

Although the statistical magnitude of results differed modestly by study design, results by study type should be considered as complementary, providing support for the role of EPA+DHA on CHD risk reduction.

The second issue that McLennan and Pepe raise is that background omega-3 polyunsaturated fatty acids (PUFA) dietary intake and baseline red blood cell membrane PUFA should be accounted for in each RCT recruitment. They suggest that if so, we would likely see more than a 6% reduction in CHD risk in our meta-analysis. Although RCT recruitment is beyond the scope of our meta-analysis, we agree that a stronger summary effect may be observed if the margin of difference in EPA+DHA levels between the treatment and control groups was greater. McLennan and Pepe recommend that future RCTs should include patients with verifiable baseline and follow-up measurements of omega-3 PUFA levels. We agree that such methodological rigor at the individual trial level may provide additional insight into the relationship between EPA+DHA and CHD risk.

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In Reply II—Prescribing More Stringent Design of Randomized Clinical Trials of Omega-3 Polyunsaturated Fatty Acids



The concerns articulated by Drs McLennan and Pepe about the high intake of omega-3 fatty acids in the

control groups of randomized controlled trials (RCTs) are critically important when evaluating this body of scientific data, and we thank these colleagues for their insightful comments. Indeed, RCTs of omega-3 supplementation performed 2 to 3 decades ago reported highly significant reductions in major adverse cardiovascular (CV) events,¹⁻³ similar to the 18% reduction noted in the recent comprehensive meta-analysis of prospective cohort studies by Alexander et al⁴ that included 732,000 individuals. However, during the past 10 to 15 years, mass media outlets have widely publicized the potential benefits of fish and fish oil supplements, and thus, not surprisingly, the individuals who agreed to participate in trials testing omega-3 in recent years tended to have higher baseline consumption of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) compared with decades earlier, which may account for the muted to absent cardioprotective effects noted with omega-3 supplementation in many of the more recent RCTs.⁵

As a general rule, nutrients are best obtained from the diet rather than supplements. However, supplementation can be important for individuals with deficiencies of essential nutrients and who are unable or unwilling to obtain them from dietary sources. From the 13th through 18th centuries, scurvy was a common and often fatal affliction among sailors during long sea voyages. In 1753, James Lind, a Scottish physician in the British Royal Navy, published his study describing how all of the lethal signs and symptoms of scurvy quickly resolved after fresh oranges and lemons (which are high in vitamin C) were added to the sailors' food rations. In stark contrast, several large RCTs over the past 20 years have documented no benefit to vitamin C supplementation among modern Western populations, in whom scurvy is very rare.⁶

Despite the broadcasting of information about potential benefits of fish and fish oil, the typical American (unlike the people who tend to volunteer for omega-3 studies) still consumes insufficient quantities of omega-3. Accordingly, the mean omega-3 levels in the cell membranes of US adults remain approximately half the levels noted among the citizens of Japan,⁷ and this difference has been postulated to be a central reason for the superior CV health and longevity of the Japanese.⁸ Among individuals who consume inadequate quantities of omega-3, a supplement providing 250 to 1000 mg of EPA and DHA will increase the tissue levels of omega-3 fatty acids and will likely improve CV prognosis.

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Potential Competing Interests: Dr O'Keefe is the chief medical officer and founder of Cardio-Tabs, a nutraceutical company, and has a major ownership interest in company, which sells products that contain omega-3. Dr Lavie is a speaker for Amarin Corp on Vascepa, has consulted for DSM Nutritional Products, made an omega-3 educational video at the American Heart Association meeting on November 14, 2016, for Global Organization for EPA and DHA Omega-3s, and has made other speaking appearances for Global Organization for EPA and DHA Omega-3s.

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