Eicosapentaenoic Acid Intake Associated with Reduced Risk of Posttraumatic Stress Disorder after the Great East Japan Earthquake and Tsunami

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Abstract

Posttraumatic stress disorder (PTSD) is a debilitating condition characterized by intrusion, avoidance, hyperarousal symptoms after exposure to traumatic events. Since polyunsaturated fatty acids (PUFAs) have been implicated, we examined the possible association of PTSD with plasma PUFA level and dietary fish intake in 563 women who was struck by the Great East Japan Earthquake and Tsunami. The impact event scale-revised (IES-R) was used to assess PTSD symptoms. Dietary intake was estimated by a self-report questionnaire. Multivariate analysis controlling for age, body mass index, and stress revealed that PTSD status (IES-R $\geq 25$) was associated with plasma eicosapentaenoic acid (EPA) level ($P = 0.039$). In the high-stress group, there were significantly inverse correlations of plasma EPA with IES-R total ($r = -0.389, P = 0.031$), intrusion ($r = -0.370$, $P = 0.04$), and hyperarousal scores ($r = -0.480, P = 0.006$), although such correlations were not found in the moderate-stress group. Fish intake that increased plasma EPA showed similar correlations with IES-R scores in the severely stressed group. Our results suggest that higher plasma EPA level and EPA-increasing fish intake are associated with a lower risk for PTSD in individuals who have suffered severe stress in a natural disaster.

Keywords: posttraumatic stress disorder, Great East Japan Earthquake, eicosapentaenoic acid, nutrition

1. Introduction

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric condition characterized by intrusion, avoidance, hyperarousal, and other symptoms, which occurs in response to an array of traumatic events including physical, sexual, or mental abuse; wartime experiences; or being the victim of a violent crime [1]. The resulting stress can cause a pro-inflammatory response in the brain characterized
primarily by the complex release of inflammatory mediators such as cytokines, prostanooids, free radicals, and transcription factors, as well as subsequent brain inflammatory responses, which further contribute to cell damage [2, 3]. Conventional treatment for PTSD includes pharmacotherapy, psychotherapy, and psychophysiological therapy, although it is often resistant to these treatments [4].

An alternative strategy might be the use of diet or nutritional care, particularly those focusing on polyunsaturated fatty acids (PUFAs) such as eicosapentaenoic acid (EPA; C20: 5n-3), docosahexaenoic acid (DHA; C22: 6n-3), and arachidonic acid (AA; C20: 4n-6) in preventing and treating PTSD [5]. A series of studies by Matsuoka and colleagues [6–9] reported that the effect of DHA on the prevention of PTSD was minimal; however, subsequent elevation of EPA level in erythrocytes was correlated with less PTSD symptoms and better quality of life. However, there is a dearth of studies on the possible relationship between blood levels of PUFAs and the risk of PTSD. The same research group found that AA and EPA levels in the serum were both inversely related to the risk for PTSD in subjects of post-motor vehicle accident [10]. Kalinic et al. reported inverse correlations of EPA, but not AA or DHA, levels in the serum with the severity of combat-related PTSD symptoms in Croatian war veterans [11]. These results were, at least in part, inconsistent, which requires further investigations.

In the present study, we examined the relationships of plasma levels and dietary intake of PUFAs with the development of PTSD among women who lived in Kitaibaraki city and struck by the Great East Japan Earthquake and Tsunami on March 11, 2011.

2. Subjects and methods

2.1 Study population

The study population consisted of volunteers who were living in the earthquake disaster zone in Kitaibaraki, Japan, a city with a population of approximately 45,000. Our study was conducted from November 2011 to August 2012. Participants were selected based on the following criteria: females who were 20 years or older on November 1, 2011 and were able to come to a local hospital on their own. The study population was limited to females in order to eliminate the gender differences reported in the response to traumatic events [12] and in effects of PUFAs [6].

Our study population comprised 563 women (mean age: 53.3 ± 15.8). A total of 113 out of the 563 participants lived along the coastline where the impact of the tsunami was particularly high. The study was fully explained to all potential participants, after which written informed consent to the participation was obtained. This study was conducted in accordance with the declaration of Helsinki [13] and approved by the ethics committees of the University of Tsukuba and the National Center of Neurology and Psychiatry, Japan.

2.2 Dividing the study population into four groups

The study population was then ultimately divided into four groups through a two-stage process: first determining stress exposure and second determining the presence of PTSD. Participants were initially asked to fill out an original four-item questionnaire developed by our group. This questionnaire is designed to assess the degree of exposure to stress caused by the earthquake and tsunami and provide a total impact score. These four items inquired the occurrence of: (1) severe injury or death among close relatives (one point per person), (2) severe inundation-related...
damage to house or apartment of the participant, (3) partial or complete destruction of a housing unit and/or household belongings, and (4) significant decrease in income. The study population was then divided into a high stress group and moderate stress group based on the results of the questionnaire. The high stress group was defined as including participants who were impacted by three or more of the abovementioned items. The moderate stress group was defined as those participants who were impacted by two or less of the items.

Next, these high-stress and moderate-stress groups were each further divided into two groups: those participants with PTSD (PTSD group) and those without PTSD (non-PTSD group) based on the IES-R questionnaire. Figure 1 shows the numbers of individuals for the four groups of high-stress/PTSD, high-stress/non-PTSD, moderate-stress/PTSD, and moderate-stress/non-PTSD.

### 2.3 IES-R questionnaire

The Japanese version of IES-R questionnaire was used to screen for PTSD symptoms because IES-R is the most widely used questionnaire in all forms of disaster-area research [14, 15]. This questionnaire consists of 22 items that comprise three subscales of intrusion (8 items), avoidance (8 items), and hyperarousal (6 items). IES-R evaluates symptom severity using a 5-point scale (0–4) for the previous 1-week period. PTSD was defined as present when the IES-R score was 25 or more, according to a previous study [16].

### 2.4 Assessment of dietary intake

Dietary intake was assessed using the brief-type self-administered diet history questionnaire (BDHQ) [17, 18]. This questionnaire assesses diet habits in the preceding month. Dietary intake, particularly fish intake, was calculated using an ad hoc computer algorithm (including weighting factors) designed specifically for the BDHQ. Dietary intake was adjusted by using the nutrient density method defined as the percentage of energy for energy-providing nutrients and amount per 1000 kcal of energy for other nutrients. In BDHQ, fish intake was assessed by six categories: category 1 (C1): squid, shrimp, lobster, and shellfish; C2: whole-eat fish; C3: canned tuna; C4: dried fish/salted fish; C5: oil-rich fish; and C6: non-oil-rich fish.

![Figure 1](image_url)
2.5 Measurement of plasma fatty acids

Non-fasting venous blood samples were collected between the hours of 9:00 and 15:00 from each participant to determine the plasma levels of EPA, DHA, and AA. These samples were collected in tubes containing ethylenediaminetetraacetic acid (EDTA) and were centrifuged at 3000g for 10 min. Plasma fatty acids were measured by gas chromatography (Gas Chromatograph, Model GC-2010, Shimadzu Corporation, Japan) [19] at the SRL Inc. (Tokyo Japan).

2.6 Statistical analysis

Participant characteristics, biochemical, and nutritional data are presented as mean ± standard deviation (SD) or the number of persons. Analysis of variance (ANOVA) was used to examine differences in demographic and clinical variables between the high-stress and moderate-stress groups as well as between the PTSD and non-PTSD groups. The X² test for independence was used to compare the prevalence of PTSD between high- and moderate-stress groups. Differences in values between PTSD and non-PTSD were examined for the blood test results and nutrients assessed by BDHQ using two-way multiple analysis of covariance (MANCOVA) after adjustment for age and body mass index (BMI). Partial correlation analysis adjusting for age and BMI was used to examine relationships of plasma EPA level and fish intake with IES-R scores. Analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 21.0 (SPSS Japan, Tokyo). Statistical significance was set at two-tailed P < 0.05.

3. Results

3.1 Characteristics of the study participants

The characteristics of the study participants are shown for the high- and moderate-stress groups after each group was further divided into PTSD and non-PTSD groups (Table 1). No significant differences were found in age, BMI, or education between the high- and moderate-stress groups or between the PTSD and non-PTSD groups. As expected, the degree of exposure to stress of the high-stress group was significantly higher than the moderate-stress group. The prevalence of PTSD was 55% for the high-stress group and 17% for the moderate-stress group [X² = 27.8, df = 1, P = 0.00000013, Cramer’s V = 0.22, odds ratio; 5.8, 95% confidence interval (CI): 2.8–11.9]. As expected, the PTSD group exhibited significantly higher scores for the total IES-R score as well as the intrusion, avoidance, and hyperarousal subscales than the non-PTSD group.

3.2 Association between plasma EPA level and PTSD

Plasma PUFA concentrations for the four groups are shown in Table 2. MANCOVA analysis controlling for age and BMI revealed that PTSD was significantly associated with plasma EPA level [F(1, 557) = 4.27, P = 0.039, partial η² = 0.008], but not with DHA [F(1, 557) = 1.98, P = 0.16, partial η² = 0.004], or AA [F(1, 557) = 0.186, P = 0.174, partial η² = 0.003] and that there was a non-significant association between PTSD and EPA/AA ratio [F(1, 557) = 3.28, P = 0.071, partial η² = 0.006]. It also detected a stress × PTSD interaction effect on plasma EPA level at a trend level [F(1, 557) = 3.281, P = 0.091, partial η² = 0.005]. As shown in Table 2, mean plasma EPA level was substantially higher in the non-PTSD group than in the PTSD group among individuals who had high stress, while it was similar for the PTSD and non-PTSD groups among
### Characteristics

| Characteristics               | High stress | Moderate stress | F value; partial $\eta^2$ | P value; high stress v. moderate stress | F value; partial $\eta^2$ | P value; PTSD v. non-PTSD |
|------------------------------|-------------|----------------|---------------------------|----------------------------------------|---------------------------|----------------------------|
| Age (years)                  | $578 \pm 14.3$ | $57.7 \pm 13.2$ | $54.6 \pm 16.7$ | $52.7 \pm 15.7$ | $F(1, 559) = 2.032$; partial $\eta^2 = 0.004$ | 0.155 | $F(1, 559) = 0.111$; partial $\eta^2 = 0.000$ | 0.739 |
| BMI (kg/cm$^2$)              | $24.7 \pm 4.9$ | $24.1 \pm 3.6$ | $23.6 \pm 3.9$ | $23.1 \pm 3.8$ | $F(1, 559) = 2.204$; partial $\eta^2 = 0.004$ | 0.138 | $F(1, 559) = 0.487$; partial $\eta^2 = 0.001$ | 0.486 |
| Education (years)            | $12.2 \pm 2.4$ | $12.0 \pm 2.2$ | $11.4 \pm 1.9$ | $12.2 \pm 2.2$ | $F(1, 559) = 0.626$; partial $\eta^2 = 0.001$ | 0.429 | $F(1, 559) = 0.402$; partial $\eta^2 = 0.001$ | 0.526 |

### The degree of exposure to stress

| Characteristics               | F value; partial $\eta^2$ | P value; PTSD v. non-PTSD |
|------------------------------|---------------------------|----------------------------|
| Total points                 | $F(1, 559) = 240.1$; partial $\eta^2 = 0.3$ | <0.001 | $F(1, 559) = 0.644$; partial $\eta^2 = 0.001$ | 0.423 |
| Death or injury in relatives, n (%) | $F(1, 559) = 45.87$; partial $\eta^2 = 0.076$ | <0.001 | $F(1, 559) = 0.487$; partial $\eta^2 = 0.001$ | 0.216 |
| Inundation damage, n (%)     | $F(1, 559) = 203.1$; partial $\eta^2 = 0.266$ | <0.001 | $F(1, 559) = 0.402$; partial $\eta^2 = 0.001$ | 0.445 |
| Material damage, n (%)       | $F(1, 559) = 12.1$; partial $\eta^2 = 0.021$ | 0.001 | $F(1, 559) = 0.402$; partial $\eta^2 = 0.001$ | 0.512 |
| Decreased income, n (%)      | $F(1, 559) = 88.3$; partial $\eta^2 = 0.004$ | <0.001 | $F(1, 559) = 0.487$; partial $\eta^2 = 0.001$ | 0.387 |

### IES-R, RIES-R

| Characteristics               | High stress | Moderate stress | F value; partial $\eta^2$ | P value; PTSD v. non-PTSD |
|------------------------------|-------------|----------------|---------------------------|----------------------------|
| IES-R score                  | $38.8 \pm 14.3$ | $13.7 \pm 6.5$ | $37.9 \pm 12.4$ | $8.7 \pm 6.8$ | $F(1, 559) = 3.629$; partial $\eta^2 = 0.006$ | 0.057 | $F(1, 559) = 0.318$; partial $\eta^2 = 0.363$ | <0.001 |
| IES-R intrusion              | $14.5 \pm 6.5$ | $5.4 \pm 2.7$ | $14.3 \pm 5.3$ | $3.4 \pm 3.0$ | $F(1, 559) = 2.647$; partial $\eta^2 = 0.005$ | 0.104 | $F(1, 559) = 2.273$; partial $\eta^2 = 0.289$ | <0.001 |
### Characteristics of the Study Participants (n = 563)

| Characteristics          | High Stress       | Moderate Stress    | F value; partial \( \eta^2 \) | P value; PTSD v. Non-PTSD |
|--------------------------|-------------------|-------------------|-------------------------------|---------------------------|
|                          | PTSD (n = 18)     | Non-PTSD (n = 15) |                 |                           |
| IES-R avoidance          | 13.7 ± 4.9        | 5.4 ± 2.9         | \( F(1, 559) = 3.50; \) partial \( \eta^2 = 0.006 \) | 0.062                     |
|                          | 13.5 ± 4.9        | 3.1 ± 3.4         | \( F(1, 559) = 182.7; \) partial \( \eta^2 = 0.246 \) | \(<0.001\)                |
| IES-R hyperarousal       | 10.6 ± 5.2        | 2.9 ± 1.6         | \( F(1, 559) = 0.670; \) partial \( \eta^2 = 0.001 \) | 0.414                     |
|                          | 10.1 ± 4.4        | 2.4 ± 2.3         | \( F(1, 559) = 214.9; \) partial \( \eta^2 = 0.278 \) | \(<0.001\)                |

\( P \) value for differences among high stress and moderate stress, as well as PTSD and non-PTSD were calculated by using analysis of variance (ANOVA). Significant results are indicated in bold letters.

Mean ± SD (standard deviation, all such values).

IES-R, impact event scale-revised.
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| Fatty acid | High stress | Moderate stress | $F$ value; partial $\eta^2$ | $P$; PTSD v. non-PTSD |
|-----------|-------------|-----------------|-----------------------------|------------------------|
|           | PTSD ($n = 18$) | Non-PTSD ($n = 15$) | PTSD ($n = 91$) | Non-PTSD ($n = 439$) |
| EPA       | 77.0 ± 33.5  | 107.4 ± 67.4    | 77.3 ± 43.3  | 76.9 ± 53.9  | $F(1, 559) = 4.27$; partial $\eta^2 = 0.008$ | 0.039* |
| DHA       | 168.8 ± 41.8 | 191.8 ± 65.6    | 168.9 ± 60.5 | 166.5 ± 63.6 | $F(1, 559) = 1.98$; partial $\eta^2 = 0.004$ | 0.160 |
| AA        | 196.8 ± 49.6 | 207.6 ± 50.6    | 186.7 ± 29.3 | 194.1 ± 42.3 | $F(1, 559) = 1.86$; partial $\eta^2 = 0.003$ | 0.174 |
| EPA/AA    | 2.40 ± 1.19  | 3.41 ± 2.06     | 2.45 ± 1.66  | 2.48 ± 1.94  | $F(1, 559) = 3.28$; partial $\eta^2 = 0.006$ | 0.071 |

AA, arachidonic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; and AA/EPA, ratio. Significant differences in plasma PUFA concentrations were found using analysis of covariance (ANCOVA) analysis after adjustment for age and BMI. Mean ± SD (all such values). *$P < 0.05$.

Table 2.
Plasma fatty acid concentrations ($\mu$g/mL) for the four groups stratified by the stress level and the presence of PTSD ($n = 563$).

![Figure 2](image-url)

Scatter plots of plasma EPA level with IES-R scores in the high-stress group. (a) IES-R total, (b) intrusion, (c) avoidance, and (d) hyperarousal. IES-R, impact event scale-revised; $r$, partial correlation coefficient, controlling for age and BMI.
3.3 Negative correlation between plasma EPA level and PTSD symptoms

Since plasma EPA was found to be associated with PTSD, we then performed the partial correlation analyses between plasma EPA level and IES-R scores, controlling for age and BMI for the high stress and moderate stress groups separately. In the high-stress group, there were significant inverse correlations of plasma EPA level with total score ($r = -0.389$, $P = 0.031$), intrusion ($r = -0.370$, $P = 0.04$), and hyperarousal ($r = -0.480$, $P = 0.006$), but not with avoidance score ($r = -0.240$, $P = 0.19$) (Figure 2). In the moderate-stress group, however, there was no significant correlation (total score: $r = 0.020$, $P = 0.64$; intrusion: $r = -0.009$, $P = 0.84$; avoidance: $r = 0.020$, $P = 0.65$).

3.4 Association of dietary fish intake and PTSD

Initially, we examined the partial correlation between fish intake and plasma EPA level in the total subjects ($N = 563$), controlling for age and BMI. Among the six categories of the fish intake (see Section 2), categories 2, 4, 5, and 6 showed a highly significant correlation with plasma EPA (C2: $r = 0.127$, $P = 0.003$; C4: $r = 0.288$, $P < 0.001$; C5: $r = 0.197$, $P < 0.001$; C6: $r = 0.158$, $P < 0.001$), while categories 1 and 3 did not (both $P > 0.05$). Then, we summed fish intakes of categories 2, 4, 5, and 6 (i.e., $C2 + C4 + C5 + C6$) to make a variable of “EPA-correlated fish intake.” This variable was used for the analysis of the relationship between fish intake and PTSD.

those who had moderate stress. This raises the possibility that higher plasma EPA may have a protective effect on the development of PTSD in the high-stress group.

Figure 3.
Scatter plots of EPA-correlated fish intake with IES-R scores in the high-stress group. (a) IES-R total, (b) intrusion, (c) avoidance, and (d) hyperarousal. IES-R, impact event scale-revised; r, partial correlation coefficient, controlling for age and BMI. As shown, there was one individual who had exceptionally high fish intake, which may have biased the results. Even when this individual was excluded, there remained inverse correlations of EPA-correlated fish intake, at least at a trend level, with IES-R total score ($r = -0.352$, $P = 0.057$), intrusion ($r = -0.343$, $P = 0.065$), and hyperarousal ($r = -0.412$, $P = 0.024$), but not with avoidance score ($r = -0.224$, $P = 0.23$). EPA-related fish intake (g/1000 kcal): energy adjusted values by density method (g/1000 kcal).
When analyses were performed similarly to plasma EPA, EPA-correlated fish intake tended to be greater in the non-PTSD group than in the PTSD group \(F(1, 29) = 2.99, P = 0.094, \text{partial } \eta^2 = 0.094\) in the high-stress group. Such relationship was not found in the moderate-stress group (data not shown).

Then, we performed partial correlation analyses between EPA-correlated fish intake and IES-R scores. In individuals who experienced high stress, there were significant inverse correlations of EPA-correlated fish intake with IES-R total score (\(r = -0.377, P = 0.037\), intrusion (\(r = -0.370, P = 0.041\)), and hyperarousal (\(r = -0.393, P = 0.029\)), but not with avoidance score (\(r = -0.290, P = 0.11\)) (Figure 3). In those who had moderate stress, however, there was no significant correlation (data not shown).

4. Discussion

Our main findings can be summarized as follows. Plasma EPA level was higher in the non-PTSD group than in the PTSD group among individuals with high stress but not among those with moderate stress. There was a negative correlation of plasma EPA level with IES-R total, intrusion, and hyperarousal scores in the high stress group. Likewise, EPA-related fish intake showed a negative correlation of plasma EPA level with IES-R total, intrusion, and hyperarousal scores in the high stress group. To our knowledge, this is the first study that elucidated the relationships of plasma EPA as well as fish intake with PTSD in a community sample who suffered from a major natural disaster.

The observed inverse correlations of plasma EPA level with IES-R scores in our study are consistent with the results of Kalinic et al. [11]. Another previous study reported that EPA and AA levels in the serum were both inversely related to the risk for PTSD in subjects of post-motor vehicle accident [10]. However, we did not find such an association for AA. We found no significant correlation of EPA or fish intake with avoidance score. One possible reason for this lack of correlation might be that our subjects were recruited from those who remained to be living in the disaster area and thus people who could not live the area because of avoidance had not been enrolled in the study.

Although the cross-sectional nature of the study precludes to determine the causal relationship, our findings raise the possibility that dietary intake or supplement to increase EPA level has a protective effect on the development of PTSD in severely stressed people. In line, there is some evidence that increase in EPA reduces the risk of PTSD. Matsuoka et al. examined the effect of DHA/EPA capsules (1 capsule: 320 mg of oil with 70% DHA and 7% EPA, 7 capsules/day) on the development of PTSD among Japanese disaster medical assistance team members after the Great East Japan Earthquake and Tsunami [6]. The DHA/EPA capsules were found to only slightly reduce PTSD symptoms among female members; however, it had no effect among male members, suggesting that DHA has no major benefit in the prevention of PTSD. However, subsequent secondary analyses revealed that elevation in erythrocyte EPA levels after the supplementation seem to be effective in alleviation of PTSD symptoms and QOL [8, 9]. These findings are consistent with our findings that plasma EPA, but not DHA, was associated with PTSD.

In our analyses, plasma EPA level was highly positively correlated with fish intake of categories 2, 4, 5, and 6, that is, whole-eat fish, dried fish/salted fish, oil-rich fish, and non-oil-rich fish. This means that eating habits are strongly reflected in plasma EPA, and taking EPA-correlated fishes may have a beneficial effect. Notably, the Great East Japan Earthquake and Tsunami caused the Fukushima nuclear power plant accident. The release of radioactive water from the nuclear power station had a negative impact upon fish consumption in the adjacent areas, including Kitaibaraki city, which may have further increased the risk of PTSD.
Accumulating evidence has suggested that inflammation plays an important role in the pathogenesis of PTSD [3]. The meta-analysis of 20 studies revealed that PTSD is associated with increased interleukin 6, interleukin 1β, TNFα, and interferon γ levels, suggesting chronic low-grade inflammation as a potential target or biomarker in PTSD treatment [20]. Recently, our group obtained further evidence for increased IL-6 in female PTSD patients, most of whom developed the illness after domestic violence, compared with controls [21]. EPA together with DHA are capable of inhibiting many aspects of inflammation including leucocyte chemotaxis, adhesion molecule expression and leucocyte-endothelial adhesive interactions, production of eicosanoids like prostaglandins and leukotrienes from the n-6 fatty acid arachidonic acid, and production of pro-inflammatory cytokines [22]. Local-acting lipid mediators termed resolvins and protectins generated from EPA and DHA have also been known to resolve inflammation and protect the tissue [23]. EPA and DHA offer different benefits, and the suppressive effect of EPA on cytokine production seems to be more pronounced as compared to DHA [24]. EPA is rapidly oxidized in the brain, and thus, it has a short lifespan [25]. Therefore, the brain may need a constant supply of EPA to inhibit neuroinflammation.

This study had several limitations. First, we used non-fasting blood samples for PUFA measurement. However, it has been suggested that fasting is largely unnecessary for routine lipid level determinations [26]. Indeed, plasma EPA level well correlated with recent fish intake (i.e., C2, C4, C5, C6) in our subjects. Second, we assessed PTSD symptoms by using the IES-R questionnaire rather than a structured interview by clinicians (e.g., clinician-administered PTSD scale by Blake et al. [27]). Third, the assessment of food intake was also performed by self-report brief questionnaire (BDHQ). Finally, the sample size was small, particularly for the subjects who experienced high stress (N = 33). Further studies in a larger sample size will be required to draw more robust results.

5. Conclusion

We examined the association of plasma PUFA levels and dietary fish intake with the development of PTSD in a population-based sample of 563 women struck by the Great East Japan Earthquake and Tsunami. Plasma EPA level was higher in the non-PTSD group than in the PTSD group among individuals with high stress but not among those with moderate stress. There was a negative correlation of plasma EPA level with IES-R total, intrusion, and hyperarousal scores in the high stress group. Similarly, EPA-related fish intake showed a negative correlation of plasma EPA level with IES-R total, intrusion, and hyperarousal scores in the high stress group. Taken together, higher plasma EPA level and EPA-increasing fish intake are associated with lower risk for PTSD in individuals who have experienced severe stress in a natural disaster. Our findings provide support for the use of nutritional intervention in preventing and alleviating PTSD.

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S.S. & T.A.: Conception and design of the study. H.K.: Conception and design of the study, supervision of the study, and manuscript writing. This study was supported by a Health and Labor Sciences Research Grant for Comprehensive Research on Persons with Disabilities (T.A. & H.K.).

**Conflict of interest**

None of the authors have any conflicts of interest.

**Abbreviations**

- **AA**: arachidonic acid
- **ANOVA**: analysis of variance
- **BDHQ**: brief-type self-administered diet history questionnaire
- **DHA**: docosahexaenoic acid
- **EPA**: eicosapentaenoic acid
- **IES-R**: impact event scale-revised
- **MANCOVA**: multiple analysis of covariance
- **PTSD**: posttraumatic stress disorder
- **PUFA**: polyunsaturated fatty acid
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References

[1] Javidi H, Yadollahie M. Post-traumatic stress disorder. Indian Journal of Occupational and Environmental Medicine. 2012;3:2-9

[2] Wilson CB, McLaughlin LD, Nair A, Ebenezer PJ, Dange R, Francis J. Inflammation and oxidative stress are elevated in the brain, blood, and adrenal glands during the progression of post-traumatic stress disorder in a predator exposure animal model. PLoS One. 2013;8:e76146

[3] Hori H, Kim Y. Inflammation and post-traumatic stress disorder. Psychiatry and Clinical Neurosciences. 2019;73:143-153. DOI: 10.1111/pcn.12820

[4] Watts BV, Schnurr PP, Mayo L, Young-Xu Y, Weeks WB, Friedman MJ. Meta-analysis of the efficacy of treatments for posttraumatic stress disorder. The Journal of Clinical Psychiatry. 2013;74:e541-e550

[5] Hashimoto M, Maekawa M, Katakura M, Hamazaki K, Matsuoka Y. Possibility of polyunsaturated fatty acids for the prevention and treatment of neuropsychiatric illnesses. Journal of Pharmacological Sciences. 2014;124:294-300

[6] Matsuoka Y, Nishi D, Nakaya N, Sone T, Hamazaki K, Hamazaki T, et al. Attenuating posttraumatic distress with omega-3 polyunsaturated fatty acids among disaster medical assistance team members after the Great East Japan Earthquake: The APOP randomized controlled trial. BMC Psychiatry. 2011;11:132

[7] Matsuoka Y, Nishi D, Hamazaki K, Yonemoto N, Matsumura K, Noguchi H, et al. Docosahexaenoic acid for selective prevention of posttraumatic stress disorder among severely injured patients: A randomized, placebo-controlled trial. The Journal of Clinical Psychiatry. 2015;76:e1015-e1022

[8] Matsuoka YJ, Hamazaki K, Nishi D, Hamazaki T. Change in blood levels of eicosapentaenoic acid and posttraumatic stress symptom: A secondary analysis of data from a placebo-controlled trial of omega3 supplements. Journal of Affective Disorders. 2016;205:289-291

[9] Noguchi H, Nishi D, Matsumura K, Hamazaki K, Hamazaki T, Matsuoka YJ. Limited effect of omega-3 fatty acids on the quality of life in survivors of traumatic injury: A randomized, placebo-controlled trial. Prostaglandins, Leukotrienes, and Essential Fatty Acids. 2017;127:1-5

[10] Matsuoka Y, Nishi D, Hamazaki K. Serum levels of polyunsaturated fatty acids and the risk of posttraumatic stress disorder. Psychotherapy and Psychosomatics. 2013;82:408-410

[11] Kalinic D, Borovac Stefanovic L, Jeroncic A, Mimica N, Dodig G, Delas I. Eicosapentaenoic acid in serum lipids could be inversely correlated with severity of clinical symptomatology in Croatian war veterans with posttraumatic stress disorder. Croatian Medical Journal. 2014;55:27-37

[12] Gill JM, Szanton SL, Page GG. Biological underpinnings of health alterations in women with PTSD: A sex disparity. Biological Research for Nursing. 2005;7:44-54

[13] World Medical Association. World medical association declaration of Helsinki: Ethical principles for medical research involving humansubjects. JAMA. 2000;284:3043-3045

[14] Asukai N, Kato H, Kawamura N, et al. Reliability and validity of the Japanese-language version of the impact of event scale-revised (IES-R-J): Four
studies of different traumatic events. The Journal of Nervous and Mental Disease. 2002;190:175-182

[15] Horowitz M, Wilner N, Alvarez W. Impact of event scale: A measure of subjective stress. Psychosomatic Medicine. 1979;41:209-218

[16] Numata T, Gunfan S, Takayama S, Takahashi S, Monma Y, Kaneko S, et al. Treatment of posttraumatic stress disorder using the traditional Japanese herbal medicine saikokeishikakyoto: A randomized, observer-blinded, controlled trial in survivors of the Great East Japan Earthquake and Tsunami. Evidence-based Complementary and Alternative Medicine. 2014;2014:683293

[17] Sasaki S, Yanagibori R, Amano K. Self-administered diet history questionnaire developed for health education: A relative validation of the test-version by comparison with 3-day diet record in women. Journal of Epidemiology. 1998;8:203-215

[18] Kobayashi S, Murakami K, Sasaki S, Okubo H, Hirota N, Notsu A, et al. Comparison of relative validity of food group intakes estimated by comprehensive and brief-type self-administered diet history questionnaires against 16 d dietary records in Japanese adults. Public Health Nutrition. 2011;14:1200-1211

[19] Takemoto Y, Suzuki Y, Horibe R, Shimozawa N, Wanders RJ, Kondo N. Gas chromatography/mass spectrometry analysis of very long chain fatty acids, docosahexaenoic acid, phytic acid and plasmalogen for the screening of peroxisomal disorders. Brain and Development. 2003;25:481-487

[20] Passos IC, Vasconcelos-Moreno MP, Costa LG, et al. Inflammatory markers in post-traumatic stress disorder: A systematic review, meta-analysis, and meta-regression. Lancet Psychiatry. 2015;2:1002-1012

[21] Imai R, Hori H, Itoh M, Lin M, Niwa M, Ino K, et al. Inflammatory markers and their possible effects on cognitive function in women with posttraumatic stress disorder. Journal of Psychiatric Research. 2018;102:192-200

[22] Calder PC. Marine omega-3 fatty acids and inflammatory processes: Effects, mechanisms and clinical relevance. Biochimica et Biophysica Acta. 2015;1851:469-484

[23] Serhan CN, Yacoubian S, Yang R. Anti-inflammatory and proresolving lipid mediators. Annual Review of Pathology. 2008;3:279-312

[24] Gorjao R, Azevedo-Martins AK, Rodrigues HG, Abdulkader F, Arcisio-Miranda M, Procopio J, et al. Comparative effects of DHA and EPA on cell function. Pharmacology & Therapeutics. 2009;122:56-64

[25] Chen CT, Liu Z, Bazinet RP. Rapid de-esterification and loss of eicosapentaenoic acid from rat brain phospholipids: An intracerebroventricular study. Journal of Neurochemistry. 2011;116:363-373

[26] Sidhu D, Naugler C. Fasting time and lipid levels in a community-based population: A cross-sectional study. Archives of Internal Medicine. 2012;172:1707-1710

[27] Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, et al. The development of a clinician-administered PTSD scale. Journal of Traumatic Stress. 1995;8:75-90