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Nutrition Discussion Forum

No effect of *n*-3 long-chain polyunsaturated fatty acid (EPA and DHA) supplementation on depressed mood and cognitive function: a randomised controlled trial – reply by Rogers *et al.*

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We recently reported a null outcome from a study of *n*-3 long-chain PUFA supplementation in depressed mood[1]. In a commentary on our study, Richardson[2] questions our choice of supplement and our interpretation of the evidence from other published studies that exposed participants to *n*-3 long-chain PUFA or fish and measured depressed mood. Possible benefits of increasing *n*-3 long-chain PUFA intake have been suggested for various mood and behavioural disorders, but evidence from observational and intervention studies to date is inconclusive[3]. Currently, there are more published studies on depression and depressed mood than on other psychological disorders; however, these studies are diverse, and they are smaller in number and scale than, for example, studies investigating effects of *n*-3 PUFA on CVD outcomes[4].

Our study was conceived during 2002. It was founded on arguments that low intake of *n*-3 long-chain PUFA in many 'modern' diets (especially coupled with high *n*-6 PUFA intakes) may have important consequences for physical and mental health[5,6], and on evidence of associations between fatty acid intakes and fatty acid status and depression. Furthermore, results of a small (*n* 30) intervention study had shown a benefit of *n*-3 long-chain PUFA supplementation (a large daily dose of EPA (6·2 g) + DHA (3·4 g)) to patients with severe depression[7]. Our aim was to investigate this dietary hypothesis in a broader population. Accordingly, we administered a supplement containing EPA (0·63 g) and DHA (0·85 g) in a ratio similar to the fatty acid composition of fish 'commonly' consumed in the UK (see Table 4.2 in the report by the Scientific Advisory Committee on Nutrition & Committee on Toxicity[8]) to individuals with mild to moderate symptoms of depression. These amounts of EPA and DHA exceed the current minimal UK dietary recommendation[8], but are realistically attainable through increased intake of oily fish (the main dietary source of *n*-3 long-chain PUFA). However, we did not use a dietary intervention because this would have been more costly, less certain to achieve substantial increases in EPA and DHA intake, and difficult to do as an adequately blinded placebo-controlled trial. We also targeted individuals with initially low *n*-3 long-chain PUFA intakes and raised levels of depressed mood on the assumption that, from within the general population, they would be the individuals most likely to benefit from supplementation[1]. Nevertheless, the study found no effect on mood of EPA + DHA supplementation.

It is also far from clear that *n*-3 long-chain PUFA supplementation provides a benefit in severe depression. Three studies[9–11] (total *n* 176) published since the report of Stoll *et al.*[7] found no effect of supplementation with EPA + DHA or DHA alone, against two smaller studies[12,13] (total *n* 48) that did show improvement of symptoms of depression. In three other studies[14–16] on severe depression in which the supplement contained EPA but no DHA a benefit of daily doses of 1 and/or 2 g was found, but 2 g was also found to be ineffective, as was 4 g. In a fourth and the largest study on EPA (*n* 116), there was no effect of a 6 g per d supplement[17]. The supplement used in all four of these studies was ethyl-EPA (a product of Laxdale Ltd, which funded two of the studies[15,16]). In total, therefore, the evidence from intervention studies is mixed. Even without taking into account publication bias (the tendency not to publish studies yielding null results, and to publish those yielding 'positive' results even with small sample sizes), this evidence sums to a modest benefit at best, and it certainly contradicts the improbably high estimates of risk of depression attributable to *n*-3 PUFA 'deficiency' derived from worldwide population data[18].

As Richardson[2] indicates, a biologically plausible mechanism for an effect of DHA on mood and behaviour is the alteration of cell membrane fluidity[19] and in turn the modulation of brain neurotransmitter function. For example, brain monoaminergic neurotransmission is susceptible to diet fatty acid composition (rats fed diets rich in fish oil containing EPA and DHA *v.* groundnut and rapeseed oil)[20]. EPA, on the other hand, via its role as a precursor of eicosanoids, might be expected to impact on vascular disease processes, one result perhaps being to protect against cognitive decline in older age[21]. However, while it is also possible to speculate about other effects of EPA, there appear to be no clearly specified mechanisms by which EPA might benefit mood. There is also no good reason to expect an inverse dose–response relationship for the effects of EPA on mood (1 g daily being effective but not 4 or 6 g daily), and if 1 g per d is an optimal dose of EPA, should we not have seen a benefit of 0·63 g EPA in our study, especially given the relatively good power we had to detect a modest effect? By contrast, a strong predictor of the results of studies of EPA and/or DHA supplementation where the primary outcome measure was depression is the size of the study. This is indicative of publication bias[22].

Another question raised in response to our study concerns our choice of placebo[23]. There are several reasons why it is very unlikely that the use of an olive oil placebo can explain the lack of a treatment effect. First, and most important,

average daily oleic acid intake in the UK is about 25 g (for example, Theodoratou *et al.* [24]). This is more than an order of magnitude higher than the amount of oleic acid provided daily by the placebo in our study, and this placebo did not have a significant effect on oleic acid status – mean plasma oleic acid concentrations before and after 12 weeks of supplementation with placebo were 21·6 (SD 3·1) and 21·6 (SD 2·9) respectively (data are percentage of total plasma fatty acids). By contrast, the EPA + DHA-containing supplement doubled EPA + DHA plasma concentration[1]. In other words, the effect of EPA + DHA supplementation on EPA + DHA intake and status was very much greater than the effect of the placebo supplement on oleic acid intake and status (see also Grenyer *et al.* [11]). Second, severity of depression was not related to oleic acid status either before or after the 12 weeks of supplementation (largest standardised $\beta = 0{\cdot}02$ (95 % CI −0·03, 0·08); $P=0{\cdot}39$). Nor was there a relationship in the placebo group between change in depression severity and change in oleic acid status from week 0 (baseline) to week 12 (largest standardised $\beta = 1{\cdot}11$ (95 % CI −0·74, 2·96); $P=0{\cdot}23$). Zhang & Li[23] predict an inverse correlation between these variables. Third, the improvement in mood in the placebo group is simply consistent with the 'spontaneous' remission of symptoms of depression apparent in many trials of antidepressant efficacy[25]. Indeed, in our study, participants' mood improved even before they received the supplements (that is, depression scores fell between screening and entry into the trial at week 0)[1]. Fourth, in studies of severe depression, the use of olive oil as a placebo has been associated with findings in favour of a benefit of *n*-3 long-chain PUFA supplementation[7,12,13] as well as null results[10,11]. It can be deduced that liquid paraffin (mineral oil) was used as the placebo in all of the studies investigating the effects of ethyl-EPA on depression[14–17]. Again, as described above, these studies have revealed mixed results. While it is logically impossible to rule out an unknown biologically mediated benefit (or harm) for mood of the placebos used in these various studies, including ours, the evidence overall is strongly against this.

There is a caveat to this conclusion, however. In many of the above studies (for example, Stoll *et al.* [7], Silvers *et al.* [10], Grenyer *et al.* [11] and Su *et al.* [12]), and in other studies of the behavioural effects of *n*-3 long-chain PUFA, the supplements also contained vitamin E, in doses approximating or greatly exceeding the RDA for adults. Vitamin E is added to reduce fatty acid oxidation. Typically, however, the placebos appear not to have contained vitamin E, although information on this is missing from some reports. There is ambiguity, therefore, as to whether the outcomes of such studies are owing to the effects of *n*-3 long-chain PUFA and/or vitamin E, especially in view of evidence of an inverse association between plasma levels of vitamin E and the severity of depression[26]. This is not a problem for our study, because our placebo and EPA + DHA supplements contained equal amounts of vitamin E.

We set out to test a dietary hypothesis. Our results showed no benefit (but also no evidence of harm) for mood of a daily EPA + DHA supplement which increased *n*-3 long-chain PUFA intakes to above those advocated in UK dietary recommendations. Inevitably, there is scope for further research to be done on this subject, in particular to compare the effects of EPA *v.* DHA – although, arguably, this question is more relevant to pharmacology than to food and nutrition. Such studies, of course, should be adequately powered, and published whatever their outcome. On the other hand, perhaps the resources needed to do this would be better invested in investigating more promising approaches to the treatment of depression.

There are no conflicts of interest.

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