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

We thank Drs McLennan and Pepe for their insightful comments on our meta-analysis of randomized controlled trials (RCTs) and prospective cohort studies of eicosapentaenoic acid and docosahexaenoic acid (EPA+DHA) supplementation vs coronary heart disease (CHD) risk. The objectives of our research were to (1) estimate the summary association between EPA+DHA intake and CHD risk in prospective cohort studies and (2) examine the effects by dose, by specific CHD outcome, and among higher-risk populations (eg, individuals with elevated triglyceride levels). To this end, we evaluated the currently available and published data across the literature.

The authors raise 2 primary issues in their letter to the editor, both dealing with the design of individual RCTs, which is not the topic addressed in our meta-analysis but still is relevant for the discourse of the state of knowledge on this topic. The first is that there is an absence of discussion pertaining to the recruitment of control groups with low baseline levels of omega-3 EPA+DHA. However, the authors focus their attention on the National Heart Foundation of Australia review, not our meta-analysis. In fact, in our discussion section, we wrote that "most RCTs did not measure baseline intake of EPA+DHA from the diet nor track EPA+DHA intake from sources other than that supplemented during the course of study…." Therefore, it is not clear if the results from the individual trials have been impacted by background dietary EPA+DHA, particularly in the control group. If so, as the authors suggest, and as we indicated in our article, the effects of EPA+DHA on CHD risk may be more protective than what is reported in our meta-analysis. Although most studies undeniably include participants with varying baseline levels of EPA+DHA, the purpose of our meta-analysis was to evaluate the relative difference between individuals with EPA+DHA provision compared with those who did not receive supplemental EPA+DHA. Globally, levels of EPA+DHA in the general population have been considered low[1]; however, it is unclear whether the participants in the RCTs we analyzed have been recruited from a "healthier" source population with higher baseline levels of EPA+DHA. If so, effects of EPA+DHA supplementation may be attenuated toward the null value. Appropriately, the summary results from our meta-analyses of RCTs should be viewed as conservative.

From a methodological standpoint, it may not be pragmatic to evaluate CHD risk among individuals receiving EPA+DHA compared with an "exposure-free" (ie, no baseline level of EPA+DHA) control population. McLennan and Pepe ask the question of whether an RCT of a β-blocker, or any novel active agent, allows the active drug to be present in the control group. Although we agree with the their position that in most *drug* trials, the active agent may not—or should not—be present in the control group, EPA+DHA is a dietary factor, not an active drug.

Again, the aim of our meta-analysis was to estimate the *relative difference* of the effect of EPA+DHA on CHD risk based on the evaluation of participants receiving supplemental EPA+DHA compared with participants not receiving supplemental EPA+DHA. We fully submit that the control groups across the volume of RCTs include participants with varying levels of EPA+DHA. The reality is that we are not evaluating a drug or prescription medication per se but rather a dietary and nutritional constituent present in commonly consumed foods. Thus, the inherent methodology in published studies is a reflection of this fact (as is the case with most RCTs of dietary factors), and the findings across the literature should be interpreted in light of the challenges when attempting to isolate the effects of a single dietary factor on a complex and multifaceted outcome, such as CHD. In other words, unless the exposure is rare and uncommon in the dietary practice of large segments of the population, the control groups in most RCTs of dietary factors typically include participants with a baseline level of exposure. Indeed, McLennan and Pepe indicate that in our analyses, the prospective cohort studies consistently reveal reductions in CHD risk between those eating fish regularly compared with those who consume fish infrequently, and the RCTs do not reproduce these strong findings. This is discussed extensively in our article in which we indicate that prospective cohort studies enable us to evaluate unrestricted populations who may not have modified their dietary habits and medications on entry into the cohort. Furthermore, most prospective cohort studies are longer in duration than RCTs, include a larger study population, and evaluate dietary intake data that may be representative of lifelong eating habits. However, RCTs offer the methodological advantage of control for confounding through random allocation of exposure and a potentially more stringent and regulated follow-up for the occurrence of a CHD event. Each study design provides insight into the relationship between EPA+DHA and CHD, which is why we conducted separate meta-analyses by RCT and prospective cohort designs.

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 al[4] 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 CardioTabs, 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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