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Relationship of food allergy with quality of life and sleep in psychiatric patients

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Abstract

Aim: Few studies have examined the relationship between food allergy (FA) and psychiatric disorders. We aimed to examine the possible relationship of FA with quality of life (QOL) and sleep in adult patients with psychiatric disorders.

Methods: Of the 812 participants (451 females, mean age: 42.7 ± 11.3 years), 430 had schizophrenia/schizoaffective disorder, 106 had depression, 124 had bipolar disorder, 40 had anxiety disorders, 38 had developmental disorders, and 11 had eating disorders; 63 were other cases. We documented FA and sleep disturbance via a questionnaire. QOL was assessed with the Medical Outcomes Study 8-Item Short-Form Health Survey (SF-8 Japanese version).

Results: There were 126 patients (15.5%) reporting FA. SF-8 physical component summary (PCS) and mental component summary (MCS) scores were both significantly lower among individuals with FA than those without. Moreover, PCS and MCS scores decreased as the number of allergens increased. Sleep disturbance was common among patients (76.0%). The proportions of individuals with sleep disturbance and nocturnal awakening were significantly higher in the group with FA, with the proportions increasing with higher number of allergens.

Conclusion: We obtained the first evidence that FA is associated with impaired QOL and sleep in psychiatric patients, which can be improved by avoiding exposure to food allergens.

KEYWORDS
allergens, immunity, mental disorders, mood disorders, quality of life, schizophrenia

1 | INTRODUCTION

According to the World Health Organization, depression increased by 18.4% and anxiety disorders increased by 14.9% worldwide in the 10 years between 2005 and 2015.[1] In Japan, the number of patients receiving psychiatric services due to mental illness has increased in recent years, exceeding 4 million in 2017.[2]

Food allergy (FA) is also a common health problem. Nwaru et al[3] reviewed epidemiological data in Europe and reported that the pooled lifetime and point prevalence of self-reported FA were 17.3% and 5.9%, respectively. They stated that while the incidence of FA appeared stable over time, there was some evidence that the prevalence may be increasing.[3] Gupta et al[4] reported that estimated convincing FA prevalence among adults in the United States was

10.8%, although 19.0% of adults self-reported a food allergy. From a global viewpoint, Loh et al[5] pointed out that the prevalence of FA diagnosed according to food tolerance tests in Western countries was as high as 10%, with its rates increasing in developing countries such as China and those in Africa. This could be attributable in part to the adoption of a westernized lifestyle in these countries.[6] Similarly, the prevalence of FA in Japan is increasing every year.[7-8]

The possible link between FA and mental illness has been reported for several decades.[9] FA is suspected to be involved in psychiatric problems, especially in childhood and adolescence.[10] However, to our knowledge, there have been few empirical studies assessing this link, especially those targeting adult psychiatric disorders. In recent years, an increasing number of studies have demonstrated the relationship between psychiatric disorders and the intestinal environment. The role of the gut-brain interaction in the pathology of psychiatric disorders has become a popular topic.[11-13] One cause for this is that intestinal inflammation derived from food affects brain function. Indeed, schizophrenia patients have higher levels of intestinal inflammation markers and their correlation with food antigen antibodies.[14] Recently, our group reported that FA is associated with clinical depression and stress symptoms, and the higher the number of allergens, the higher the odds ratio for them.[15]

Although pharmacotherapy is the main strategy in the treatment of psychiatric diseases, accumulating evidence suggests that intervention for lifestyle habits and comorbid lifestyle-related diseases is also important. Several researchers have pointed out that nutritional approaches play an important role in the treatment and prevention of psychiatric diseases such as depression.[16-19] Food allergy may also be one of the important factors; however, few studies have examined the relationship between FA and psychiatric disorders. To our knowledge, there has been no research that clarifies how FA affects quality of life (QOL) and sleep in patients with mental illness. Thus, the purpose of this study is to clarify the relationship of FA with QOL and sleep in psychiatric patients in the hope of providing evidence that intervention for FA may improve QOL of the patients.

2 | METHODS

2.1 | Participants

Participants were individuals with psychiatric disorders who were members of the Community Mental Health & Welfare Bonding Organization, a certified non-profit organization. Those with dementia or intellectual disabilities were excluded due to their possible inability to read or understand the survey participation request or questionnaire. At the time the monthly magazine for members of this organization was distributed, we included a survey cooperation request form and called for participation in the study. The explanation of the research was provided in a simply worded document intended to be easily understood, and consent for participation was obtained by signing the document (for those who responded to the paper questionnaire) or by providing consent on the internet (for those who responded using the internet). This study was carried out in accordance with the Declaration of Helsinki with the approval of the Ethics Committee of the National Center of Neurology and Psychiatry (approval number: A2016-140).

2.2 | Data collection

Demographic and clinical data such as diagnoses, FA, and sleep disturbance were obtained by a questionnaire. Regarding FA, respondents were asked to answer the question: "Have you ever had (do you have) food allergies?" with a "Yes" or "No." Those who chose "Yes" were further asked to answer, "What foods have you been allergic to?". For sleep disturbance, they were asked to answer if they experienced the presence or absence of sleep disturbances (initial insomnia, nocturnal awakening, and early morning awakening).

The Medical Outcomes Study 8-Item Short-Form Health Survey (hereinafter, SF-8), a shortened version of SF-36, which is a widely used health-related quality of life scale, was used to assess QOL.[20-24] The questionnaire consists of eight items, and most people are able to complete it within a few minutes. The eight health concepts that can be measured by SF-8[24,25] are: physical functioning (PF), role physical (RP), bodily pain (BP), general health perception (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). Physical component summary (PCS) is obtained by multiplying the subscale scores of these 8 items by the respective physical weighting factors to obtain a total adding a constant. Similarly, the Mental component summary (MCS) is calculated by multiplying the mental weighting factor to obtain the sum and adding a constant. The Japanese version SF-8 has been validated.[25]

2.3 | Statistical analysis

Demographic data are shown as mean ± standard deviation (SD). The score distribution of SF-8 according to the Shapiro-Wilk test indicated that these data did not meet the assumption of a normal distribution. As such, the nonparametric tests such as Mann-Whitney *U* test and Kruskal-Wallis test were used for between-group comparisons. Categorical data were analyzed with a Chi-squared test. Statistical analyses were performed using SPSS Ver.26 (IBM). A two-tailed *P*-value of $<.05$ was deemed significant.

3 | RESULTS

Among the members of the Community Mental Health and Welfare Bonding Organization (total number: 7950), 864 individuals (10.9%) showed their intention to participate in the study. The number of valid respondents was 812 (451 females [55.5%]; mean age: 42.7 ± 11.3 years). There were 126 respondents (15.5%) who had any FA, consisting of 78 females (17.3%) and 48 males (13.3%). There was no significant difference in the prevalence of FA between

males and females ($X^2 = 2.45$, $df = 1$, $P = .12$). The main diagnoses of the participants included 430 people (52.9%) with schizophrenia/schizoaffective disorder, 106 (13.1%) with depression, 124 (15.3%) with bipolar disorder, 40 (4.9%) with anxiety disorder, 38 (4.7%) with developmental disorders, 11 (1.4%) with eating disorders, and 63 (7.8%) categorized as other. Frequencies of FA by psychiatric diagnosis were as follows: 63 (14.7%) cases of schizophrenia, 19 (17.9%) depression, 23 (18.5%) bipolar disorder, and 21 (13.8%) other diseases. There was no significant difference in the proportion of individuals with FA by disease ($X^2 = 1.92$, $df = 3$, $P = .59$). Among the 812 participants, 75 (9.2%) were allergic to only one food, 21 (2.6%) to two foods, and 23 (2.8%) to three or more foods. For the top five foods listed by the Japanese Consumer Affairs Agency, there were 22 (2.7%) cases of shrimp, 19 (2.3%) of eggs, 19 (2.3%) of mackerel, 14 (1.7%) of dairy food, and 11 (1.4%) of crabs.

3.1 | Food allergy and SF-8

SF-8 PCS ($U = 34\ 948$, $P = .001$ by Mann-Whitney U test) and MCS ($U = 37\ 459$, $P = .032$) scores were both significantly lower among individuals with FA than in those without (Figure 1). In addition, regarding the 7 out of 8 subscale items, the score was significantly lower in the allergy group compared with the non-allergy group (Table 1).

When the relationship between SF-8 scores and the number of allergens was examined, there was a significant difference in PCS ($H = 12.34$, $P = .006$ by Kruskal-Wallis test) and MCS ($H = 8.14$, $P = .043$). As shown in Figure 2, these SF-8 scores tended to decrease as the number of allergens increased. Similarly, significant differences in scores by the number of allergens were observed in 7 out of 8 subscale items (Table S1).

3.2 | Food allergies and sleep disturbances

There were 809 valid responses for sleep disturbances, with those reported at a high frequency in 615 (76.0%) participants, which was expected since the participants were all psychiatric patients. The percentage of people with sleep disturbances was significantly higher in the FA group than in the non-FA group (Table 2). Comparing each of the sleep difficulty categories: initial insomnia, nocturnal awakening, and early morning awakening, the ratio of nocturnal awakening was significantly higher in the FA group than in the non-FA group (Table 2).

Frequencies of sleep disturbances according to the number of allergens are shown in Table S2. The differences in the rate of sleep disturbances according to the number of allergens fell slightly short of statistical significance ($P = .069$).

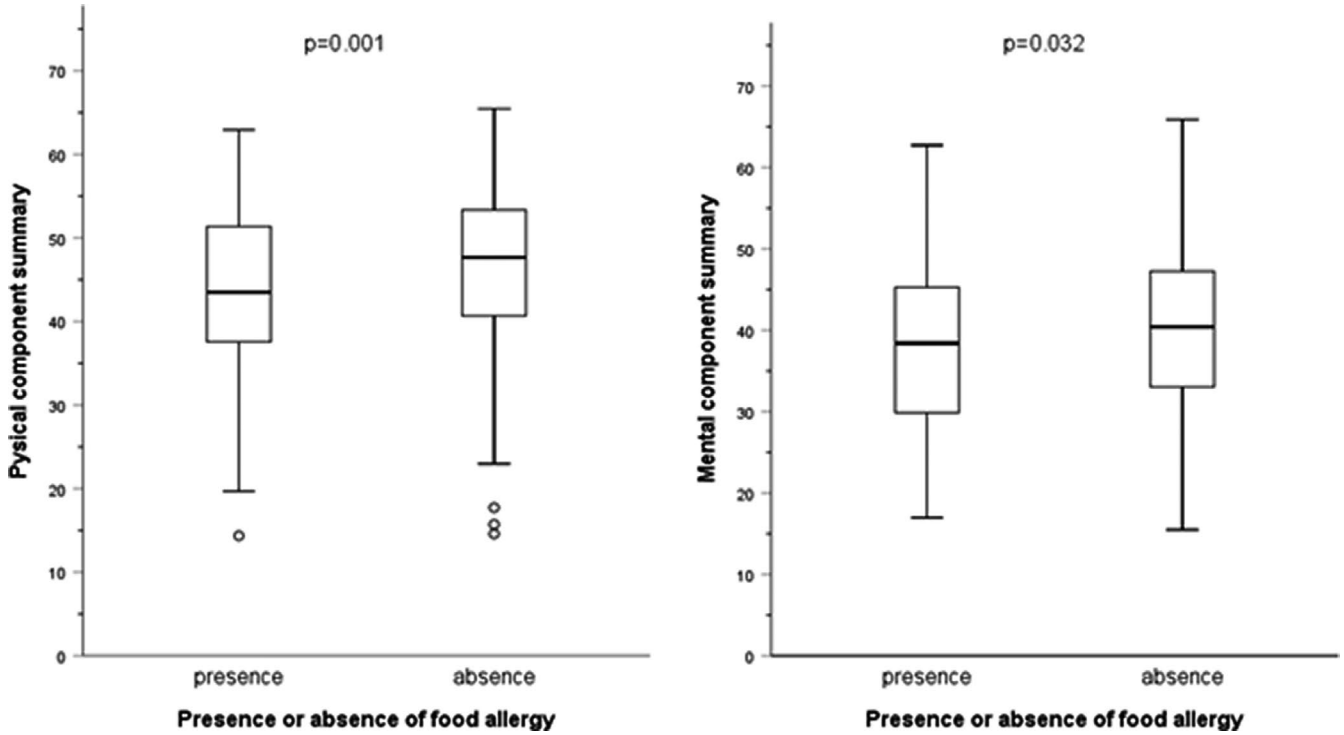

FIGURE 1 Physical component summary (PCS) and Mental component summary (MCS) scores by the presence or absence of food allergy. PCS and MCS were significantly higher in those with food allergies than in those without. Results are expressed as percentage of respondents. Box-and-whisker plot description: box center line: median; box upper end: upper quartile value; box lower end: lower quartile value; upper end of whisker: maximum value; lower end of whisker: minimum value. ○: Outlier. *P*: statistical significance calculated by Mann-Whitney *U* test

TABLE 1 Presence or absence of food allergies and SF-8

SF-8 subscale items	Food allergy	N	Not at all	Very little	Somewhat	Quite a lot	Could not do physical activities	Mann-Whitney *U* Test
Physical functioning (PF)	Food allergy (+)	126	41 (32.5%)	17 (13.5%)	36 (28.6%)	24 (19.0%)	8 (6.3%)	$U = 36\ 286, P = .003$
	Food allergy (−)	683	280 (41.0%)	125 (18.3%)	181 (26.5%)	77 (11.3%)	20 (2.9%)	
	Total	809	321 (39.7%)	142 (17.6%)	217 (26.8%)	101 (12.5%)	28 (3.5%)	
	Food allergy	N	Not at all	Very little	Somewhat	Quite a lot	Could not do daily work	
Role physical (RP)	Food allergy (+)	126	30 (23.8%)	19 (15.1%)	33 (26.2%)	28 (22.2%)	16 (12.7%)	$U = 33\ 731, P = .000$
	Food allergy (−)	682	232 (34.0%)	147 (21.6%)	171 (25.1%)	106 (15.5%)	26 (3.8%)	
	Total	808	262 (32.4%)	166 (20.5%)	204 (25.2%)	134 (16.6%)	42 (5.2%)	
	Food allergy	N	None	Very mild	Mild	Moderate	Severe	Very severe
Bodily pain (BP)	Food allergy (+)	126	27 (21.4%)	18 (14.3%)	32 (25.4%)	33 (26.2%)	13 (10.3%)	3 (2.4%) $U = 38\ 949, P = .075$
	Food allergy (−)	685	189 (27.6%)	119 (17.4%)	158 (23.1%)	138 (20.1%)	64 (9.3%)	17 (2.5%)
	Total	811	216 (26.6%)	137 (16.9%)	190 (23.4%)	171 (21.1%)	77 (9.5%)	20 (2.5%)
	Food allergy	N	Excellent	Very good	Good	Fair	Poor	Very poor
General health (GH)	Food allergy (+)	126	7 (5.6%)	8 (6.3%)	43 (34.1%)	28 (22.2%)	19 (15.1%)	21 (16.7%) $U = 37\ 502, P = .015$
	Food allergy (−)	684	23 (3.4%)	53 (7.7%)	292 (42.7%)	205 (30.0%)	70 (10.2%)	41 (6.0%)
	Total	810	30 (3.7%)	61 (7.5%)	335 (41.4%)	233 (28.8%)	89 (11.0%)	62 (7.7%)
	Food allergy	N	Very much	Quite a lot	Some	A little	None	
Vitality (VT)	Food allergy (+)	126	9 (7.1%)	24 (19.0%)	40 (31.7%)	24 (19.0%)	29 (23.0%)	$U = 37\ 770, P = .019$
	Food allergy (−)	685	25 (3.6%)	160 (23.4%)	311 (45.4%)	123 (18.0%)	66 (9.6%)	
	Total	811	34 (4.2%)	184 (22.7%)	351 (43.3%)	147 (18.1%)	95 (11.7%)	
	Food allergy	N	Not at all	Very little	Somewhat	Quite a lot	Could not do social activities	
Social functioning (SF)	Food allergy (+)	126	22 (17.5%)	28 (22.2%)	34 (27.0%)	30 (23.8%)	12 (9.5%)	$U = 37\ 221, P = .012$
	Food allergy (−)	684	169 (24.7%)	165 (24.1%)	187 (27.3%)	127 (18.6%)	36 (5.3%)	
	Total	810	191 (23.6%)	193 (23.8%)	221 (27.3%)	157 (19.4%)	48 (5.9%)	
	Food allergy	N	Not at all	Very little	Somewhat	Quite a lot	Could not do daily activities	
Role emotional (RE)	Food allergy (+)	126	15 (11.9%)	23 (18.3%)	35 (27.8%)	32 (25.4%)	21 (16.7%)	$U = 35\ 676, P = .002$
	Food allergy (−)	683	131 (19.2%)	131 (19.2%)	211 (30.9%)	179 (26.2%)	31 (4.5%)	
	Total	809	146 (18.0%)	154 (19.0%)	246 (30.4%)	211 (26.1%)	52 (6.4%)	
	Food allergy	N	Not at all	Slightly	Moderately	Quite a lot	Extremely	
Mental health (MH)	Food allergy (+)	126	4 (3.2%)	18 (14.3%)	37 (29.4%)	26 (20.6%)	41 (32.5%)	$U = 37\ 465, P = .016$
	Food allergy (−)	684	54 (7.9%)	119 (17.4%)	179 (26.2%)	193 (28.2%)	139 (20.3%)	
	Total	810	58 (7.2%)	137 (16.9%)	216 (26.7%)	219 (27.0%)	180 (22.2%)	

Note: No response to PF: 3 people; no response to VT: 1 person; no response to RP: 4 people; no response to SF: 2 people; no response to BP: 1 person; no response to RE: 3 people; no response to GH: 2 people; no response to MH: 2 people.

Of these, 1 person did not respond to 8 items (no food allergy), 2 persons did not respond to 2 items (PF and RP), and for others, 1 item was unanswered in 8 people.

Abbreviations: BP, bodily pain; GH, general health perception; MH, mental health; PF, physical functioning; RE, role emotional; RP, role physical; SF, social functioning; SF-8, The Medical Outcomes Study 8-Item Short-Form Health Survey; VT, vitality.

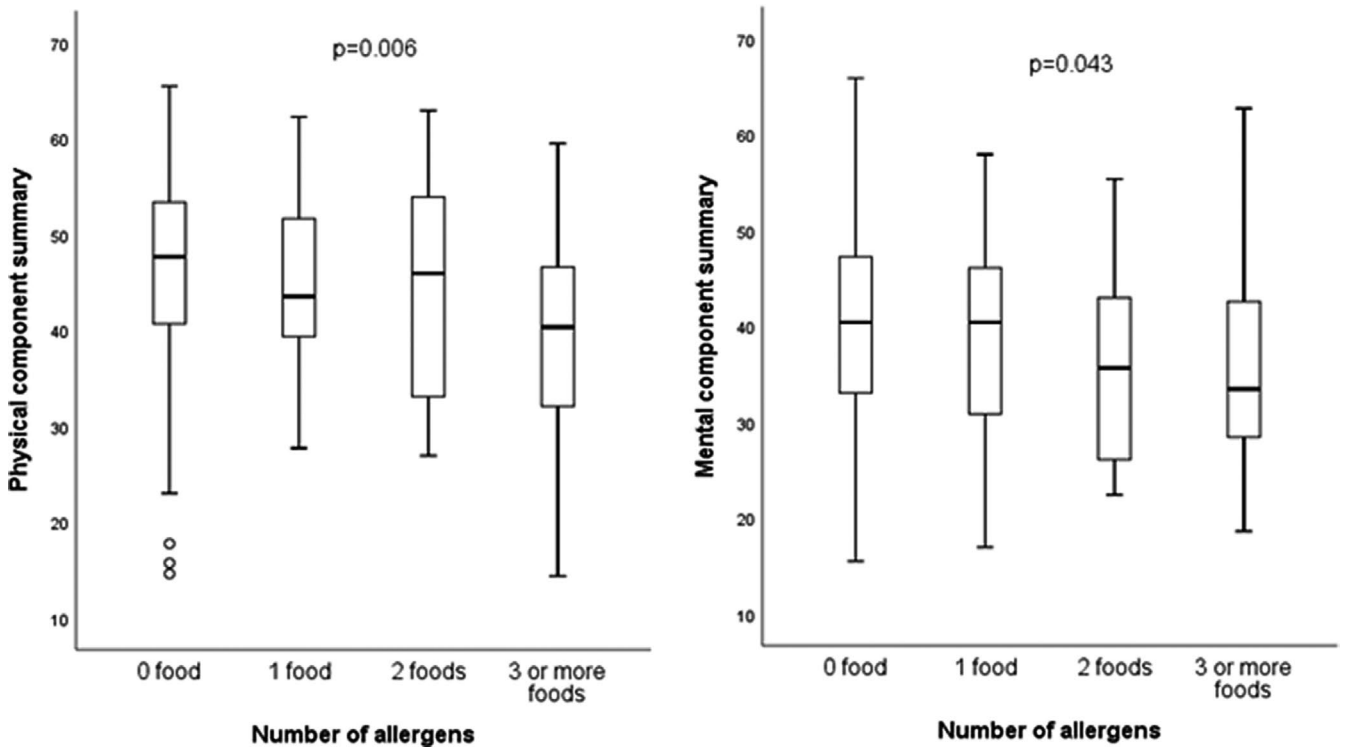

FIGURE 2 Number of Allergens and Physical component summary (PCS) and Mental component summary (MCS). PCS and MCS decrease with the number of allergens increase. Results are expressed as percentage of respondents. Box-and-whisker plot description: box center line: median; box upper end: upper quartile value; box lower end: lower quartile value; upper end of whisker: maximum value; lower end of whisker: minimum value. ○: Outlier. *P*: statistical significance calculated by Kruskal-Wallis test

TABLE 2 Presence or absence of food allergy and sleep disturbance

	N	Sleep disturbance (+)	Chi-squared test
Food allergy (+)	126	105 (83.3%)	$\chi2 = 4.38$, $df = 1$, $P = .036$ OR = 1.70, 95% CI: 1.03-2.79
Food allergy (−)	683	510 (74.7%)	
Total	809	615 (76.0%)	
	N	Initial insomnia (+)	
Food allergy (+)	124	49 (39.5%)	$\chi2 = 1.25$, $df = 1$, $P = .26$ OR = 1.25, 95% CI: 0.84-1.85
Food allergy (−)	682	234 (34.3%)	
Total	806	283 (35.1%)	
	N	Nocturnal awakening (+)	
Food allergy (+)	125	61 (48.8%)	$\chi2 = 6.41$, $df = 1$, $P = .011$ OR = 1.64, 95% CI: 1.12-2.40
Food allergy (−)	682	251 (36.8%)	
Total	807	312 (38.7%)	
	N	Early morning awakening (+)	
Food allergy (+)	126	42 (33.3%)	$\chi2 = 0.73$, $df = 1$, $P = .39$ OR = 1.19, 95% CI: 0.80-1.79
Food allergy (−)	684	202 (29.5%)	
Total	810	244 (30.1%)	

Note: 3 for sleep disorders, 6 unanswered for difficulty falling asleep, 5 unresponsive for awakening, and 2 people have not answered about early morning awakening.

Abbreviations: CI, confidence interval; OR, odds ratio.

4 | DISCUSSION

Depression and other psychiatric disorders are chronic diseases that are deeply related to lifestyle habits such as eating habits, sleep, and exercise habits. In addition to controlling patients' symptoms, it is important to assist in the improvement of lifestyle habits to enhance QOL.[16-19] In recent years, FA has been increasing in Japan and a previous study clarified that food allergy is associated with clinical depression.[15] To our knowledge, no studies have thus far examined whether FA can influence the QOL of psychiatric patients. In this study, for the first time, we have clarified the relationship of FA with QOL and sleep disturbance in a large sample of patients with psychiatric disorders.

We found that the rate of having at least one FA (based on self-report) was 15.5% in our psychiatric patients, which is comparable with the rate reported by Hidese et al[15] who found 14.5% of 11 876 Japanese people in an internet survey. This may indicate that FA has no major role in the development of psychiatric illnesses in our sample. Regarding SF-8, mean scores of our patients were 45.97 ± 9.21 for PCS and 39.52 ± 9.57 for MCS, while the 2007 national standard values of SF-8 in Japanese[25] were 48.60 ± 7.24 for PCS and 49.44 ± 6.78 for MCS, indicating that QOL of our patients was poorer than that of the general population both physically and mentally, as expected. Concerning insomnia, the rate of having sleep disturbance was 76.0% in our psychiatric patients, while the prevalence of insomnia in Japanese adults was reported to be 17.3%–22.3% for men and 20.5%–21.5% for females,[26] which showed that the rate of insomnia was much higher in our psychiatric subjects. Our comparison of SF-8 between the group with FA and the group without FA revealed that the score was significantly lower among PCS and MCS in patients with FA than those without. The seven subscale items of the SF-8 also demonstrated a similar trend in the same direction. These results suggest that FA acts as a factor that reduces QOL involving physical, mental, and social functions.

The mechanism of the relationship between food allergy and psychiatric disorders remains elusive; however, the following mechanisms are thought to be involved. When a food allergen enters the body, the allergen binds to the specific IgE antibody on the mast cells and activates the mast cells. They produce Th2 cytokines such as interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13), and chemokines, which induce inflammation by inflammatory cells, mainly eosinophils.[27] In addition, a growing body of research suggests that mast cells play a crucial role in the pathogenesis of inflammation in central nervous system disorders.[28-30] Zhou et al[31] found that both ovalbumin (allergen)-specific IgG1 and ovalbumin-specific IgG2a in the cerebral cortex of food-allergic mice were significantly increased compared with control mice. It is speculated that the increase in ovalbumin-specific IgG is due to entry into the brain via the blood-brain barrier or the entry of peripheral IgG-secreting cells into the brain. The chymase level of the mast cell activation marker in the cerebral cortex of food-allergic mice was also significantly increased compared with control mice. It was, thus, suggested that FA may cause an increase in allergic factors not only in peripheral organs but also in the brain. Furthermore, the number of total microglia and the ratio of activated microglia in both the cerebral cortex and the hippocampal CA1 region were significantly increased in food-allergic mice, and the level of a proinflammatory cytokine tumor necrosis factor-α (TNF-α) was increased. It is currently believed that the activation of microglia releases inflammatory cytokines such as TNF-α and IL-6, causing an inflammatory response and exacerbating psychiatric disorders such as depression, schizophrenia, and autism.[32-34] These mechanisms may underlie our findings that PCS, MCS, and seven subscale items were significantly lower in the FA group than in the non-FA group. The current study further revealed that the higher the allergen number, the significantly lower the SF-8 score in PCS, MCS, and the seven subscale items. This observation is consistent with that of Hidese et al[15] in that the higher the number of allergens, the higher the proportion of people with depression and severe stress symptoms.

The percentage of people with sleep disturbances was higher in our FA group than in the non-FA group. In particular, the percentage of people with nocturnal awakening was higher in the former than in the latter. This result is consistent with the study by Wasilewska et al,[35] which indicated that children with allergic diseases, including FAs, had significantly fewer days they were able to sleep without awakening than healthy children. It is also consistent with another study[36] demonstrating that children with FA were at an increased risk of waking up twice or more at night. To our knowledge, no research has been conducted on the mechanisms of FA and sleep disorders. Further basic and clinical research on this relationship is warranted.

One might expect that not only FA, but also other allergic diseases such as drug allergies, asthma, hay fever, and atopy may also have detrimental effects on QOL and sleep. In this study, however, we focused specifically on FA because we were interested in gut-brain interaction and the potential use of intervention in food habits. It would be intriguing to examine the possible association of the other allergic conditions with QOL and sleep in future.

As a result of targeting patients with psychiatric disorders, it was suggested that FA may reduce QOL and sleep quality. Given this evidence, obtaining information on the history of FA and specific allergens may be important for improving the QOL and sleep. It is possible that some patients are potentially unwell due to excessive intake of noodles, breads, and other foods that are easily accessible. A case study[37] reported that a gluten-free diet improved mental function and decreased symptom severity in schizophrenia patients, and another study revealed increased gliadin antibodies in schizophrenia patients.[37,38]

FA is diagnosed by confirming the possibility that specific food intake induces allergic symptoms that may be mediated by immunological mechanisms such as specific IgE antibodies. It is diagnosed by immunological tests such as an oral food challenge test and a specific IgE antibody test for possible food allergies after detailed inquiry. However, this study was limited in that our grasp of the patients' FA history was based on their self-reporting. This study was also limited by the use of

self-report on sleep disturbances but not using objective indicators such as actigraphy and polysomnography. Interpretation of our results requires caution because our study was subject to selection bias (relatively active member of the Community Mental Health and Welfare Bonding Organization), report bias due to cognitive decline in psychiatric diseases, influence of different diagnoses, influence of complications of physical disease, effect of drugs, etc Finally, we did not take into account the multiple testing in the statistical analyses. We compared the effects of FA on PCS and MCS (2 items). If the Bonferroni correction was applied, the *P*-value of .032 (MCS) was not significant any more, which indicates that caution is required in the interpretation of the results.

In conclusion, the results of this study indicate that FAs may reduce QOL and sleep quality, in patients with psychiatric disorders. This suggests that for patients with mental illness, inquiring about their history of food allergies and allergens and avoiding exposure to these foods as much as possible in their diet may improve their QOL and sleep. Further research is needed to clarify the mechanism by which FA can be attributed as a risk factor for poor QOL and sleep disorders.

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CONFLICT OF INTEREST

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Hiroshi Kunugi contributed to conceptualization, funding acquisition, resources, and writing—review and editing. Yuuki Yokota involved in data curation and investigation. Chiho Gomi and Hiroshi Kunugi involved in formal analysis. Hiroshi Kunugi and Yuuki Yokota contributed to methodology. Hiroshi Kunugi, Yuuki Yokota, and Chiho Gomi contributed to software.: Hiroshi Kunugi and Sumiko Yoshida involved in supervision and validation Chiho Gomi contributed to visualization and writing—original draft. Chiho Gomi., Sumiko Yoshida, and Yuuki Yokota.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

The protocol for this research project has been approved by the Ethics Committee of the National Center of Neurology and Psychiatry, and it conforms to the provisions of the Declaration of Helsinki. (Approval number: A2016-140.)

INFORMED CONSENT

Informed consent was obtained from all subjects.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. The raw data belonged to the present study cannot be made publicly available, because the disclosure of personal data was not included in the research protocol of the present study.

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