

Influence of Dietary Habits on Depression Among Patients With Rheumatoid Arthritis: A Cross-Sectional Study Using KURAMA Cohort Database

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Abstract

Background

Although depression is one of the most common comorbidities of rheumatoid arthritis (RA) and is known as a critical influence on RA remission rates, there is little knowledge regarding a possible therapeutic strategy for depression in a RA population. Most recently, clinical evidence of dietary improvement for depression has emerged in a general population, but the relationship between dietary habits and depression has not been investigated in RA. The purpose of this study is to elucidate clinical associations between depression, dietary habits and disease activity/physical function in patients with RA.

Methods

A cross-sectional study was performed with 267 female outpatients from the KURAMA database. Using the Hospital Anxiety and Depression Scale (HADS), we classified the participants into three groups by depression state, and their characteristics were compared. Using the 20-items on the self-reported food frequency questionnaire, we investigated the relationship between dietary habits and depression or anxiety, adopting a trend test and a multivariate standardized linear regression analysis for the HADS score as a dependent variable.

Results

Classification of the depressive state revealed that current disease activity and physical dysfunction (28-Joint RA Disease Activity Score-C-reactive protein (DAS28-CRP) as well as the health assessment questionnaire disability Index (HAQ)) were significantly increased according to the stage of depression. Trend analysis identified three of 20 foods, i.e., fish, vegetables and fruit, the consumption of which was inversely associated with the depression score. Furthermore, multiple linear regression analysis revealed that the depression score was negatively associated with frequent fish intake (> 3 times per week) (Estimate -0.53, $p = 0.033$) as well as remission of HAQ (Estimate -0.88, $p \leq 0.001$). For the anxiety score, none of the dietary habits showed any correlation in the multiple regression analysis.

Conclusion

Depression state assessed by HADS score was significantly and independently associated with both fish intake frequency and remission of physical dysfunction in an RA population. Modification of dietary habits, such as that by increased fish consumption, may have a beneficial effect on the depression state in RA patients.

Background

Rheumatoid arthritis (RA) is a chronic inflammatory disorder that causes joint destruction and physical disability. RA patients have increased risk for several comorbidities compared to the general population [1]; accumulated comorbidities worsen treatment response, mortality and quality of life [2, 3]. Although

new RA therapeutics such as biological Disease Modifying Anti-Rheumatic Drugs (b-DMARDs) and Janus kinase (JAK) inhibitors can successfully improve joint inflammation [4], they are insufficient to reduce extra-articular manifestations including cardiovascular disease, sarcopenia and mental health disorders. Thus, comprehensive management of RA-related comorbidities remains a considerable unmet clinical need in the era of biologics.

Depression is one of the most common comorbidities of RA, and its prevalence is approximately two times greater than that in the general population [5, 6]. The depressive state has a critical influence on RA remission rates, as it worsens adherence to medication, treatment response, clinical symptoms (e.g., tender joints and fatigue) and functional status [7, 8]. Mental disorder and RA disease activity are closely interconnected by crosstalk between neurocircuits and inflammation [9], which are implicated in the pathophysiology of depression [10]. Psychological stress can activate inflammatory responses via several immunomodulatory pathways [11], and elevated inflammatory markers are clinically associated with resistance to conventional antidepressant therapy [12]. Although small-scale studies suggest that some kinds of b-DMARDs such as infliximab can attenuate depressive status in medically healthy adults with treatment-resistance depression [13], there is little evidence regarding a possible therapeutic strategy for RA patients.

Recently, clinical evidence of dietary improvement as a lifestyle intervention for depression has emerged in the general population. As shown in previous studies including meta-analyses and randomized control trials (RCTs) [14–16], fish, fruits and vegetables can ameliorate depression. These foods contain a wide-variety of nutrients beneficial for depression (e.g., calcium, magnesium, iron, vitamin C and folic acid) [16] and especially n-3 poly-unsaturated fatty acids (PUFAs) as demonstrated in prospective studies [17, 18]. In addition, since many of these foods and nutrients are well known for their anti-inflammatory effects in various diseases including RA [19], they might be expected to bring benefits both on depression and RA disease activity. However, clinical associations between dietary habits and depression have not been analyzed in an RA population.

To elucidate the relationships among the depression state, dietary habits and the disease state of RA patients, we performed a cross-sectional study using the Kyoto University Rheumatoid Arthritis Management Alliance cohort (KURAMA) database. We assessed the clinical features of RA patients by the score of Hospital Anxiety and Depression Scale (HADS), a widely used method for estimation of depression state, and a self-reported food frequency questionnaire.

Methods

Participants and study settings

We recruited female RA outpatients from the KURAMA cohort database [20]. Participants were enrolled from May 2014 to December 2014 who visited the Kyoto University Hospital, were over 18 years old, and met the diagnostic criteria of the ACR/EULAR RA classification [21]. Of a total of 388 outpatients, we

excluded 82 patients for incomplete data set or incomplete responses to the food intake questionnaire, 33 patients with incomplete responses to HADS questionnaire, and 6 patients for loss of data of current disease activity in 2014. A cross-sectional study was performed with the remaining 267 RA patients to elucidate the association between dietary habits, depression state, and RA disease state.

Ethics

This study complied with the principles of the Declaration of Helsinki and its procedures, and protocols were approved by the Medical Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (Approval number: E1308).

Informed consent was obtained from all subjects.

Evaluation of dietary habits

We obtained dietary records of RA outpatients using self-reported food questionnaire as previously reported [22, 23]. Participants filled out a questionnaire form regarding how often they had eaten food and drink items on an eight-point category scale ranging from 1 = “< 1 time/month”, 2 = “1–3 times/month”, 3 = “1–2 times/week”, 4 = “3–4 times/week”, 5 = “5–6 times/week”, 6 = “1 time/day”, 7 = “2 times/day”, 8 = “3 times/day”. The following 20 items of foods and beverages were surveyed: (1–3) staple food (bread, noodles, or rice) for breakfast (1), lunch (2), and dinner (3), (4) meat, (5) fish, (6) *tofu* (soybean curd), (7) eggs, (8) milk, (9) vegetables, (10) fruits, (11) deep-fried foods, (12) cakes, (13) juice or isotonic drinks, (14) junk foods, (15) sweets like candies and chocolates, (16) frozen foods, (17) pickles, (18) ham, sausage or *kamaboko* (boiled fish paste), (19) *miso* soup (fermented soybean paste) and (20) alcohol.

Estimation of depressive state

We assessed patients' depressive state using the Hospital Anxiety and Depression Scale (HADS), which is widely used to evaluate emotional health of outpatients [24, 25]. HADS consisted of a 7-items questionnaire for depression state and is scored on a 4-point Likert scale (range 0–3), with total scores ranging 0–21. The following commonly used criteria were adopted to classify the groups: Scores between 0 and 7 = 'no', 8 to 10 = 'possible', and 11 to 21 = 'probable'. The favorable internal consistency (> 0.85) for HADS depression subscale was established by several reports [25, 26].

Estimation of clinical parameters

We evaluated RA disease activity and physical dysfunction using a 28-Joint RA Disease Activity Score-C-reactive protein (DAS28-CRP), the patient Visual Analogue Scale (patient VAS), Steinbrocker's stage and class, and the health assessment questionnaire disability Index (HAQ). The clinical remission of current disease activity and physical function was defined using DAS28-CRP and HAQ as follows: DAS28-CRP < 2.6 and HAQ ≤ 0.5 [27]. The data on current RA therapeutics including methotrexate (MTX), prednisolone (PSL) and biological agent were obtained from the KURAMA database. Other epidemiologic information including age, duration of RA disease, body mass index (BMI) were also collected from the KURAMA database.

Statistical analysis

Continuous variables are expressed as the mean \pm standard deviation (SD), categorical variables as numbers (%). For comparison of participant characteristics according to depression status, a Steel-Dwass test or a Fisher's exact test was conducted for continuous variables and for categorical variables, respectively.

To investigate association between dietary habits and depression in RA patients, we first performed a Jonckheere-Terpstra trend test as a univariate analysis. We also adopted the same analysis for exploring the relationship between dietary habits and anxiety. After detecting significant variables in the frequency of food intake, we then opted for a multiple standardized linear regression analysis with each depression and anxiety score (HADS) as a dependent variable. In this multiple regression analysis, we adopted the following clinically relevant factors as simultaneous independent variables: disease duration (continuous variable), RA therapeutics (methotrexate, prednisolone and biological agents, 0 = no, 1 = yes), DAS28-CRP (0 = < 2.6 , 1 = $2.6 \leq$) and HAQ (0 = ≤ 0.5 , 1 = $0.5 <$). As for the factors of dietary habits, because their distribution differs greatly among foods, we redistributed intake frequency into the following binary variables based on the median: fish (0 = low frequency (≤ 2 times/weeks), 1 = high frequency (3 times/week \leq), vegetable and fruits (0 = low frequency (≤ 6 times/week), 1 = high frequency (1 time/day \leq). Statistical analysis was performed by the use of JMP 15.2.0 (SAS Institute Inc., Cary, NC, USA) and SPSS Statistics 26 software (IBM, Armonk, NY, USA).

Results

Characteristics of participants

Baseline demographics are shown in Table 1. A total of 267 female patients with RA were subjected to the following analyses. The mean (\pm standard deviation) age was 60.7 (± 12.8) years and the disease duration of RA was 13.4 (± 12.6) years. The following therapeutics were used: methotrexate in 74.2%, prednisolone in 28.1%, and biological agent in 46.1%. In the context of these treatments, the mean (\pm standard deviation) DAS28-CRP was 1.87 (± 0.80) and the majority of the participants was under remission of disease activity (DAS28-CRP < 2.6 , 80.1%). The remission rate of physical function was 55.3% (HAQ ≤ 0.5). As for the mental health of participants, according to HADS depression score, 12.0% were categorized as 'probable depression' (score ≥ 11), 15.4% as 'possible depression' (score 8 ~ 10) and 72.7% as 'no depression' (score ≤ 8), which represent a higher prevalence of depression than that in the general population [28]. Regarding anxiety state, according to HADS depression score, 8.6% were categorized as 'probable depression' (score ≥ 11), 9.0% as 'possible depression' (score 8 ~ 10) and 82.4% as 'no depression' (score ≤ 8).

Table 1. Baseline characteristics of study population

Items	N = 267	Items	
Age, years	60.7 ± 12.8	<u>Depression and anxiety</u>	
Body mass index, kg/m ²	21.9 ± 3.5	Depression score (HADS-D)	5.58 ± 3.74
<u>Laboratory data</u>		Score 0-7, n (%)	194 (72.7)
Hemoglobin, g/dL	12.4 ± 1.4	Score 8-10, n (%)	41 (15.3)
Albumin, g/dL	3.91 ± 0.33	Score 11-, n (%)	32 (12.0)
CRP, mg/dL	0.31 ± 0.62	Anxiety score (HADS-A)	4.66 ± 3.78
<u>RA-related parameters</u>		Score 0-7, n (%)	220 (82.4)
Duration, years	13.4 ± 12.6	Score 8-10, n (%)	24 (9.0)
DAS28-CRP	1.87 ± 0.80	Score 11-, n (%)	23 (8.6)
DAS28-CRP remission, n (%)	214 (80.1)	<u>Dietary habits **</u>	
HAQ score	0.63 ± 0.65	Fish dishes	3.78 ± 1.01
HAQ remission, n (%)	139 (55.3)	Meat dishes	3.83 ± 1.08
Pain VAS	27.7 ± 24.0	Egg dishes	4.05 ± 1.24
Stage*	2.73 ± 1.18	Vegetable dishes	6.26 ± 1.36
Class*	1.72 ± 0.60	Fruits	4.93 ± 1.76
<u>RA therapeutics</u>		Milk	4.53 ± 2.14
Methotrexate use, n (%)	198 (74.2)		
Prednisolone use, n (%)	75 (28.1)		
Biological agent use, n (%)	123 (46.1)		

Data are presented as the mean (± standard deviation) for continuous variables, and as numbers (%) for categorical variables. The remission of DAS28-CRP and HAQ is defined as follows: DAS28-CRP < 2.6 and HAQ < 0.5.

* Steinbrocker's classification

** Food intake frequency: 0 = seldom, 1 = < 1 time/month, 2 = 1-3 times/month, 3 = 1-2 times/week, 4 = 3-4 times/week, 5 = 5-6 times/week, 6 = 1 time/day, 7 = 2 times/day, 8 = 3 times/day.

Abbreviations: *RA* rheumatoid arthritis, *CRP* C-reactive protein, *DAS28-CRP* 28-joint Disease Activity Score using C-reactive protein, *HAQ* health assessment questionnaire, *VAS* visual analogue scale, *HADS* hospital

anxiety and depression scale,

Comparison of RA-related factors according to depression state

To ascertain participant RA characteristics according depression state, we separated the patients into three groups (No/Possible/Probable depression) and compared the RA-related factors (Table 2). As the stage of depression increased, the degree of current disease activity and physical function including DAS28-CRP, patient VAS and HAQ were significantly increased, whereas age, disease duration and laboratory data including hemoglobin, albumin and CRP were unchanged. Regarding therapeutic drugs, although there was no statistical difference, the use of methotrexate tended to decrease with the degree of depression, while the use of prednisolone tended to increase.

Table 2 Participants characteristics according to the depression state

Depression state	No	Possible	Probable	
HADS score	0 ~ 7	8 ~ 10	11 <	
(N = 267)	<i>n</i> = 194 (72.7%)	<i>n</i> = 41 (15.4%)	<i>n</i> = 32 (12.0%)	P value *
Age, year	60.4 ± 13.6	63.0 ± 10.4	59.5 ± 10.7	0.42
Body mass index, kg/m ²	21.9 ± 3.5	22.2 ± 3.8	21.4 ± 3.1	0.63
Laboratory data				
Hemoglobin, g/dL	12.5 ± 1.3	12.2 ± 1.7	12.2 ± 1.3	0.24
Albumin, g/dL	3.93 ± 0.30	3.85 ± 0.42	3.82 ± 0.33	0.086
CRP, mg/dL	0.29 ± 0.60	0.30 ± 0.61	0.39 ± 0.70	0.71
RA disease characteristics				
Disease duration, year	12.8 ± 12.3	14.2 ± 13.4	16.0 ± 13.8	0.39
DAS28-CRP	1.80 ± 0.76	1.89 ± 0.76	2.28 ± 0.95	0.0065
HAQ	0.53 ± 0.59	0.79 ± 0.74	1.02 ± 0.65	<0.0001
Pain VAS	24.5 ± 21.9	30.4 ± 26.1	43.5 ± 27.3	<0.0001
Stage	2.72 ± 1.21	2.73 ± 1.10	2.72 ± 1.14	1.00
Class	1.62 ± 0.58	1.90 ± 0.49	2.03 ± 0.69	0.0001
Current therapeutic agent				
Methotrexate use, <i>n</i> (%)	155 (77.3)	28 (68.3)	20 (62.5)	0.14
Methotrexate dose, mg	7.31 ± 2.87	7.57 ± 2.85	8.70 ± 2.85	0.12
Biological agent use, <i>n</i> (%)	91 (46.9)	16 (39.0)	16 (50.0)	0.59
Prednisolone use, <i>n</i> (%)	47 (24.2)	16 (39.0)	12 (37.5)	0.072
Prednisolone dose, mg	4.76 ± 4.49	4.22 ± 1.91	4.17 ± 2.04	0.83

Participants are divided into the following three groups for comparison: of characteristics: No (HADS score 0 ~ 7), Possible (8 ~ 10), and Probable (11 <). Data are expressed as the mean (± standard deviation) for continuous variables, and as numbers (%) for categorical variables.

Abbreviations: *HADS* hospital anxiety and depression scale, *RA* rheumatoid arthritis *CRP* C-reactive protein, *DAS28-CRP* 28-joint Disease Activity Score using C-reactive protein, *HAQ* health assessment questionnaire, *VAS* visual analogue scale,

Specific dietary habits including increased fish intake are significantly associated with depression state in RA patients

Although it is emerging that certain dietary factors directly influence depression state in the general population [15, 16], the relationship between dietary habits and depression is unexplored in RA patients. We therefore conducted the following analyses regarding the association between depression and food intake patterns. Trend analysis revealed that 3 out of 20 items taken at higher food intake frequency were negatively associated with the HADS depression score: fish (Fig. 1A), vegetables (Fig. 1B) and fruits (Fig. 1C). Regarding anxiety state, 1 of 20 items of higher food intake frequency were negatively associated with the HADS depression score: fish (Supplementary Fig. 1). Next, to identify whether these three dietary factors independently contributed to the depression state, we opted for a multiple standardized linear regression analysis with depression score (HADS) as a dependent variable. We used not only dietary factors but also disease duration, RA therapeutics, disease activity and physical function as covariates. Because there is some debate about whether the remission of physical function or disease activity contributes more to depression [6, 29], we constructed the following three models: HAQ remission (model 1), DAS28-CRP remission (model 2) or both remissions (model 3) as covariates. As a consequence, we found that in dietary habits, frequent fish intake (> 3 times/week) was inversely and significantly associated with depression score in the model that used RA-related factors and HAQ remission (Table 3 left) (Estimate - 0.53, $p = 0.032$). In other models using the remission of DAS28-CRP (Table 3 middle) or both remission of DAS-CRP and HAQ (Table 3 right) as covariates, the same relationships were confirmed. (Estimate - 0.55, $p = 0.023$ in Table 3 middle, Estimate - 0.53, $p = 0.033$ in Table 3 right). The use of methotrexate and HAQ remission were also significantly and negatively associated with depression score in all models. A similar analysis was also performed for anxiety scores, but no dietary factors were identified (Supplementary Table 1). These results raise the possibility that frequent fish intake has a beneficial effect on the depression state of RA patients.

Table 3 Multivariate analyses for independent factors associated with depression scores including factors of dietary habits

Dependent variables	Depression score	model 1		model 2		model 3	
Independent variables		Estimates	p-value	Estimates	p-value	Estimates	p-value
Dietary habits	Fish dishes	-0.53	0.032	-0.55	0.023	-0.53	0.033
	Vegetable dishes	-0.30	0.33	-0.28	0.36	-0.30	0.34
	Fruits	-0.13	0.61	-0.19	0.48	-0.12	0.65
Current disease activity	DAS28-CRP remission			-0.70	0.016	-0.26	0.41
Physical function	HAQ remission	-0.97	< 0.0001			-0.88	0.00080
	Prednisolone (+)	0.032	0.90	0.11	0.67	0.0050	0.99
	Biological agents (+)	-0.13	0.58	-0.016	0.94	-0.098	0.68
	Methotrexate (+)	-0.60	0.023	-0.65	0.013	-0.60	0.023
	Duration (10 years)	0.016	0.94	0.016	0.40	0.011	0.96

Results of multiple regression analysis with dietary habits and RA-related factors. Model was adjusted for RA duration, dietary habits (intake frequency of fish, vegetables and fruits), RA therapeutics (use of prednisolone, biologics and methotrexate) and HAQ remission (model 1) or DAS28-CRP remission (model 2) or both remission scores (model 3).

Binary variables were constructed as follows: DAS28-CRP (0 = $2.6 \leq$, 1 = < 2.6) and HAQ (0 = $0.5 <$, 1 = ≤ 0.5), fish (0 = low frequency (≤ 2 times/weeks), 1 = high frequency (3 times/week \leq), vegetable and fruits (0 = low frequency (≤ 6 times/week), 1 = high frequency (1 time/day \leq))

Abbreviations: *HADS* hospital anxiety and depression scale, *DAS28-CRP* 28-joint Disease Activity Score using C-reactive protein, *HAQ* health assessment questionnaire, *RA* rheumatoid arthritis

Discussion

The present study is the first to reveal a significant association between depression state and specific dietary patterns in a RA population. RA disease indicators (HAQ and DAS28-CRP) were significantly higher

in patients with increased HADS depression score, a commonly used scale for depression state. This result accords with previous findings that depression closely interacts with RA inflammation and has a pivotal influence on disease remission rates [29]. The HADS depression score was also inversely associated with intake frequency of fish, fruits and vegetables in univariate trend analyses. Furthermore, in multivariate analyses, the HADS depression score was negatively correlated with frequent fish intake as well as with RA remission.

Accumulating evidence in the general population associates specific dietary habits and nutrients in the development or prevention of the depressive state. A meta-analysis confirmed that higher intakes of fish, whole grains, fruits and vegetables are associated with a reduced likelihood of depression [30], whereas dietary patterns including more processed food, sugary products and saturated fats may increase depression risk [31, 32]. In addition, recent RCTs have also shown that such healthy diets improve clinical levels of depression both in young and middle-aged adults [15, 33, 34]. Furthermore, prospective cohort studies in Japan have shown that higher intake of fish or its n-3 PUFAs are significantly associated with reduced risk for depression during the follow-up periods [17, 18]. Based on these findings and the results of the present study, specific dietary patterns including frequent fish consumption may have beneficial effects on mental distress in RA patients.

Recently, the mutual interplay between systemic inflammation and depression has been spotlighted as a proposed cycle model of the exacerbation of RA [9]. Increased peripheral pro-inflammatory cytokines such as TNF α and IL-6 can affect blood-brain barrier permeability [35, 36], and are implicated in the pathophysiology of depression [10, 37]. Indeed, some genetic epidemiological studies have shown significant associations between the severity of depression and polymorphisms in inflammatory cytokine genes encoding IL-1 β , IL-6, TNF and CRP [38, 39]. Psychological stress, in turn, is thought to promote the inflammatory response via several immunomodulatory pathways [10, 40, 41], and can also exacerbate clinical symptoms and impair medical adherence, treatment response, and physical activity [7, 8, 42]. In addition, a large-scale cohort study has shown that exposure to a stress-related disorder is a risk factor for subsequent autoimmune disease [43]. Thus, impeding this interconnection may be a strong candidate therapeutic target for depression in patients under chronic inflammatory condition; the current study provides clinical evidence that a healthy diet could be effective in the mental health portion of this cycle in RA patients. Furthermore, some of the beneficial diets for depression such as fish rich in n-3 PUFAs, fruits and vegetables are also well-known for their anti-inflammatory effects against RA disease activity, as shown in clinical reports including a previous one from our group [23, 44, 45]. Taken together, dietary improvement would seem to be a fruitful co-adjuvant therapy for RA patients with mental disorders. (Fig. 2) Further research is required to see if dietary improvements including encouragement of fish intake is a significant therapeutic option for mental health in RA patients, who are about twice as likely as the general population to develop depression.

The strong point of the present study is that we have combined the HADS score with a food frequency questionnaire (FFQ) for evaluation of both the depression state and dietary habits in a large-scale population study. The HADS score is well-known as a simplified and valid instrument for assessing

depression and anxiety, and is often applied to medical patients including those with RA [25]. FFQ is also a widely used method for quantitative evaluation of eating habits in RA patients as well as in the general population [22, 23]. Our combination of reliable self-reporting forms is a versatile platform for evaluating dietary habits and depression state in various study populations, and can potentially provide new insights into clinical applications of nutrition therapy.

There are several notable limitations in the present study. Only female participants were enrolled, although female sex is highly dominant both in patients with RA and in those with depression [46]. Although in the general population, but not in RA patients, meta-analyses and RCT studies have proven the effectiveness of dietary interventions [14, 15, 34], there remains the possibility of reverse causation as depression itself could promote unfavorable lifestyle choices such as unhealthy eating habits. In addition, there still could remain unadjusted confounding variables between depression and dietary habits. Finally, both the HADS score and FFQ are self-reported assessment tools and might not reflect the objective depression state or the actual food consumption.

Conclusions

In conclusion, depression state showed a significant negative association with fish intake frequency and a positive one with current disease state in a RA population. Dietary intervention such as encouragement of fish consumption could be a potential clinical approach to improve the mental health of RA patients.

Abbreviations

RA: rheumatoid arthritis, KURAMA: Kyoto University Rheumatoid Arthritis Management Alliance cohort, HADS: hospital anxiety and depression scale, DAS28-CRP: 28-joint Disease Activity Score using C-reactive protein, HAQ: health assessment questionnaire, MTX: methotrexate, PSL: prednisolone, BMI: Body mass index, FFQ: food frequency questionnaire

Declarations

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Competing interests

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Author Contributions

H.M. and M.H. are responsible for study conception and design. H.M. and M.K contributed to interpretation of the data, drafted the manuscript, and revised the manuscript. M.H., Y.F and M.T. contributed to interpretation of the data and revised the manuscript. K.I., N.I., Y.O., W.Y, R.W., K.M. (Murakami), K.M. (Murata), K.N. (Nishitani), M.T., H.I., M.U., K.N. (Nin), H.A., S.M., A.M., and N.I. contributed to supervision of the manuscript for intellectual content. All authors have approved the final manuscript for publication and have agreed to be personally accountable for the authors' contributions.

Availability of data and materials

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

Ethics approval and consent to participate

This study complied with the principles of the Declaration of Helsinki and its procedures, and protocols were approved by the Medical Ethics Committee of Kyoto University Graduate School and Faculty of Medicine (Approval number: E1308). Informed consent was obtained from all subjects.

Consent for publication

Not applicable

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Figures

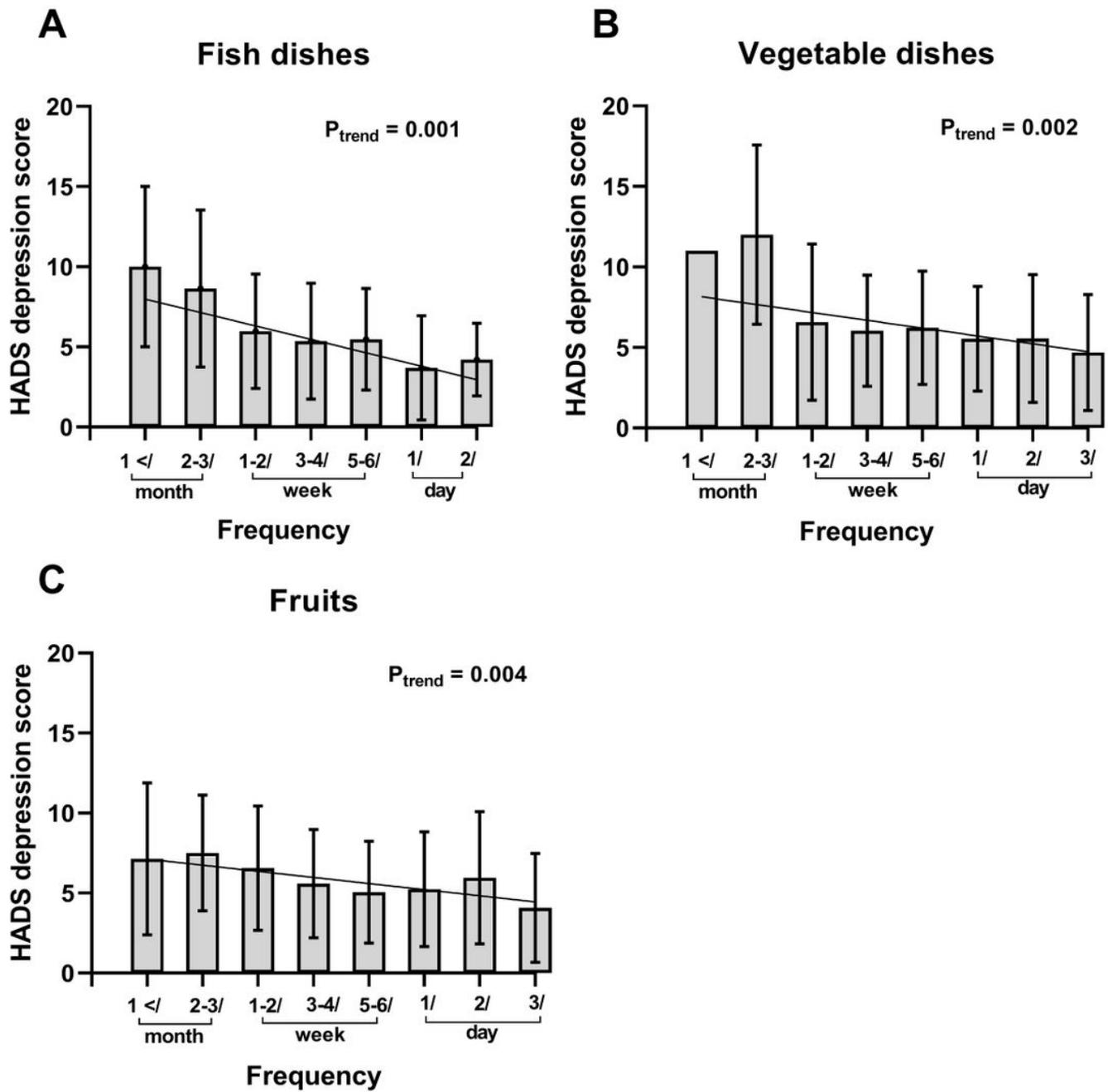


Figure 1

Trends of depression score by intake frequency The vertical axis represents HADS depression score and the horizontal axis represents intake frequency of each category. 3 of 20 groups are negatively associated with HADS depression score; fish (A), vegetable (B), and fruits (C). P_{trend} values are calculated by a Jonckheere-Terpstra trend test. Abbreviations: HADS hospital anxiety and depression scale

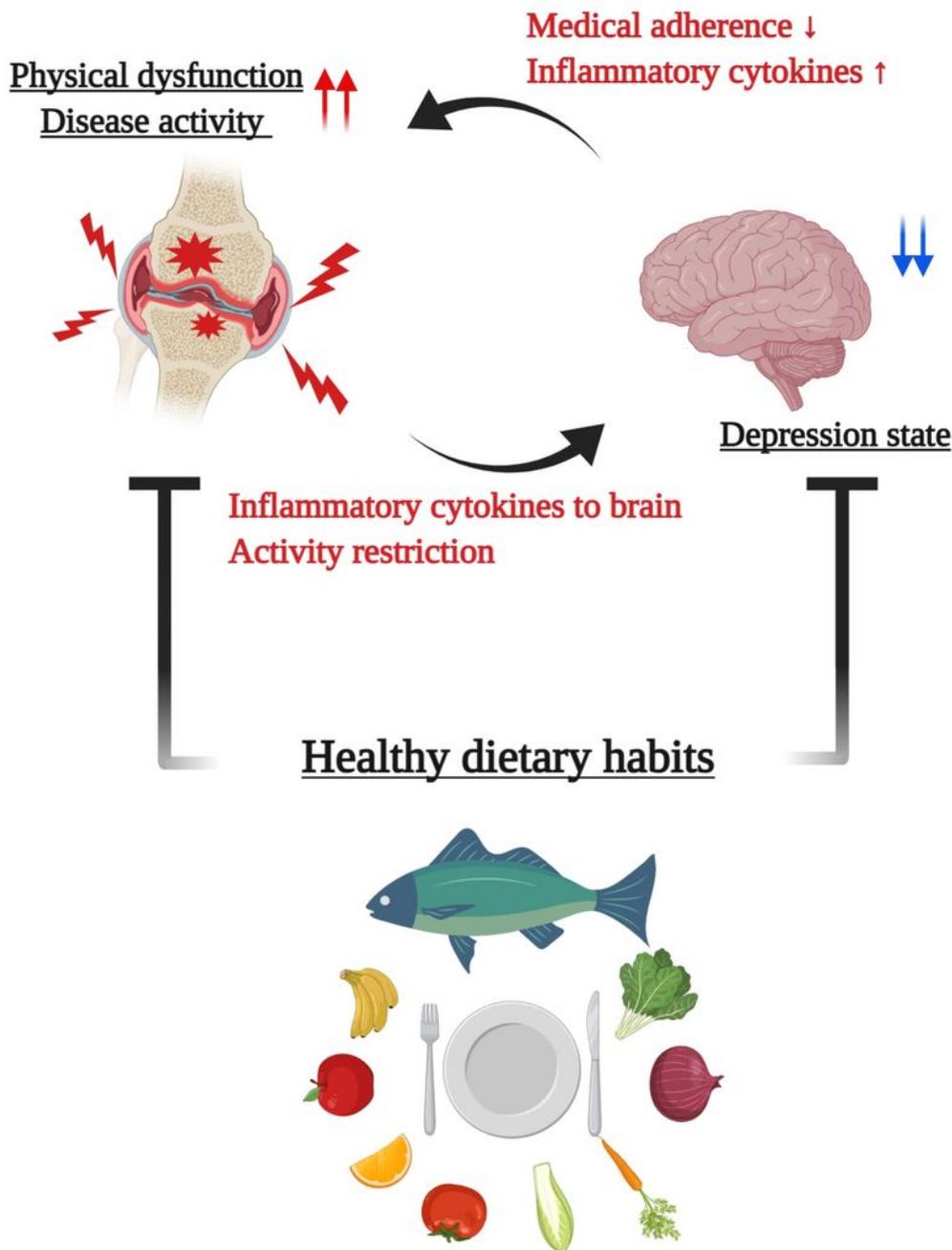


Figure 2

A model of the beneficial effect of healthy dietary habit on depression state in RA patients Depression state and disease activity/physical dysfunction in RA could be mutually influential as follows: depression affects decreased adherence to adequate treatment and is thought to promote inflammatory response via several immunomodulatory pathways, resulting in exacerbation of RA, which influences psychological distress because of increased pain and activity restriction and because of direct inflammation to brain.

Healthy dietary habit including fish, vegetable and fruit intake may have a positive impact on both depression and disease activity and may be a potential therapeutic target to prevent exacerbation of the vicious cycle mentioned above. Abbreviations: RA rheumatoid arthritis

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