No differential effect between docosahexaenoic acid and oleic acid in preventing cognitive decline

Dear Sir:

Recently, Dangour et al (1) published the results from a randomized clinical trial (RCT) on the effects in participants of a 24-mo supplement intervention with eicosapentaenoic acid (EPA; 200 mg/d) and docosahexaenoic acid (DHA; 500 mg/d) compared with a control group who received an undisclosed amount of olive oil. The main objective of the study was to slow cognitive decline in people aged 70–79 y living in the United Kingdom (OPAL (Older People And n–3 Long-chain polyunsaturated fatty acid) study). As indicated by the authors, although this is the largest and longest study of its nature, the results did not provide evidence to reject the null hypothesis of no differential effect between the intervention and the control treatment. However, this was not a type II error study but rather showed that the null hypothesis is true.

The study was a well-designed RCT with a low rate of attrition. The study included 867 randomly assigned individuals, of whom 434 were assigned to receive long-chain polyunsaturated fatty acid (LC PUFA) supplements, and the sample size was calculated to provide 90% statistical power at 1% significance (1). The study population was selected among those individuals not consuming daily fish-oil supplements and in individuals with no mild cognitive impairment (ie, a Mini-Mental State Examination score >24 but with a risk of age-associated cognitive decline (ARCD) or in those with normal (nonpathologic, normative, usual) cognitive aging (2) (ie, maintaining cognitive function in later life). In this regard, cognitive function was assessed at baseline and 24 mo later with a battery of tests including the California Verbal Learning Test (CVLT) measuring a range of cognitive domains including memory to executive functions, and which were used to develop a global cognitive function algorithm (1).

The possible weakness in the study, as indicated by the authors, is that the study population might already consume a sufficient amount of LC PUFA:s in their diets and thus not be sensitive to the dose of DHA/EPA provided. However, the lipid profile in the authors’ Table 3 (1) showed that mean serum DHA concentrations increased by 35%, EPA concentrations increased by 27%, and arachidonic acid (ARA) concentrations decreased by 14% in individuals in the intervention group compared with those receiving the control. These biochemical changes characterized a dose-response to LC PUFA supplements and a substantial effect in their metabolism as the result of a reduction in serum ARA concentrations (3). The increase in serum DHA is notable because it suggests that a nonsaturable DHA concentration existed in this population before the intervention, and it raises the possibility that the observed increase in plasma correlated well with an increase in brain DHA (4).

Moreover, the same lipid profile in the authors’ Table 3 may offer an alternative explanation for the observed lack of differential effect between the LC PUFA supplement and control. Mean serum oleic acid concentration increased by 7% in individuals receiving the control treatment compared with those receiving the LC PUFA supplement (1). This is significant because others have shown health benefits of olive oil supplements with smaller increases in plasma oleic acid concentrations. An increase in plasma oleic acid of 2–3% in populations with sporadic olive oil intakes (eg, northern and central European populations) has been associated with lowering blood pressure (5). Thus, these findings suggest that the intake of olive oil in the control group might result in maintaining cognitive function in later life comparable to the effects of DHA/EPA, albeit by different mechanisms.

Prospective studies have shown that the Mediterranean diet is associated with slower cognitive decline and a reduced risk of progression from mild cognitive impairment to Alzheimer disease (see reference 6 and references therein). The Mediterranean diet combines several food-derived factors such as antioxidants, dietary fatty acids, and micronutrients. Dietary fatty acids may play a significant role in the development of ARCD (6). Of these, LC PUFA:s have been given the most attention from observational epidemiologic studies, but monounsaturated fatty acids (MUFAs) such as oleic acid [18:1(n–9)] may also be responsible (6, 7). Although evidence suggests that high fish consumption and high intake of LC PUFA:s may be protective against ARCD and reduce mild cognitive impairment, the traditional Mediterranean diet is not centered on fish consumption as much as on a high intake of olive oil (7). Olive oil is more than a MUFA fat; it is a functional food that, besides having a high amount of MUFAs, contains other minor components with biological properties such as natural antioxidants including phenolic compounds (7). However, the major component, oleic acid, has recently been shown to provide a satiety factor, oleoylethanolamide, which enhances memory consolidation without crossing the blood-brain barrier (8). These animal studies showed that oleic acid, through its gut conversion into oleoylethanolamide and its peripheral signals transmitted to the brain by the autonomic nervous system, enhances memory of training in a water maze (8). This is a task that assesses memory of context, which is important in verbal learning, organization, and memory (9), all of which are measured by the CVLT. These effects as well as its potential neuroprotective role during sleep deprivation in humans (10) suggest that oleoylethanolamide is a mediator in maintaining cognitive function that it is not related to vascular or other nonvascular biological mechanisms (ie, metabolic, oxidative, and inflammatory) as a potential causal pathway between the complex Mediterranean diet and a reduced risk of cognitive dysfunction.

Together, this evidence suggests that Dangour et al (1) should consider the benefits of oleic acid as well as DHA/EPA in protecting against ARCD and maintaining cognitive function in later life.

The author works for Abbott Nutrition Research and Development, which produces nutritional products that may contain some of these fatty acids, but he does not have a conflict of interest regarding this letter.

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Reply to FJ Rosales

Dear Sir:

We thank Rosales for his generous review of the Older People And n–3 Long-chain polyunsaturated fatty acid (OPAL) study (1) and are grateful for the opportunity to respond to some points raised in his letter.

We would first like to state that, contrary to the title of Rosales’ letter, the OPAL study compared the effect of 500 mg docosahexaenoic acid plus 200 mg eicosapentaenoic acid with olive oil on cognitive function in older people. Second, as stated in our report, participants in the placebo arm were asked to consume two 650-mg capsules containing olive oil daily—equal to ~1.3 g olive oil/d. Third, we would like to correct the misapprehension that our Table 3 provides information on change in serum fatty acid profile in study participants between baseline and 24 mo. In fact, as we did not measure baseline serum fatty acid concentrations, Table 3 compares serum fatty acid concentrations in the intervention and placebo arms after 24 mo of intervention. Without information on baseline serum oleic acid concentrations it is not possible to comment on the potential health effects of any putative changes in concentrations. And finally, we concur that there is a growing body of epidemiologic evidence suggestive of an association of consumption of a Mediterranean-style diet with cognitive function in later life, although we are skeptical that the small amount of olive oil provided in the OPAL study could mimic these possible benefits.

Over the past 2 y, 4 randomized controlled trials evaluating the effect of n–3 long-chain polyunsaturated fatty acids on various measures of cognitive function in older people have been published: 2 trials used olive oil as the placebo (1, 2) and 2 used a mixture of corn and soy oil as the placebo (3, 4). Unfortunately, the results of all 4 of these trials have been largely negative, suggesting that factors other than the content of the placebo supplement are important in determining the outcome of long-term intervention studies on cognitive function in later life (5).

The authors had no conflicts of interest to declare.

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