Letter to the Editor

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Generalizability of Findings from a Randomized Controlled Trial of Fish Oil Supplementation for Attenuating Posttraumatic Stress Symptoms among Rescue Workers in Japan

Ryoko Susukida a,*, Daisuke Nishi b, Yuzuru Kawashima a, Yuichi Koido a, Ramin Mojtabai c, Yutaka J. Matsuoka d, h

a Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, and b Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA; c Department of Mental Health Policy and Evaluation, National Institute of Mental Health, National Center of Neurology and Psychiatry, d Department of Public Mental Health Policy, Graduate School of Medicine, The University of Tokyo, e Clinical Research Institute, National Disaster Medical Center, f Head Office, Japan Disaster Medical Assistance Team, g Division of Health Care Research, Center for Public Health Sciences, National Cancer Center Japan, and h Department of Psychiatry, National Disaster Medical Center, Tokyo, Japan

There is growing attention being paid to fish oil as one of the promising supplementations to improve symptoms of posttraumatic stress disorder (PTSD) by facilitating hippocampal neurogenesis [1] and clearance of fear memory [2]. Fish oil supplementation potentially has great scalability and could be an alternative to traditional treatment for those with slight-to-moderate PTSD symptoms. Nishi et al. [3] conducted a randomized controlled trial (RCT) of omega-3 polynsaturated fatty acid (omega-3 PUFA) supplementation among disaster rescue workers in Japan and showed that omega-3 PUFA supplementation improved PTSD symptoms among female rescue workers. A more recent RCT by Matsuoka et al. [4] among accident-injured patients showed overall null treatment effect of omega-3 PUFA supplementation on PTSD symptoms; however, they found that female patients responded slightly better to the supplementation.

While evidence for the treatment effect of omega-3 PUFA supplementation on PTSD symptoms among females has accumulated despite its relatively small estimated effect [3, 4], it is unknown whether and to what extent the findings of these RCTs of omega-3 PUFAs can be generalized to target populations. Well-conducted RCTs ensure internal validity of the causal effect of treatments; however, they do not necessarily guarantee external validity of the findings to the target populations for whom treatments are intended. A growing number of studies have indicated that RCT samples often do not represent the target populations well [5], and the findings from RCTs have limited generalizability [6]. In the area of treatments for PTSD and anxiety disorders, studies have also suggested that exclusion criteria typically used in the RCTs tend to limit the representativeness of the RCT samples [7, 8]. Assessing generalizability of the RCT findings is critical even when the estimated treatment effect is small because the estimated effect might have been biased toward null due to a lack of real-world representativeness of RCT samples. The purpose of this study was to examine the generalizability of the findings from a novel RCT of omega-3 PUFA supplementation in attenuating PTSD symptoms among rescue workers (Disaster Medical Assistance Team, DMAT) in Japan.

DMAT rescue workers consist of doctors, nurses, and medical/administrative staff with a specialized training, who are deployed to the disaster-affected areas as a mobile medical team. An RCT of omega-3 PUFA supplementation was conducted for DMAT rescue workers deployed after the Great East Japan Earthquake, which occurred on March 11, 2011. In this study, a sample of DMAT rescue workers voluntarily participating in the omega-3 PUFA supplementation RCT (n = 172) was compared with the target population of all the non-RCT participating DMAT workers in Japan (n = 10,829). The RCT was approved by the Ethics Committee of the National Disaster Medical Center, Tokyo, Japan, on April 1, 2011, and registered at UMIN Clinical Trials Registry (UMIN000005367). The RCT was a single-blind and parallel-group trial without a placebo group, the details of which are described elsewhere [9].

Generalizability of the treatment effects on the following outcomes was assessed with a selection model approach: (1) total score of the Impact of Event Scale-Revised (IES-R), (2) three subscales of the IES-R (hyperarousal, intrusion, and avoidance), (3) the Center for Epidemiologic Studies Depression Scale (CES-D), (4) the Kessler 6 Scale (K6), and (5) the shortened 14-item version of the Resilience Scale (RS14). A selection model approach is similar to inverse probability weighting method in nonexperimental studies, where the causal impacts are estimated by making the distributions of unexposed groups resemble those of exposed groups [10]. This approach has been recently used to generalize the findings from RCTs of substance use disorder treatments to the target populations [11].

Using 3 commonly observed variables (age, occupation, and prefecture where a rescue worker’s hospital was located) in the RCT sample and non-RCT target DMAT population, we estimated probabilities of RCT participation (p). The participation probabilities were estimated with the R package “randomForest” [12]. The detailed method was documented in Susukida et al. [11]. Using a sample weight, (1 − p)/p, we estimated weighted population effects on all the outcomes with the STATA pweight command [13]. This study examined the generalizability of the RCT findings by sex, following the original RCT study reporting stratified outcomes by sex of DMAT workers [3]. All regression analyses were adjusted for age and baseline outcome scores.

Table 1 presents the unweighted and weighted effects of omega-3 PUFA supplementation. The unweighted effects represent the...
effects directly estimated with the RCT sample, while the weighted effects represent the effects that would be expected when the distribution of the RCT sample was made similar to the distribution of the target population. In unweighted analyses, treatment was associated with significantly lower total IES-R score (estimated coefficient: –3.91, 95% CI: –7.53, –0.28) and IES-R hyperarousal subscale score (estimated coefficient: –1.94, 95% CI: –3.36, –0.52) only among female DMAT workers. After weighting the data by target population generalizability weights, the significant treatment effect on both the total IES-R score (estimated coefficient: –3.79, 95% CI: –7.58, –0.01) and the IES-R hyperarousal subscale score (estimated coefficient: –1.79, 95% CI: –3.28, –0.29) among female DMAT workers remained statistically significant. The treatment effects on the rest of the outcomes among female DMAT workers and all the outcomes among male DMAT workers were statistically insignificant both in the unweighted and weighted regression analyses.

The study has some limitations. First, the number of observable characteristics between the RCT sample and the target population was limited. Hence, the estimated RCT participation probabilities did not reflect other unobserved characteristics that may have been different between the RCT sample and the target population. Second, the original RCT did not have a placebo group. Therefore, significant treatment effects among female DMAT workers both in unweighted and weighted models might have included a placebo effect.

Acknowledging these limitations, this study provides the first supportive evidence to the external validity of the findings from an RCT of omega-3 PUFA supplementation. The significant findings of an RCT of omega-3 PUFA supplementation in attenuating PTSD symptoms appear to be generalizable to the target population of the female DMAT rescue workers in Japan. Future studies should investigate whether the findings of this study hold for omega-3 PUFA supplementation in different contexts and target populations.

### Table 1. Comparison of unweighted (randomized controlled trial sample effect) and weighted (population effect) regression coefficients of treatment effect (β)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Males unweighted</th>
<th>Males weighted</th>
<th>Females unweighted</th>
<th>Females weighted</th>
</tr>
</thead>
<tbody>
<tr>
<td>IES-R (total)</td>
<td>0.22 (–2.27, 2.72)</td>
<td>0.05 (–2.48, 2.58)</td>
<td>–3.91* (–7.53, –0.28)</td>
<td>–3.79* (–7.58, –0.00)</td>
</tr>
<tr>
<td>IES-R (hyperarousal)</td>
<td>–0.14 (–1.02, 0.75)</td>
<td>–0.08 (–1.05, 0.89)</td>
<td>–1.94** (–3.36, –0.52)</td>
<td>–1.79* (–3.28, –0.29)</td>
</tr>
<tr>
<td>IES-R (intrusion)</td>
<td>–0.12 (–1.07, 0.82)</td>
<td>–0.13 (–1.07, 0.81)</td>
<td>–1.29 (–2.95, 0.36)</td>
<td>–1.18 (–2.93, 0.58)</td>
</tr>
<tr>
<td>IES-R (avoidance)</td>
<td>0.60 (–0.38, 1.59)</td>
<td>0.41 (–0.56, 1.18)</td>
<td>–0.41 (–1.90, 1.08)</td>
<td>–0.52 (–1.87, 0.83)</td>
</tr>
<tr>
<td>CES-D</td>
<td>0.55 (–1.51, 2.62)</td>
<td>0.97 (–1.09, 3.04)</td>
<td>–2.78 (–6.37, 0.81)</td>
<td>–0.62 (–4.84, 3.60)</td>
</tr>
<tr>
<td>K6</td>
<td>0.25 (–0.68, 1.18)</td>
<td>0.09 (–0.88, 1.06)</td>
<td>0.13 (–1.87, 2.12)</td>
<td>–0.47 (–3.05, 2.11)</td>
</tr>
<tr>
<td>RS14</td>
<td>1.75 (–1.99, 5.48)</td>
<td>1.72 (–2.59, 6.04)</td>
<td>3.74 (–1.48, 8.95)</td>
<td>8.44 (–2.67, 19.55)</td>
</tr>
</tbody>
</table>

Age and baseline score for each outcome were included in the regression analyses. Confidence intervals are in parentheses. IES-R, Impact of Event Scale-Revised; CES-D, Center for Epidemiologic Studies Depression Scale; K6, Kessler 6 Scale; RS14, shortened 14-item version of the Resilience Scale. * p < 0.05, ** p < 0.01.

#### References