



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

Norio Watanabe<sup>a,\*</sup>, Yutaka Matsuoka<sup>b</sup>, Mie Kumachi<sup>c</sup>, Kei Hamazaki<sup>d</sup>, Masaru Horikoshi<sup>e</sup>, Toshi A. Furukawa<sup>a</sup>

<sup>a</sup> Department of Health Promotion and Human Behavior and of Clinical Epidemiology, Kyoto University Graduate School of Medicine / School of Public Health, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan

<sup>b</sup> Division of Health Care Research, Center for Public Health Sciences, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, 104-0045 Tokyo, Japan

<sup>c</sup> Psychiatric Mental Health Nursing, Japanese Red Cross Akita College of Nursing, 17-3 Azananawashirozawa, Kamikitatesaruta, Akita 010-1493, Japan

<sup>d</sup> Department of Public Health, Faculty of Medicine, University of Toyama, 3190 Gofuku, Toyama 930-8555, Japan

<sup>e</sup> National Center for Cognitive Behavior Therapy and Research, National Center of Neurology and Psychiatry, 4-1-1 Ogawahigashicho, Kodaira, Tokyo 187-0031, Japan

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### 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

\* Corresponding author.

E-mail addresses: [watanabe.norio.6x@kyoto-u.ac.jp](mailto:watanabe.norio.6x@kyoto-u.ac.jp) (N. Watanabe), [yumatsuo@ncc.go.jp](mailto:yumatsuo@ncc.go.jp) (Y. Matsuoka), [leoaru47@gmail.com](mailto:leoaru47@gmail.com) (M. Kumachi), [keihama@med.u-toyama.ac.jp](mailto:keihama@med.u-toyama.ac.jp) (K. Hamazaki), [mhorikoshi@ncnp.go.jp](mailto:mhorikoshi@ncnp.go.jp) (M. Horikoshi), [furukawa@kuhp.kyoto-u.ac.jp](mailto:furukawa@kuhp.kyoto-u.ac.jp) (T.A. Furukawa).

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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 (Vltmer 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  $\geq 11$  (Kugaya

et al., 1998) or not; and working as a nurse for  $\geq 1$  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  $\geq 9$  for possible cases and  $\geq 11$  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 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.,

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