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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 – comments by Zhang and Li

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We agree with Dr Richardson's viewpoint put forth in her accompanying commentary[1] that the study of Rogers *et al.* [2] 'represents a wasted opportunity to find out if the existing evidence that *n*-3 fatty acids can help patients with mood disorders might extend into the general population'. The study of Rogers *et al.* [2], however, may provide additional evidence indicating that olive oil is not the ideal placebo in fish oil studies. Following from the early work of Stoll[3], the correspondence between Stoll and others[3–5] presented a scholarly discussion on the pros and cons of using olive oil as the placebo. Rogers *et al.* [2] is an important contribution to the ongoing dialogue regarding the choice of placebo in clinical studies of fatty acids. We agree with others[5,6] that olive oil should not be used as the placebo to test the putative protective effects of *n*-3 fatty acids or fish oil on the development of mood disorders.

The predominant fatty acid in olive oil is oleic acid. Although it remains unclear how much of the benefit of olive oil is due to oleic acid compared with the benefits derived from the antioxidant and anti-inflammatory actions of the phenolics, or the relatively high content of squalene, the convincing evidence from epidemiological, biochemical and metabolic data does indicate that oleic acid has a protective effect against various health conditions, including cancers[7,8] and CVD[9,10]. Oleic acid is biologically active and olive oil is certainly not an ideal placebo. However, observations that oleic acid has psychoactive properties are just anecdotal. Our group prospectively assessed the association between dietary oleic acid and the risk of severe depressed mood among 2909 women aged 25 to 74 years who were examined in 1971–5 as a part of a national follow-up survey. Intakes of oleic acid were obtained at baseline from a 24 h recall and categorized into tertiles. Severely depressed mood was defined as Center for Epidemiologic Studies Depression Scale score ≥ 22 or taking anti-depression medication after more than 10 years follow-up. We observed that the relative risks were 1 (reference), 0·88 (95 % CI 0·56, 1·38) and 0·48 (95 % CI 0·25, 0·95) respectively for women with the lowest, middle and highest tertile of oleic fatty acid intake (P for trend $= 0{\cdot}0347$). These estimates were obtained after adjustment for a large array of confounding factors, including socio-economic status and total dietary energy intake at baseline, and a history of major physical illnesses at the follow-up. We believe that our observation is the first tangible evidence supporting the beneficial effects from olive oil on the development of mood disorders and may explain why Rogers *et al.* [2] and others[11,12] who used olive oil as the placebo failed to observe a significant difference of mood improvement between control and treatment groups after a period of treatment of fish oil or *n*-3 fatty acid supplements. Actually, in almost all of these studies using olive oil as the placebo[2,3,11,12], significant and sustained improvements in depressive symptoms have been demonstrated in both treatment and control groups, suggesting that strong placebo effects were operating. There might have been effects from both olive oil and fish oil or *n*-3 fatty acids. Finally, it is noteworthy that in the meta-analyses published earlier by Rogers' group, a single trial[11], which also used olive oil as the placebo and obtained a negative outcome, received 20 % of the total weight[13]. The overall conclusion of the meta-analyses was heavily driven by this trial, although positive results in patients with diagnosed mood disorder were indicated by all other studies included in the analysis.

We declare that we have no conflict of interest.

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