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EDITORIAL COMMENT

Fishin' Mission on Emissions*

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Particulate air pollution is the single most important preventable environmental risk factor globally, with recent estimates suggesting >8 million deaths annually (1,2). The deaths attributable to air pollution are mostly cardiovascular in etiology, with countries like China and India contributing to the largest proportion of the global burden (3). Although there is heightened sensitivity and international resolve to reduce particulate matter <2.5 μm (referred to as $PM_{2.5}$), the sources of air pollution emission such as power generation, automobiles, shipping, and practices reliant on fossil fuels, are so deeply embedded in the fabric of industrial economies that regulation of air pollution levels is only possible through a profound shift to renewable energy sources. Even with rapid transition to clean technologies occurring in China and India, it may be difficult to further reduce levels to current "clean" levels in North America, within the next decade. Recent studies in the United States and Canada continue to highlight a continued association of $PM_{2.5}$ with mortality, even at "clean" levels <12 $\mu g/m^3$, the current annual average national ambient air quality standard (4,5). There is therefore, a significant imperative to develop practical approaches that help protect vulnerable populations using personalized devices (e.g., mask) and/or pharmacological interventions.

Interest in the relationship between dietary marine fish oils and prevention of heart disease was initiated by a study in the 1970s by Bang and Dyerberg conducted in Umanak, a town located 500 km north of the Arctic Circle. Contrary to popular myth, the original study did not study prevalence of coronary artery disease, but food composition and plasma lipoproteins in the Eskimo population (6). It is unlikely that these investigators or others that have followed, who have noted that purified marine-derived omega-3 fatty acids (ω3) such as eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA) may have cardiovascular effects, would have conceived a use for fish oils to combat air pollution-mediated health effects.

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Although there have been multiple studies using surrogate markers assessing the efficacy of personal devices such as indoor air filters, N95 respirators, and medications such vitamins and statins on air pollution health effects, the study by Lin et al. (7) in this issue of the *Journal* is one of the first to test ω3 in an environment where ambient air pollution levels are known to be markedly elevated (1,8). In a prior controlled exposure trial to inhaled concentrated ambient particulate matter, in predominantly postmenopausal women, olive oil, but not fish oil, prevented depression in flow-mediated dilation, attenuated endothelin-, and increased tissue plasminogen activator concentration, in response to $PM_{2.5}$ exposure (9). The design of the experiment was a parallel-group, randomized, double-blind, placebo-controlled trial in 65 healthy college students (7). There were 4 different measurement points over 2 months, including some over weekends, to ensure that a broad range of exposure values were included (weekend exposure levels in China are lower). Participants received placebo or 2.5 g of omega-3 fatty acids. Each capsule contained 1.5 g of n-3 fatty acids, of which EPA/DHA content was 900 and 600 mg, respectively. EPA levels were low (mean EPA levels of 0.1 μg/ml) when compared with previous reported values, although the number of patients and measurement approaches limit direct comparisons (10). Exposure

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assessment of $PM_{2.5}$ occurred within the campus in Shanghai, whereas that for gaseous pollutants occurred from a regional monitor 3.5 km away. Multiple surrogate outcome measures (n = 18) comprising plasma measures of inflammation, thrombosis, redox stress, lipid peroxidation, antioxidant measures, endothelial function, stress markers, and insulin resistance were assessed. The trial had appropriate statistical approaches and secondary analysis to examine the impact of gaseous copollutants and baseline dietary nutrients.

$PM_{2.5}$ was associated with multiple markers of inflammation, insulin resistance, and measures of thrombosis that were eradicated with supplementation by ω3, but not placebo. The magnitude of effect of ω3 and the time point of maximal effect varied by the type of biomarker and the lag duration of exposure. The effect of the intervention was particularly prominent for IL-6 at the delayed time points of 24 and 48 h. By contrast, early increases (3 to 6 h) in von Willebrand factor, E-selectin, and oxidized low-density lipoprotein in response to $PM_{2.5}$, were significantly attenuated by ω3. These results are consistent with the generally accepted principle that oxidative stress is the first hierarchic response to air pollution exposure in humans, followed by a more delayed response in other cardiovascular variables when specifically examined (1).

The study by Lin et al. (7) comes at the heels of 3 very large randomized controlled clinical trials of ω3 to reduce cardiovascular events (11,12). In 2 of these studies (ASCEND [A Study of Cardiovascular Events iN Diabetes] trial in type 2 diabetics and the VITAL [Vitamin D and Omega-3 Trial] in an asymptomatic primary prevention cohort), supplementation with an identical dose of EPA/DHA 460/380 mg as a 1-g capsule or placebo (olive oil) once daily, over a mean duration of 5.3 to 7.4 years, did not reduce major adverse cardiovascular events (11,12). In the REDUCE-IT trial (Reduction of Cardiovascular Events With EPA – Intervention Trial), patients with established cardiovascular disease or diabetes and risk factors on statin therapy were randomized to 2 g twice daily of icosapent ethyl (a highly purified ethyl ester of eicosapentaenoic acid, Vascepa [icosapent ethyl]; Amarin Pharma, Dublin, Ireland) or placebo. This trial noted a 26% reduction in major adverse cardiovascular outcomes with a number needed to treat of 21. A >300% increase in EPA levels from a baseline of 26.1 mg/ml in the trial was also noted (13). The impressive efficacy of this agent has renewed enthusiasm for supplementation with EPA, although debate on the type, dose, and combination(s) of ω3 will likely continue. It would be of great interest to see whether the use of fish oils in these studies preferentially benefited patients living in areas with higher levels of air pollution.

How do the levels of air pollution in this study compare with levels in the United States? $PM_{2.5}$ during the exposure period averaged 38 $\mu g/m^3$ (range of 32 to 41 $\mu g/m^3$ before health examinations), and were not very different from annual averages reported by the World Health Organization for the city of Shanghai in 2016 (14). Using the U.S. $PM_{2.5}$ annual average threshold of 12 $\mu g/m^3$, below which air quality is considered clean, the cleanest cities in China (annual average of 24 $\mu g/m^3$) are at least 2 times the annual average of the dirtiest cities in North America, suggesting that air quality in China still has a long way to go (14).

Finally, what if any recommendations can the practicing physician draw from this trial that may be relevant to practice? Although the results are promising, given the lack of evidence regarding the efficacy of ω3 as well as other personalized interventions to protect against clinical cardiovascular events induced by air pollution, it is premature to recommend their wide-scale usage. We have previously made a clarion call for definitive outcome trials testing personal-protection approaches (e.g., N95 respirators, indoor air filters) in patients at the highest risk such as those with acute coronary syndrome or other vulnerable populations, especially in heavily polluted nations (15). Given the recent spate of emission-related events around the globe including increase in forest fires across the western United States during the past decade, trials to test community- and personal-level protection actions in this setting are desperately needed. Until such trials are completed, vulnerable patients such as those with pre-existing cardiovascular disease should follow existing Air Quality Index recommendations and use commonsense actions such as avoidance whenever possible of heavily polluted locations (e.g., roadways) and environments.

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