2321	7466	2241	7113	1945	0.246	6819	2471	7125	1931	7470	2341	7372	2579	0.001	6828	2370	7286	2008	7200	2375	7471	2588	0.002
Energy (kcal/d)	1663	671	1732	555	1784	536	1700	465	0.246	1630	591	1703	461	1785	560	1762	616	0.001	1632	567	1741	480	1721	568	1786	619	0.002
Total fat (% of energy)	23.6	6.5	26.9	4.7	28-1	4.2	28-4	4-8	<0.001	22.5	5-8	26-2	4.2	28-0	4-1	30.3	4-4	<0.001	25.1	6.6	27-0	4.5	27.3	4.7	27.5	5.5	<0.001
SFA (% of energy)	6-8	2-2	7.5	1.7	7.7	1.5	7.7	1.6	<0.001	6-1	1.8	7.1	1.3	7.8	1-4	8-6	1.7	<0.001	7.2	2.2	7-6	1.6	7.6	1.7	7.3	1.8	0.653
n-3 PUFA (% of energy)	1.0	0.3	1.2	0.3	1.4	0.3	1.5	0.4	<0.001	1.2	0.5	1.3	0.4	1.3	0.3	1.3	0.3	0.004	1.0	0.3	1.2	0.3	1.3	0.3	1.5	0.5	<0.001
Ca (mg/4184 kJ)	212	72	277	63	319	65	394	103	<0.001	302	130	306	95	301	90	293	85	0.199	295	115	298	94	299	95	311	100	0.051
Mg (mg/4184 kJ)	104	18	127	14	147	17	175	28	<0.001	141	41	141	30	139	28	132	30	<0.001	132	38	134	30	138	30	149	30	<0.001
Fe (mg/4184 kJ)	3.2	0.7	4.0	0.6	4.6	0.6	5.5	1.0	<0.001	4.3	1.4	4.4	1-0	4.4	0.9	4.3	1.0	0.925	4.1	1.3	4.2	1.0	4.4	1.0	4.6	1-0	<0.001
Zn (mg/4184 kJ)	4.0	0.4	4.4	0.5	4.7	0-4	5.0	0.6	<0.001	4.6	0.7	4.6	0.6	4-6	0.6	4.4	0.6	<0.001	4.4	0.6	4.6	0.5	4.5	0.5	4.6	0.7	<0.001
β-Carotenoids (μg/4184 kJ)	1049	565	1759	622	2363	802	4185	1829	<0.001	2355	1975	2489	1553	2340	1302	2167	1430	0.070	2711	2128	2311	1349	2097	1362	2234	1300	<-001
Vitamin D (µg/4184 kJ)	4.6	2-8	6.7	3.2	8.7	3.8	9.6	5.2	<0.001	8-2	5.3	7.9	4.4	7.3	3.7	6.3	3-4	<0.001	5.0	2.6	6.7	3.1	8-0	3.8	10-1	5.5	<0.001
Vitamin E (mg/4184 kJ)	3-1	0.9	3.8	0.6	4.4	0.6	5.2	0.9	<0.001	3.6	1.3	4.2	0.9	4.3	0.9	4.5	1.0	<0.001	3.9	1.3	4-1	0.9	4.2	0.9	4.4	1-1	<0.001
Vitamin B <sub>6</sub> (mg/4184 kJ)	0.50	0.13	0.64	0.09	0.75	0.09	0.90	0.14	<0.001	0.69	0.23	0.73	0.18	0.71	0.16	0.68	0.17	0.262	0.64	0.21	0-68	0.16	0.70	0.17	0.78	0.17	<0.001
Vitamin B <sub>12</sub> (μg/4184 kJ)	3.5	1.9	4.8	2.0	5.9	2.2	6.2	2.8	<0.001	5.2	2.7	5-4	2.6	5.1	2.3	4.7	2.2	0.003	3.4	1.5	4.6	1.6	5.5	2.2	6.9	2.9	<0.001
Folate (µg/4184 kJ)	124	37	166	30	203	36	280	71	<0.001	190	90	199	70	194	63	190	69	0.751	197	93	190	66	189	66	196	66	0.846
Vitamin C (mg/4184 kJ)	43	20	58	14	73	18	101	27	<0.001	62	34	71	26	70	26	71	31	0.001	70	38	69	26	68	26	68	26	0.418
Total fibre (g/4184 kJ)	4.6	1.0	6.0	0.9	7.1	0.9	9.7	2.0	<0.001	6.9	2.8	6.9	2.1	6.9	1.9	6.6	2.1	0.152	7.2	2.8	6-8	2.0	6.7	2.0	6.7	2.0	0.004

<sup>\*</sup>Linear regression analysis, assigning ordinal numbers 0-3 to quartile categories of each dietary patterns.



Table 5 OR and 95 % CI for depressive symptoms to quartile of dietary pattern scores

			Quartiles of	dietary pa	ttern scores			
	Q1 (low)		Q2		Q3	Q	4 (High)	
	OR	OR	95 % CI	OR	95 % CI	OR	95 % CI	P <sub>for trend</sub>
Healthy Japanese pattern								
Age-adjusted*	Reference	0.79	0.57, 1.10	0.61	0.43, 0.86	0.58	0.41, 0.82	0.001
Multivariate-adjusted*,†	Reference	0.85	0.57, 1.26	0.74	0.48, 1.13	0.69	0.45, 1.06	0.076
Sweets-fat pattern			·		•		•	
Age-adjusted*	Reference	0.81	0.57, 1.16	1.20	0.85, 1.69	1.19	0.85, 1.69	0.098
Multivariate-adjusted*,†	Reference	0.69	0.46, 1.05	0.95	0.64, 1.41	0.97	0.65, 1.45	0.730
Seafood-alcohol pattern			•		•		•	
Age-adjusted*	Reference	0.80	0.56, 1.15	1.00	0.71, 1.42	1.13	0.80, 1.59	0.295
Multivariate-adjusted*,†	Reference	0.86	0.58, 1.29	0.94	0.63, 1.39	0.99	0.65, 1.48	0.984

<sup>\*</sup>Adjusted OR and 95 % CI were based on multiple logistic regression analysis.

large prospective Japanese cohort study in relation to another health outcomes, such as all-cause and CVD mortality<sup>(19-21)</sup>, were almost the same food components of the 'healthy Japanese' pattern, though green tea was added occasionally.

Furthermore, dietary patterns are identified a posteriori (via a principal component analysis or factor analysis using food/nutrition intake) or a priori (via a theoretical score or index such as the Mediterranean diet score, Healthy Eating Index and Alternate Healthy Eating Index). In previous studies reporting a posteriori dietary patterns, the Japanese food score (a priori dietary patterns) was proposed<sup>(39)</sup>. The Japanese food score consists of seven food groups: beans and bean products, fresh fishes, vegetables, Japanese pickles, fungi, seaweeds and fruits, which were almost the same food components as those in the 'healthy Japanese' pattern derived from this study. The adherence to this Japanese food score was associated with a decreased risk of all-cause and CVD mortality in a large-scale cohort study. However, the 'healthy Japanese' pattern included specific Japanese food groups that reduce depressive symptoms and better health outcomes and involve quite different food components compared with dietary patterns found in Western populations.

Higher quartiles of the 'healthy Japanese' pattern in this study involved higher intake of the anti-inflammatory nutrients we selected, while the other dietary patterns had no such higher intakes. Notably, higher quartiles of the 'sweets-fat' pattern marked a lower intake of Mg, Zn, vitamin D and B<sub>12</sub> and a higher intake of total fat and SFA. According to the DII<sup>(36)</sup>, individually, these nutrients we selected have antioxidant and anti-inflammatory properties, especially fibre,  $\beta$ -carotenes, vitamin E and vitamin C. Participants with a higher DII score (representing the most pro-inflammatory dietary potential) were demonstrated as having a higher risk of developing depression compared with participants with lower DII scores (those consuming diets with the greatest anti-inflammatory

potential)(40). The total fat and the SFA were most proinflammatory in terms of their high DII score. Thus, we wager that the 'healthy Japanese' pattern has stronger anti-inflammatory effects than both the 'sweets-fat' pattern and the 'seafood-alcohol' pattern. Furthermore, our study participants with depressive symptoms had lower intakes of almost all selected nutrients and significantly lower intakes of Mg, Zn, vitamin B<sub>6</sub> and vitamin C than participants without depressive symptoms.

According to the food group intakes, the 'healthy Japanese' pattern, as a rich source of antioxidants and anti-inflammatory foods such as fish(41), seaweed(42) and soya products(42,43), has an inverse association with the prevalence of depressive symptoms in the Japanese population. Mushrooms are one of the few food sources in which the precursor to vitamin D occurs naturally. According to a meta-analysis of observational studies and randomised controlled trials, participants with lower vitamin D levels demonstrated stronger associations with depression than control participants (44). Thus, higher intake of not only vegetables and fruits but also fish, seaweed, sova products and mushrooms might be the reason that the 'healthy Japanese' pattern was associated with depressive symptoms in this study. On the other hand, higher quartiles of the dietary pattern in both the 'sweets-fat' and the 'seafood-alcohol' pattern were not higher in such anti-inflammatory food group intakes. This might be the reason there was no relationship with depressive symptoms.

There are several hypotheses regarding the possible aetiological basis for this positive effect of the 'healthy Japanese' pattern on depressive symptoms. First, depression shares common mechanisms (e.g. insulin resistance, higher plasma homocysteine levels, endothelial dysfunction and so on) with obesity, CVD, diabetes and cancer. Cardioprotective food patterns, such as the healthy or Mediterranean dietary patterns, are also protective against depressive symptoms<sup>(45)</sup>. Furthermore, inflammatory processes, such as increased production of pro-inflammatory



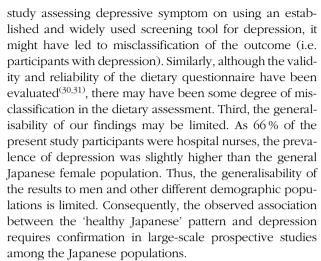
<sup>†</sup>Adjusted for age, family structure, household income, marriage status, working hours, frequent eating out, skipping breakfast, family meal at dinner, alcohol drinking, rest from sleep, sleeping duration and self-reported stress.

cytokines, seem to be the more important factors responsible for the link between depression and cardio-metabolic disorders. Pro-inflammatory cytokines cross the bloodbrain barrier and interact with a number of pathophysiologic mechanisms associated with depression<sup>(7,39,46)</sup>. In the Mediterranean population, a pro-inflammatory diet was associated with a significantly higher risk of depression. The high levels of antioxidants (fibre,  $\beta$ -carotenes and vitamins A, C, D and E) in fruits and vegetables have beneficial effects against depression<sup>(40,47)</sup>. Higher consumption of fish, which has n-3 PUFA with known anti-inflammatory properties, has been associated with reduced levels of depression<sup>(48)</sup>. To be sure, the high amount of anti-inflammatory properties of the 'healthy Japanese' pattern may protect against depression.

Second, vitamin  $B_6$ , vitamin  $B_{12}$  and folate are involved in neurochemical pathways and the synthesis of monoamines such as serotonin and noradrenaline related to the risk of depression. Deficiencies in vitamin  $B_6$ , vitamin  $B_{12}$  and folate can lead to reduced synthesis of monoamines and decrease their availability in the synapses. Folate deficiency leads to decreasing homocysteine, which has a neurotoxic effect, and higher serum folate concentrations have been associated with a decreased prevalence of depressive symptoms. There has also been a suggestion of a positive association between homocysteine concentrations and depressive symptoms  $^{(50)}$ .

Third, the gastrointestinal microbiota plays an important role in mental health. Its involvement in the bidirectional communication between the brain and the gastrointestinal tract via the gut–brain axis is presumably a fundamental link between the microbiota and depression<sup>(51)</sup>. Recent findings suggest that a lack of dietary fibre, important in modulating gut microbiota, leads to a substantial loss of diversity in this microbial community and influences the effect of gut bacteria. Subsequently, the intake of dietary fibre derived from fruits and vegetables is reported to be inversely related to depression symptoms These possible explanations support our hypothesis that the 'healthy Japanese' pattern might be inversely associated with depression.

Although the associated interests were examined by adjusting for potential confounders, there are several limitations in this study. First, an association derived from this cross-sectional study does not necessarily indicate causality regarding the temporal direction of the relationship between dietary patterns and depression. Some mental illnesses might influence appetite and alter an individual's food choices; therefore, poor diet quality may be the result of mental health symptoms, rather than a causative factor. Thus, longitudinal and prospective studies would be highly informative. Second, we assessed depression with a self-report rating scale (CES-D), rather than definite cases of depression based on a clinician-administered structured diagnostic interview. Although this was an epidemiological



In conclusion, the present study found that the higher 'healthy Japanese' pattern was inversely associated with depressive symptoms with significant dose-response relationships; however, this significant association disappeared after multivariate adjustment. Specific Japanese food groups, such as seaweed, mushrooms, soyabean products and potatoes, as well as vegetables, fish/shellfish and fruit from the 'healthy Japanese' pattern were rich sources of anti-inflammatory nutrients and connected nutrients with the synthesis of monoamines and the gastrointestinal microbiota. This finding supports our hypothesis: the 'healthy Japanese' dietary pattern may well be associated with low depressive symptoms. However, further prospective studies are required to assess the associations between dietary patterns derived from the Japanese population and depressive symptoms as well as the biological mechanisms underlying these associations.

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Helsinki, and all procedures involving study participants were approved by the Ethics Committee of Matsumoto University. Written informed consent was obtained from all patients.

#### Supplementary material

For supplementary material accompanying this paper visit https://doi.org/10.1017/S1368980020001548

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