Journal of Psychiatric Research 102 (2018) 72–80

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Omega-3 fatty acids for a better mental state in working populations - Happy Nurse Project: A 52-week randomized controlled trial

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ARTICLE INFO

Keywords:
Anxiety
Burn out
Depression
Fatty acids
Omega-3
Presenteeism

ABSTRACT

The efficacy of omega-3 fatty acids for maintaining a better mental state has not been examined among working populations. We aimed to explore the effectiveness of omega-3 fatty acids for hospital nurses. In a multi-center randomized trial, 80 junior nurses were randomly allocated to either omega-3 fatty acids (1200 mg/day of eicosapentaenoic acid and 600 mg/day of docosahexaenoic acid) or identical placebo pills for 13 weeks. The primary outcome was the total score of the Hospital Anxiety and Depression Scale (HADS), determined by a blinded rater at week 26 from the study enrolment. Secondary outcomes included the total score of the HADS at 13 and 52 weeks; incidence of a major depressive episode; severity of depression, anxiety, insomnia, burnout, and presenteeism; utility scores; and adverse events at 13, 26 and 52 weeks. The mean HADS score at baseline was 7.2. At 26 weeks, adjusted mean scores on the HADS were 6.32 (95% CIs of standard errors: 5.13, 7.52) in the intervention and 6.81 (5.57, 8.05) in the placebo groups, respectively. The coefficient of the group by time interaction was not statistically significant at 0.58 (−1.35, 2.50; P = 0.557). Although the intervention group showed significant superiority on the HADS score at 52 weeks, depression severity at 52 weeks, insomnia severity at 13 weeks, and absolute presenteeism at 26 weeks, no significant superiority or inferiority was observed on the other outcomes. The additive value of omega-3 fatty acids was not confirmed regarding mental state and self-evaluated work efficiency.

Clinical trial registry number and website:

ClinicalTrials.gov: NCT02151162 (registered on May 27, 2014) https://clinicaltrials.gov/ct2/show/NCT02151162.

1. Introduction

Antidepressive effects of omega-3 polyunsaturated fatty acids (PUFAs), in particular eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been examined by many previous studies. A recent Cochrane review showed that omega-3 PUFA supplementation resulted in a small or modest benefit for depressive symptomatology compared to placebo for patients with a primary diagnosis of unipolar or major depressive disorder (MDD), with a standardized mean difference of −0.3 (95% CI, −0.10 to −0.50) by pooling results from 25 randomized controlled trials (RCTs) (Appleton et al., 2015).

Some other previous RCTs have examined the effects of omega-3 PUFAs in terms of preventing depression in non depressed population, especially for pregnant women who are either mentally healthy (Blasi et al., 1989; Krauss-Etschmann et al., 2007; Makrides et al., 2010; Mattes et al., 2009; Vaz et al., 2017) or at risk for postpartum depression (Doornbos et al., 2009). However, to the best of our knowledge, trials investigating the efficacy of PUFAs in preventing depression or maintaining healthy mental state among ordinary people, including working populations, are sparse. In a recently published meta-analysis (Grosso et al., 2014), omega-3 PUFAs were effective in patients diagnosed as MDD, but not in preventing depression in healthy subjects. In this analysis, three parallel RCTs investigating preventive effects for

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https://doi.org/10.1016/j.jpsychires.2018.03.015
Received 17 January 2018; Received in revised form 27 March 2018; Accepted 29 March 2018

depression in healthy subjects were assessed with a follow-up duration of 3–6 months. The studies employed a daily dose of 1060 mg EPA and 274 mg DHA (Mozurkewich et al., 2013), 3000 mg EPA and 600 mg DHA (DeFina et al., 2011), or 2085 mg EPA and 348 mg DHA (Kiecolt-Glaser et al., 2012). However, a high daily EPA dose between 1000 and 1500 mg/d with a ratio of 2:1 with DHA has been argued as optimal for affective disorders (McNamara, 2009). We believe that another methodologically rigorous trial employing optimal doses of EPA and DHA with long-term follow-up is needed.

Hospital nurses are vulnerable to psychological stress and mental disorders (Calnan et al., 2001), especially depression. The prevalence of depressive symptoms above a clinical cut-off among hospital-employed nurses is 18% in the U.S. (Letvak et al., 2012). Nurses with depression are not only likely to suffer personally, but their illness may also have an impact on the quality of care for patients due to presenteeism. In terms of the monetary burden of patient care, the costs due to increased falls and medication errors caused by presenteeism are estimated at 1346 USD per nurse annually (Letvak et al., 2012).

Hence, the present study aimed to explore the effectiveness of omega-3 PUFAs in maintaining a healthy mental state among hospital nurses. The protocol of the study has already been published elsewhere (Watanabe et al., 2015).

2. Materials and methods

2.1. Trial design

A factorial-design trial was conducted with 1:1:1:1 allocation, with a 52-week follow-up. Participants were randomly assigned to one of the following four intervention arms: a) omega-3 PUFAs plus mindfulness-based stress management program; b) placebo plus mindfulness-based stress management program; c) omega-3 PUFAs plus psychoeducation leaflet; and d) placebo plus psychoeducation leaflet. These interventions were terminated within 13 weeks from the registration of the participant. The present paper focuses on the comparison between combined groups of a) and c), and b) and d).

2.2. Participants

The inclusion criteria for participants were 1) female, aged between 20 and 59 years, because a previous study demonstrated that omega-3 PUFAs were effective in females but not in males (Nishi et al., 2012). We focused on females to maximize the benefit; 2) nurses who worked in inpatient wards at four general hospitals and at one psychiatric hospital in Tama area, Tokyo, Japan; 3) and those mainly engaged in caring for patients but not in administrative responsibilities. Thus, head or senior nurses were excluded. A previous study showed that senior nurses are less burnout than junior nurses (Voltmer et al., 2013).

The exclusion criteria for participants were those 1) planning to resign for any reasons within 26 weeks; 2) engaging in structured psychotherapy; 3) seeing a physician regularly for the treatment of any mood or anxiety disorders; 4) taking antidepressants, mood stabilizers, anticonvulsants or antipsychotics; 5) taking omega-3 PUFAs for four or more weeks within 52 weeks; 6) clinically depressed, judged by satisfying a total score of 11 or more on the Hospital Anxiety and Depression Scale (HADS) Depression Subscale (Kugaya et al., 1998) and that of 15 or more on the Patient Health Questionnaire (PHQ-9) (Spitzer et al., 1999); 7) consuming fish as the main course of a meal four or more times a week; or 8) taking anticoagulant drugs at entry or history of stroke or myocardial infarction.

2.3. Procedures

The participants were randomly assigned to one of the four intervention arms via the EDC using a minimization method, which controlled for place of work; a total score on the HADS of ≥11 (Kugaya et al., 1998) or not; and working as a nurse for ≥1 year or not.

2.4. Interventions

Omega-3 PUFA capsules were formulated to contain 1200 mg EPA and 600 mg DHA according to expert recommendations (McNamara, 2009). The participants took the capsules once a day for 90 days. Placebo capsules contained rapeseed oil (47%), soybean oil (25%), olive oil (25%), and fish oil (3%) and have identical appearance and similar odor to omega-3 PUFA capsules. To assess adherence to the regimen, all the remaining capsules were collected after the 13-week assessment.

Participants who stopped taking the capsules were still asked to complete the assessments. Participants assigned to the placebo group were asked not to take omega-3 PUFA supplements for the first 26 weeks.

2.5. Assessment measures

2.5.1. Primary outcome

The primary outcome was the blindly rated total score of the 14-item HADS (Herrmann, 1997; Zigmond and Snaith, 1983) at week 26, assessed through their mobile phone by a blinded rater located at Kyoto University. All participants were requested not to reveal the assigned treatment to the assessors, in order to keep the assessors' blindness to the groups. After each assessment, an assessor guessed which group the participant has been assigned to, making it possible to examine if the blinding was successful.

The total score of the HADS (HADS-T) ranges from 0 to 42, higher scores indicating more symptoms. The HADS has two sub-scores, each ranging from 0 to 21: HADS-D (depression) and HADS-A (anxiety). The recommended cutoffs of the HADS-T were ≥9 for possible cases and ≥11 for probable cases of anxiety or depressive disorders (Zigmond and Snaith, 1983).

2.5.2. Secondary outcomes

All self-reported measures other than the HADS were gathered through the EDC system, where the participants could input their own data through the Internet at home. Participants were notified at 13, 26, and 52 weeks to fill in the assessment questionnaires within the following 14, 30, and 30 days, respectively.

2.5.2.1. Depression and anxiety symptoms. The HADS was administered at baseline, 13 and 52 weeks as secondary outcomes through their mobile phone by a blinded rater.

2.5.2.2. Major depressive episode. A current major depressive episode, according to DSM-5, were determined using the Primary Care Evaluation of Mental Disorders (PRIME-MD) algorithm in the depression module of the PHQ-9 (Spitzer et al., 1999). The PHQ-9 has been used to assess major depressive disorder, according to DSM-5 (Fried et al., 2013).

2.5.2.3. Anxiety. The GAD-7 (Spitzer et al., 2006) was used to assess the severity of anxiety symptoms in the participants. Total scores from 5 to 9, 10–14, or 15–21 indicate mild, moderate, or severe anxiety symptoms, respectively.

2.5.2.4. Burnout. The Maslach's Burnout Inventory (MBI) (Maslach et al., 1996) was used to assess degree of burnout among nurses. The MBI is a tool for detecting and measuring the severity of burnout syndrome. It is a 22-item questionnaire that assesses the degree of burnout according to the following three subscales: emotional exhaustion (EE), depersonalization (DP) and personal accomplishment (PA).

2.5.2.5. Insomnia. The Insomnia Severity Index (ISI) (Bastien et al.,

2001; Morin and Espie, 2004) was used to assess insomnia. The ISI is now considered a standard global measure for assessing the severity of insomnia and is used in many studies (Morin et al., 2009; Watanabe et al., 2011). Total scores from 8 to 14 and 15–28 indicate subthreshold insomnia and clinical insomnia, respectively.

2.5.2.6. Presenteeism. The World Health Organization Heath and Work Performance Questionnaire (HPQ) was used to assess two types of presenteeism: the absolute presenteeism score, which is calculated as the difference between the score for self over the past 28 days and the score for the average worker in the same job and ranges from 0 (total lack of performance during time on the job) to 100 (no lack of performance during time on the job); and the relative presenteeism score, which is a ratio of actual performance to possible performance (the performance of most workers in the same job) and ranges from 0.25 to 2.0. The validity of the scale has been confirmed in previous studies (Kessler et al., 2004; Kessler and Ustun, 2004).

2.5.2.7. Quality of life (QoL). The EuroQol (EQ-5D) (EuroQol Group, 1990) was used to assess health-related QoL. The five domains include mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. The following are the three levels of severity for each domain: no problems, some or moderate problems, and severe or extreme problems. Each pattern of responses is assigned to an individual utility score, which ranges from 0 (death) to 1 (perfect health).

2.5.2.8. Adverse events and other outcomes. Information about types and severity of an adverse event and degree affecting normal life was collected through the EDC. Information about sick leave and consultations on personal mental state was also collected.

2.6. Sample size

The sample size was based on a power analysis conducted for the HADS scores, basically for the comparison between the stress management program and leaflet groups, because, to the best of our knowledge, there had been no published trial on the efficacy of omega-3 PUFAs in preventing depression among workers. Based on trials that have used nurses as psychotherapists and the HADS as the primary outcome (Romeo et al., 2011), we estimated the mean difference in the HADS scores between the groups to be 4 ± 6 (SD). To detect a significant difference at P = 0.05 (two-tailed) with a power of 0.9, and allowing for a 20% dropout rate, 60 participants would need to be recruited per group, which is a total of 120 participants. We considered that this number was not too small for the comparison between the omega-3 PUFA and placebo groups, because previous trials on the efficacy of omega-3 PUFA for depression in a Cochrane meta-analysis (Appleton et al., 2015) enrolled the median number of participants at around 50 in total.

However, in the interim follow-up during the study, considering extremely low dropout rate for the primary outcome assessment (5% in total), delay in recruitment process, and running out of research grant, we decided to set a new target number of the participants at 80 in total, in July 2015.

2.7. Data management and analysis

All of the participants who were randomized at baseline were included in the primary analyses (intention-to-treat, ITT). First, a descriptive analysis of the variables at baseline was performed. We did not plan any statistical tests to detect a difference at baseline among the trial arms because we aimed to avoid multiple tests; however, when clinically important differences at baseline were noted, we planned to perform our analyses by adjusting for all such possible confounds.

Second, for all the continuous outcomes assessed at 13, 26, and 52 weeks, treatment-by-time interactions were examined using a mixed model repeated measures analysis. The model included participants for a random effect and included treatment, time (categorical), treatment-by-time interaction, and baseline scores for fixed effects. When missing data existed for categorical variables, which were all negative outcomes, an ITT principal was applied by assuming that all dropouts did not satisfy the outcomes.

A P value of < 0.05 was set to test the null hypothesis for all analyses. We did not plan to perform interim analyses to examine the study hypotheses. All the analyses were conducted blindly in terms of the assigned groups, and the results were interpreted before breaking the group assignment. We used IBM SPSS statistics 23 for all analyses.

We, a priori, planned in the protocol to conduct our analyses in the present article by focusing on the efficacy of omega-3 PUFAs and to report that of mindfulness-based intervention in another article. Moreover, in our post-hoc analysis investigating the interaction between the efficacy of omega-3 PUFAs and that of mindfulness-based stress management program, we did not observe any interactions at 13 weeks (P = 0.872), 26 weeks (P = 0.927), and 52 weeks (P = 0.378), respectively. We believe that this may support our decision to report our results from the factorial-design trial in multiple articles.

2.8. Ethical issues

The present study complied with the ethical principles established for research on human beings stipulated in the Declaration of Helsinki and further amendments thereto.

The study protocol was approved by the institutional review boards of the National Center of Neurology and Psychiatry (A2014-017), Kyoto University (C0881) and of Toyama University (26–24). Written informed consent was obtained from all participants. Data for each participant were handled with sequentially assigned numbers to keep participant's confidentiality.

3. Results

3.1. Enrollment and baseline characteristics of the participants

Between June 11, 2014 and August 27, 2015, 83 nurses were assessed for eligibility, of whom 80 were enrolled and randomized to the omega-3 PUFAs (n = 40) or placebo (n = 40) groups. We did not find any clinically important differences between these two groups (Table 1).

3.2. Attrition, adherence and study integrity

We obtained data from 76 participants (95%) for the HADS and 75 (94%) for the other outcomes at 52 weeks (Fig. 1). Reported adverse events were not associated with dropouts.

The remaining capsules were collected from 39 participants (98%) in the omega-3 PUFA group and from 36 (90%) in the placebo group. The mean proportion of taking pills over the total amount provided was 84% (95% CIs: 77%, 91%) in each of the groups, and the median was 91% and 89% for omega-3 PUFAs and placebo groups, respectively. These indicated that the blinding of the participants appeared to be successful.

The agreement rate and kappa value for agreement between the actual assignment and those guessed by blind assessors at 24 weeks were 52.0% and 0.03. These indicated that the blinding of the assessors was successful.

Only one participant in the omega-3 PUFA group reported taking omega-3 PUFA supplements between 13 and 26 weeks, but none did in the placebo group and between 26 and 52 weeks.

Table 1
Characteristics of participants at baseline.

Continuous data: mean ± SD (range)	All (N = 80)	Omega-3 fatty acids (N = 40)	Placebo (N = 40)
Age	30.1 ± 8.4 (21–55)	29.6 ± 9.1 (21–55)	30.5 ± 7.8 (21–49)
Duration of experience as a nurse (year)	4.7 ± 5.6 (0–32)	4.0 ± 6.2 (0–32)	5.4 ± 5.0 (0–20)
Consultation for physical illness	18 (22.5%)	10 (25.0%)	8 (20.0%)
Marital status (Married; Unmarried; Divorced/Widowed)	14; 59; 7	6; 30; 4	8; 29; 3
Education for qualification for a nurse (Vocational school; College; Postgraduate course)	6; 45; 29	3; 21; 16	3; 24; 13
HADS total	7.2 ± 4.6 (0–20)	7.4 ± 4.8 (1–19)	7.1 ± 4.5 (0–20)
HADS depression	3.2 ± 2.7 (0–11)	3.3 ± 2.8 (0–11)	3.1 ± 2.5 (0–9)
HADS anxiety	4.0 ± 2.5 (0–11)	4.0 ± 2.4 (0–9)	4.0 ± 2.7 (0–11)
PHQ-9 total	4.9 ± 3.4 (0–15)	5.1 ± 3.4 (0–12)	4.7 ± 3.4 (0–15)
GAD-7 total	3.1 ± 2.9 (0–14)	3.0 ± 3.0 (0–10)	3.2 ± 2.9 (0–14)
ISI total	5.7 ± 4.1 (0–16)	6.4 ± 4.5 (0–16)	5.0 ± 3.5 (0–13)
MBI Emotional Exhaustion	21.5 ± 11.1 (3–50)	20.9 ± 7.6 (3–50)	19.4 ± 10.0 (5–49)
MBI Depersonalization	7.0 ± 4.9 (0–22)	6.9 ± 4.6 (1–22)	7.1 ± 5.2 (0–20)
MBI Lack of Personal Accomplishment	21.7 ± 8.4 (4–41)	20.9 ± 7.6 (4–40)	22.6 ± 9.1 (6–41)
Absolute presenteeism	50.6 ± 16.4 (10–90)	48.8 ± 16.2 (10–80)	52.5 ± 16.6 (20–90)
Relative presenteeism	0.88 ± 0.29 (0.25–1.80)	0.83 ± 0.28 (0.25–1.50)	0.92 ± 0.30 (0.25–1.80)
Utility score	0.91 ± 0.12 (0.66–1.0)	0.90 ± 0.13 (0.66–1.0)	0.92 ± 0.12 (0.66–1.0)
N of incidents in the last 13 weeks	1.3 ± 1.2 (0–5)	1.4 ± 1.3 (0–5)	1.2 ± 1.2 (0–4)
N of accidents in the last 13 weeks	0.1 ± 0.3 (0–2)	0.1 ± 0.4 (0–2)	0.1 ± 0.3 (0–1)

Abbreviations: HADS, Hospital Anxiety and Depression Scale; ISI, Insomnia Severity Index; MBI, Maslach's Burnout Inventory; PHQ-9, Patient Health Questionnaire-9.

3.3. Primary outcome

At 26 weeks, adjusted mean scores in the HADS-T score were 6.32 (95% CIs of standard errors: 5.13, 7.52) and 6.81 (5.57, 8.05) in the omega-3 PUFA and placebo groups, respectively (Table 2, Fig. 2). The coefficient of the group by time interaction was not statistically significant at 0.58 (−1.35, 2.50; P = 0.557).

3.4. Secondary outcomes

Regarding major depressive episode at 26 weeks, four and three participants satisfied the episode in the omega-3 PUFA and placebo groups, respectively, and there was no statistical difference (P = 0.692) (Table 3). No statistically significant differences were also observed at 13 weeks or at 52 weeks.

Statistically significant superiority was observed in favor of the omega-3 PUFA group in terms of the HADS-T score at 52 weeks (group by time interaction 1.52; 0.46, 2.58; P = 0.005), the HADS-D score at 52 weeks (1.50; 0.26, 2.73; P = 0.018), the Insomnia Severity Index at 13 weeks (2.05; 0.34, 3.76; P = 0.019), and absolute presenteeism at 26 weeks (−6.29; −12.56, 0.02; P = 0.049) (Table 2). No significant superiority or inferiority was observed in the other outcomes, including anxiety, burnout, QoL (Table 2), psychiatrist consultation, or psychotropic medication intake (Table 3).

Adverse events were rare in both groups (Table 3). We did not observe any serious adverse events.

4. Discussion

To the best of our knowledge, this study is the first to investigate the effectiveness of omega-3 PUFAs for depression and anxiety symptom prevention among workers. However, no significant differences between the omega-3 PUFA and placebo groups were observed in terms of our primary outcome, the total score of depression and anxiety at 26 weeks. Although some statistically significant results favorable to the omega-3 PUFA group were observed in the secondary outcomes, including the total score of depression and anxiety at 52 weeks, the insomnia severity score at 13 weeks, and absolute presenteeism at 26 weeks, we may not be able to eliminate the possibility that these plausible results are chance findings due to multiple tests. Moreover, these differences are difficult to be explained biologically, when we consider effects of omega-3 PUFAs on depression which could occur as a result of changes in cell membrane structure and function, leading to impacts on cell communication, inflammatory processes and neurotransmitter activities (Haag, 2003; James et al., 2000). The intervention was terminated at the end of the first 13 weeks, and may not benefit the long-term outcomes without short-term effects.

On the other hand, no significant results of the incidence of adverse events or dropouts were observed between the two intervention arms. We, therefore, concluded that omega-3 PUFAs provide neither benefit or harm in terms of maintaining healthy mental health state and preventing depression among working populations.

A recent systematic review and meta-analysis have shown that omega-3 PUFAs do not prevent depressive symptoms among

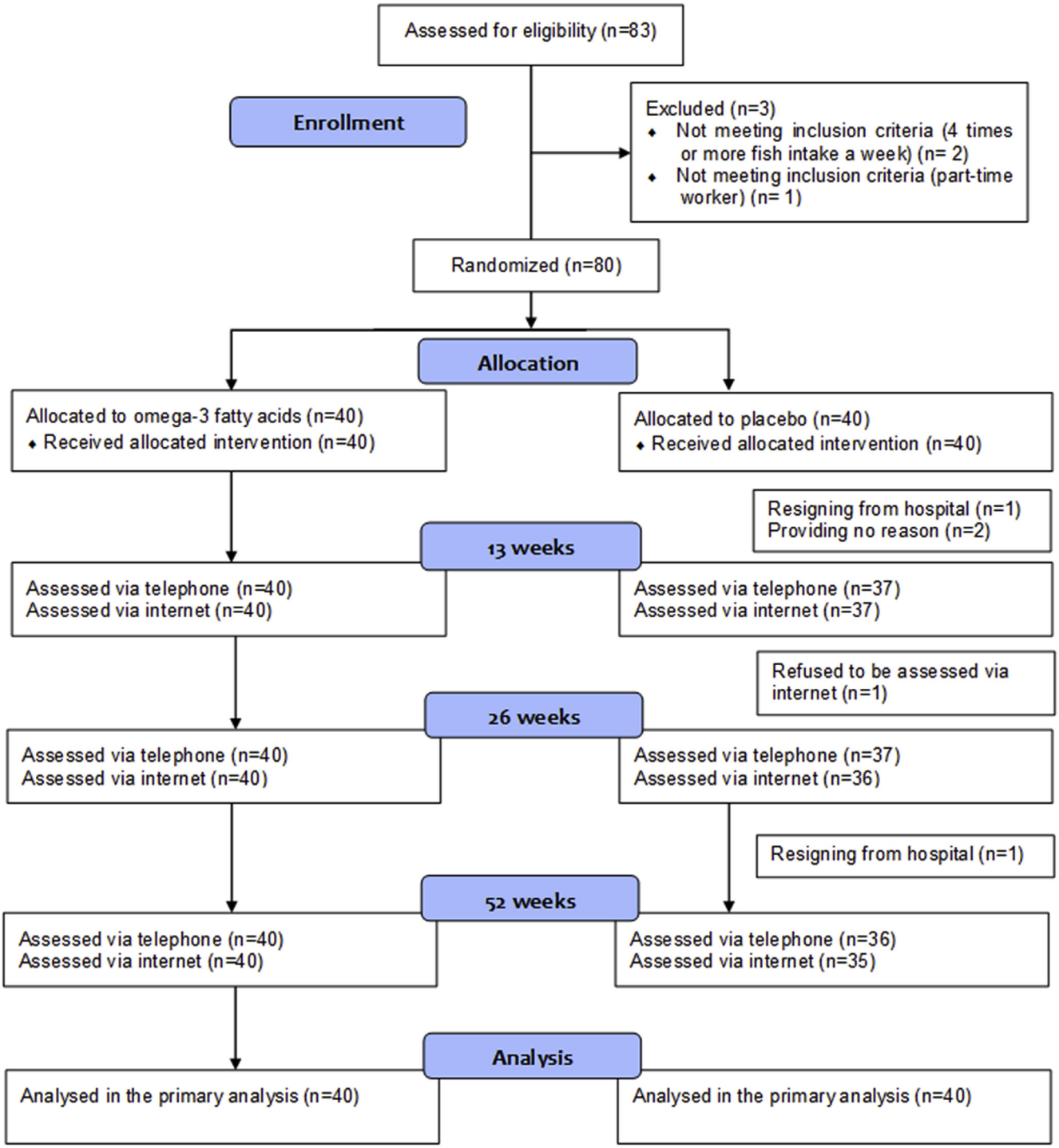

Fig. 1. Participant flow diagram.

populations not diagnosed for depression (Hallahan et al., 2016). Other trials not included in the systematic review and focusing on healthy participants also did not show additional benefit of omega-3 PUFAs in terms of mood (Antypa et al., 2009; van de Rest et al., 2008). Adding the results of optimal dose administration of omega-3 PUFAs from the present study to the current evidence, we would conclude that omega-3 PUFAs were unlikely to be a primary prevention strategy for depressive symptoms in mentally healthy people including working populations.

The present study is not without methodological limitations. First, we did not manage to recruit the number of participants we initially set from a power analysis in the protocol, probably because nurses in the hospitals might think participating in the present study would be burdensome or humiliating. However, our post-hoc analyses showed that the effect size (Cohen's d) (Cohen, 1988) of the primary outcome for the completers was −0.03, with 95% CIs from −0.48 to 0.42. Thus, even from the most optimistic view, the efficacy of PUFAs could only lead to small effect sizes. Hence, we believe that our conclusion that omega-3 PUFAs are unlikely to provide benefit in terms of preventing depression, is accurate.

Secondly, although we reminded participants to take assigned pills

Table 2
Estimated marginal means of Omega-3 and placebo arms for the continuous outcomes.

	Estimated marginal means: mean (95% confidence intervals of standard errors)			
	Baseline	Week 13	Week 26	Week 52
HADS total				
Omega-3 fatty acids	7.20 (6.00, 8.40)	6.40 (5.20, 7.60)	6.32 (5.13, 7.52)	5.85 (4.65, 7.05)
Placebo	7.11 (5.491, 8.31)	7.60 (6.36, 8.83)	6.81 (5.57, 8.05)	8.32 (7.07, 9.58)
Group by time interaction		1.28 (−0.64, 3.21)	0.58 (−1.35, 2.50)	2.56 (0.63, 4.50)
		P = 0.190	P = 0.557	P = 0.010
HADS depression				
Omega-3 fatty acids	3.24 (2.56, 3.92)	2.84 (2.16, 3.52)	2.69 (2.01, 3.37)	2.36 (1.68, 3.04)
Placebo	3.16 (2.50, 3.83)	3.54 (2.84, 4.24)	3.05 (2.35, 3.75)	3.80 (30.9, 4.51)
Group by time interaction		0.78(-0.27, 1.84)	0.45 (−0.61, 1.50)	1.52 (0.46, 2.58)
		P = 0.144	P = 0.404	P = 0.005
HADS anxiety				
Omega-3 fatty acids	3.97 (3.30, 4.64)	3.57 (2.90, 4.24)	3.65 (2.98, 4.32)	3.50 (2.83, 4.17)
Placebo	3.95 (3.28, 4.62)	4.05 (3.36, 4.74)	3.75 (3.06, 4.44)	4.51 (3.82, 5.21)
Group by time interaction		0.50 (−0.54, 1.53)	0.13 (−0.91, 1.16)	1.04 (−0.01, 2.08)
		P = 0.345	P = 0.812	P = 0.050
PHQ-9				
Omega-3 fatty acids	4.94 (4.02, 5.86)	5.42 (4.50, 6.33)	5.39 (4.47, 6.31)	5.42 (4.50, 6.33)
Placebo	4.82 (3.90, 5.74)	5.83 (4.78, 6.88)	5.31 (4.35, 6.26)	4.79 (3.83, 5.76)
Group by time interaction		0.53 (−0.89, 1.95)	0.04 (−1.39, 1.46)	−0.50 (−1.94, 0.93)
		P = 0.460	P = 0.960	P = 0.491
GAD-7				
Omega-3 fatty acids	3.08 (2.33, 3.83)	3.40 (2.65, 4.15)	3.85 (3.11, 4.60)	3.75 (3.01, 4.50)
Placebo	3.13 (2.38, 3.88)	3.45 (2.67, 4.22)	3.30 (2.52, 4.09)	3.73 (2.94, 4.52)
Group by time interaction		−0.01 (−1.18, 1.16)	−0.60 (−1.78, 0.57)	−0.08 (−1.26, 1.10)
		P = 0.986	P = 0.313	P = 0.893
Insomnia Severity Index				
Omega-3 fatty acids	5.94 (4.83, 7.06)	5.07 (3.96, 6.18)	6.09 (4.98, 7.21)	6.07 (4.96, 7.18)
Placebo	5.45 (4.36, 6.56)	6.62 (5.47, 7.77)	5.36 (4.20, 6.21)	5.34 (4.16, 6.51)
Group by time interaction		2.05 (0.34, 3.76)	−0.24 (−1.96, 1.47)	−0.24 (−1.96, 1.49)
		P = 0.019	P = 0.780	P = 0.786
MBI EE				
Omega-3 fatty acids	22.0 (19.3, 24.8)	21.7 (19.0, 24.4)	23.6 (20.9, 26.3)	22.0 (19.3, 24.8)
Placebo	20.8 (18.2, 23.6)	23.0 (20.2, 25.8)	22.3 (19.4, 25.1)	23.5 (20.6, 26.3)
Group by time interaction		2.47 (−2.69, 6.63)	−0.11 (−4.28, 4.07)	2.62 (−1.58, 6.81)
		P = 0.244	P = 0.960	P = 0.221
MBI DP				
Omega-3 fatty acids	6.92 (5.46, 8.38)	8.17 (6.71, 9.63)	8.00 (6.53, 9.46)	9.22 (7.76, 10.68)
Placebo	7.02 (5.60, 8.49)	7.78 (6.27, 9.30)	7.76 (6.23, 9.30)	8.44 (6.89, 10.00)
Group by time interaction		−0.49 (−2.93, 2.00)	−0.33 (−2.79, 2.12)	−0.88 (−3.35, 1.59)
		P = 0.694	P = 0.789	P = 0.484
MBI PA				
Omega-3 fatty acids	21.7 (19.7, 23.8)	20.3 (18.3, 22.4)	23.0 (21.0, 25.0)	22.3 (20.2, 24.3)
Placebo	22.0 (20.0, 24.1)	23.5 (21.4, 25.6)	21.2 (19.1, 23.4)	22.0 (19.9, 24.2)
Group by time interaction		2.88 (−0.28, 6.04)	−2.11 (−5.28, 1.06)	−0.56 (−3.75, 2.63)
		P = 0.00.74	P = 0.192	P = 0.728
Absolute presenteeism				
Omega-3 fatty acids	49.9 (44.4, 55.4)	53.2 (48.7, 57.8)	64.4 (59.9, 68.9)	62.4 (57.9, 66.9)
Placebo	51.7 (47.2, 56.3)	53.0 (48.4, 57.7)	59.9 (55.3, 64.6)	61.8 (57.0, 66.5)
Group by time interaction		−2.05 (−8.31, 4.21)	−6.29 (−12.56, 0.02)	−2.48 (−8.77, 3.82)
		P = 0.520	P = 0.049	P = 0.440
Relative presenteeism				
Omega-3 fatty acids	0.86 (0.78, 0.95)	0.92 (0.83, 1.01)	0.95 (0.86, 1.03)	0.88 (0.79, 0.96)
Placebo	0.90 (0.82, 0.99)	0.85 (0.76, 0.94)	0.86 (0.77, 0.95)	0.82 (0.73, 0.91)
Group by time interaction		−0.12 (−0.25, 0.02)	−0.13 (−0.27, 0.01)	−0.10 (−0.24, 0.03)
		P = 0.088	P = 0.056	P = 0.141
Utility score				
Omega-3 fatty acids	0.90 (0.86, 0.94)	0.84 (0.80, 0.88)	0.86 (0.82, 0.90)	0.87 (0.83, 0.92)
Placebo	0.92 (0.88, 0.97)	0.87 (0.83, 0.92)	0.87 (0.83, 0.92)	0.87 (0.82, 0.91)
Group by time interaction		1.1 (−0.06, 0.08)	−0.01 (−0.08, 0.06)	−0.03 (−0.10, 0.04)
		P = 0.813	P = 0.744	P = 0.376

Group by time interaction is presented as a coefficient, its 95% CIs, and P-value.
Abbreviations: HADS, Hospital Anxiety and Depression Scale; ISI, Insomnia Severity Index; MBI, Maslach's Burnout Inventory; PHQ-9, Patient Health Questionnaire.

regularly by sending monthly e-mails, adherence rates of taking pills, calculated by counting the remains, were the mean of 84% and the median of 90% in both the omega-3 PUFA and the placebo groups, respectively. These seem to be smaller than those in previous trials reporting actual adherence rates among participants in trials on the omega-3 PUFA intervention on mental states among non-clinical depressive participants, including 89% (Poppitt et al., 2009), 93% (Sinn et al., 2012), 96% (van de Rest et al., 2008), and around 97% (Kiecolt-Glaser et al., 2012).

Third, because fish consumption is higher in Japan than in other countries, one may doubt applicability of the findings about omega-3 PUFAs from the present study. A high consumption of fish has been reported to be correlated with a lower countrywide prevalence of major depression, according to a study published in 1998 (Hibbeln, 1998).

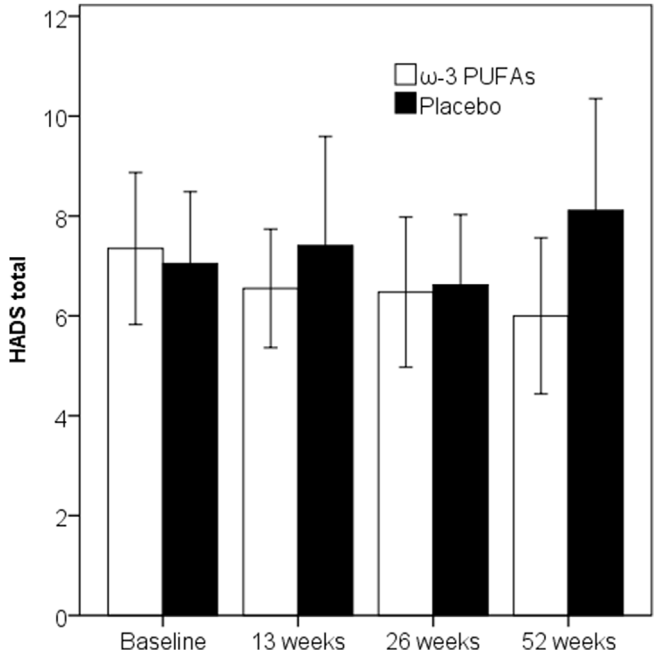

Fig. 2. Hospital Anxiety and Depression Scale scores for the assessment completers (N = 36)
Abbreviations: HADS, Hospital Anxiety and Depression Scale; PUFA, polysaturated
fatty acid.

However, we excluded participants who consumed fish as the main course of meal four or more times a week. We believe that our findings can be applied to the other countries.

Fourth, the overall effects of omega-3 PUFAs might be attenuated by counteracting effects of omega-6 PUFAs (Marventano et al., 2015). We did not collect information about diet including omega-3 PUFAs from the participants during the study, because we aimed a pragmatic trial. Future studies may need to investigate the association between the n-3: n-6 PUFAs ratio and incidence of depression.

5. Conclusion

The additive value of omega-3 PUFAs was not confirmed in terms of mental state and self-evaluated work efficiency in work populations. We do not recommend omega-3 PUFAs for the general population who are willing to maintain their mental health and looking for something beneficial.

Role of the funding source

This study was funded by Intramural Research Grant (25-8) for Neurological and Psychiatric Disorders of National Center of Neurology and Psychiatry, Japan. The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Potential conflicts of interests

The authors have no conflicts of interests to declare, that may be affected by the publication of the manuscript.

Dr Watanabe has received research funds from the Japanese Ministry of Health Labor and Welfare, the Japanese Ministry of Education, Science, and Technology and National Center of Neurology and Psychiatry, Intramural Research Grant for Neurological and Psychiatric Disorders. He has also received royalties from Sogensha and Akatsuki.

Dr Matsuoka has received a Grant-in-Aid for Scientific Research (B) from the Japan Society for the Promotion of Science, an intramural research grant for Neurological and Psychiatric Disorders from the National Center of Neurology and Psychiatry Japan (27-3-2), and a grant from Pfizer Health Research Foundation and SENSHIN Medical Research Foundation.

Dr Kumachi has received research funds from Japan Society for the Promotion of Science.

Dr Hamazaki received Grant-in-Aid for Scientific Research (C) (17K00849), a grant from the First Bank Foundation and intramural research Grant (27-3) for Neurological and Psychiatric Disorders from the National Center of Neurology and Psychiatry, Japan.

Dr Furukawa has received lecture fees from Eli Lilly, Janssen, Meiji, Mitsubishi-Tanabe, MSD and Pfizer. He has received royalties from Igaku-Shoin and Nihon Bunka Kagaku-sha publishers. He has received research support from Mitsubishi-Tanabe and Mochida. He is diplomate of the Academy of Cognitive Therapy.

All the other author reports no conflicts of interest.

Table 3
Numbers of participants satisfying secondary dichotomous outcomes at each assessment.

	Number satisfying the outcome/Number remained in the arm		
	Week 13	Week 26	Week 52
Major depressive episode			
Omega-3 fatty acids	1/39	4/40	4/40
Placebo	3/37	3/36	1/35
P-value for ITT analysis	P = 0.305	P = 0.692	P = 0.166
P-value for completers	P = 0.279	P = 0.802	P = 0.216
Consulting psychiatrists			
Omega-3 fatty acids	0/39	1/40	1/40
Placebo	0/37	0/36	1/35
P-value for ITT analysis		P = 0.340	P = 0.924
P-value for completers		P = 0.314	P = 1.000
Taking psychotropic medication			
Omega-3 fatty acids	0/39	1/40	0/40
Placebo	0/37	1/36	1/35
P-value for ITT analysis		P = 1.000	P = 0.282
P-value for completers		P = 1.000	P = 0.314
Adverse events			
Dropouts due to adverse events			
Omega-3 fatty acids	0/39	0/40	0/40
Placebo	0/37	0/36	0/35
Any adverse events			
Omega-3 fatty acids	3/39	1/40	0/40
Placebo	1/37	1/36	0/35
Headache			
Omega-3 fatty acids	1/39	1/40	0/40
Placebo	0/37	0/36	0/35
Nausea			
Omega-3 fatty acids	2/39	0/40	0/40
Placebo	1/37	1/36	0/35
Depression			
Omega-3 fatty acids	0/39	1/40	0/40
Placebo	0/37	0/36	0/35
Other			
Omega-3 fatty acids	1/39	0/40	0/40
Placebo	1/37	1/36	0/35

Abbreviations: ITT, intention to treat.

Contributors

Norio Watanabe - Participated in the conception and design of the

study, recruited participants, collected data, performed the analysis and wrote the manuscript.

Yutaka Matsuoka - Participated in the conception and design of the study, and recruited participants.

Mie Kumachi - Participated in the conception and design of the study, recruited participants, and collected data.

Kei Hamazaki - Participated in the conception and design of the study, and collected data.

Masaru Horikoshi - Participated in the conception and design of the study.

Toshi A. Furukawa - Participated in the conception and design of the study, collected data, and performed the analysis.

All authors revised the article critically for important intellectual content and approved the final manuscript.

Disclaimer statements

None.

Previous presentation

None.
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Acknowledgement of assistance

We thank all the collaborators (Tomomi Narisawa, CP, Miyuki Makino, CP, RN, Yuki Oe, CP, Issei Shinmei, CP at National Center of Neurology and Psychiatry, and Masato Usuki, MD, PhD at National Disaster Medical Center), technical assistant staff (Shizuko Takebe at University of Toyama), and the administrative staff (Mayuko Yamano at National Center of Neurology and Psychiatry). We also thank Shinako Ushijima, RN at National Center of Neurology and Psychiatry Hospital, Keiko Osada, RN and Masami Harasawa, RN at National Disaster Medical Center, Miyuki Hatada, RN and Noriko Miyajima, RN at Tokyo Metropolitan Tama Medical Center, Chieko Kosaka, RN and Masako Tanaka, RN at Tama-Hokubu Medical Center, and Jun-ichi Watanabe, RN at Inokashira Hospital for their great assistance in recruiting participants in the study.

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