Variability in the cardiometabolic effects of ω-3 long-chain PUFAs: background diet, timing, and genetics

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Omega-3 long-chain PUFAs (LC-PUFAs) have received considerable attention over many years for their proposed health benefits, particularly in relation to cardiovascular disease. More recently, there has been interest in the potential for ω-3 LC-PUFAs to favorably influence other metabolic variables, including inhibiting weight gain during exposure to “obesogenic” diets and aiding in the loss of body weight and body fat. Despite some encouraging data from in vitro and animal studies and a plausible biological basis for the favorable effects of ω-3 LC-PUFAs on these outcomes, the results from human studies have been less than conclusive. Current meta-analyses in the cardiovascular field, for example, conclude that there is no strong evidence that dietary or supplemental ω-3 fats alter the risk of combined cardiovascular events, either in individuals at high risk or in the general population (1). The conclusions of the most recent systematic review of studies focused on ω-3 LC-PUFAs and body composition are somewhat more positive and indicate that fish or fish-oil supplementation produces greater losses in body weight, BMI, and waist circumference in comparison to placebo (2); however, it is important to note the much lower number of studies on this topic and that supplementation is typically applied on top of reduced overall energy intake.

A feature of the ω-3 fatty acid literature, as with many nutritional fields, is the variability in the effects reported in different studies. Part of this inconsistency is likely to be due to differences in study design (e.g., dosage and timing of intervention) and the background ω-3 status of the population. It is also clear, however, that the effects of ω-3 LC-PUFA intake and supplementation can vary substantially between individuals, a phenomenon that appears to be at least in part a result of interindividual differences in the relation between fatty acid intakes and the concentrations of their downstream bioactive mediators (3). The implication of this is that conclusions based on studies in the general population, or in one ethnic group, may be limited in informing whether there are particular subgroups who are more likely to benefit. This issue of the Journal features 3 new studies that investigate the relation between ω-3 LC-PUFA intake, ω-3 LC-PUFA status, background diet, timing, and genetics and cardiometabolic variables.

In the first study, Jakobsen et al. (4) investigate the relation between dietary intake and adipose tissue content of ω-3 LC-PUFAs and 5-y changes in body weight and waist circumference in Danish adults. Despite some interesting trends, they found no consistent or appreciable association between habitual ω-3 LC-PUFA intake or status at baseline and weight or waist circumference changes over the subsequent 5-y period. The findings align with those of the most recent systemic review, which suggested that although short-term periods of supplementation (<2 mo) could favorably influence weight loss, there was no evidence of associations with longer-term intakes (2). The study by Jakobsen et al. also found no evidence to suggest that the effects of ω-3 LC-PUFAs on weight or waist circumference are dependent on the carbohydrate-to-protein ratio or glycemic index of the background diet, a finding reported in previous animal studies (5, 6). This is perhaps not surprising when one examines the composition of the diets used in the animal studies, which encompassed much greater extremes of both ω-3 and macronutrient intakes than in this human study. This finding thus highlights the inherent difficulty in extrapolating results of dietary studies in animals to the range of nutritional intakes commonly encountered in human diets. In contrast to these findings, the study by Loy et al. (7), also featured in this issue of the Journal, reports that higher ω-3 LC-PUFA intakes or status at 26–28 wk of pregnancy were associated with lower weight retention at 18 mo postpartum in Singaporean women. Although it is not possible to assess causality in either of these observational studies, and there is the potential of residual confounding, they nevertheless raise the possibility that any effects of ω-3 LC-PUFAs on body weight may be dependent on the timing of intervention, and perhaps the physiologic status of the individual (i.e., whether they are in positive or negative energy balance).

Genetic factors have also been shown to influence the response of individuals to dietary ω-3 supplementation. Much of this work to date has focused on the impact of single nucleotide polymorphisms

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in the fatty acid desaturase (FADS) genes that encode the 2 major desaturase enzymes in the PUFA metabolic pathway and has identified interactions between the FADS genotype and ω-3 LC-PUFA intakes for a range of outcomes (8). The study by Yu et al. (9) in this issue of the Journal, conducted in Costa Rican Hispanics, indicates that this interaction extends to a genetic variant in proprotein convertase subtilisin/kexin type 9 (PCSK9) that has been implicated in increased risk of early-onset myocardial infarction. Yu et al. report a significant interaction between the PCSK9 single nucleotide polymorphism and ω-3 LC-PUFA intake on nonfatal myocardial infarction, such that higher ω-3 intakes confer protection only in protective allele carriers, although interestingly, no effects were observed when comparable analyses were performed with adipose tissue ω-3 LC-PUFA content (9). Although further studies are required, these findings could potentially have important implications when it comes to evaluating the benefits of increased ω-3 LC-PUFA intakes in primary and secondary prevention of cardiovascular disease and moving toward stratified or individualized approaches for preventing and treating disease.

So, what overall conclusions can we draw from these 3 studies? They clearly highlight the complexity of the relation between ω-3 LC-PUFA intake, ω-3 LC-PUFA status, and effects on body weight and cardiovascular variables in humans. This adds to our understanding of why responses to ω-3 LC-PUFA supplementation can vary so dramatically between individuals, and thus between studies and populations. In addition, these studies highlight the major challenge in accurate quantification of dietary fat intake and provide support for the need to include objective measures of ω-3 LC-PUFA status in place of (or at the very least in conjunction with) measures of ω-3 LC-PUFA intake.

The search for the optimal nutritional strategy for optimizing cardiometabolic health will no doubt continue, and it seems likely that ω-3 LC-PUFAs will continue to feature in this search. The evidence to date, however, including that contained in the articles in this issue, provides little support that high habitual ω-3 LC-PUFA intakes can protect against weight gain or cardiovascular disease at a population level, and that these effects may vary considerably across population groups. Thus, if ω-3 LC-PUFAs are to contribute to improving these, and indeed other, health outcomes in human populations, in addition to well-designed and -powered randomized controlled trials, future research focused on developing effective screening approaches for ω-3 LC-PUFA responders and nonresponders would appear to have considerable relevance.

BSM serves on the Advisory Board for the Nestlé Nutrition Institute and has given presentations on early-life nutrition for Danone Nutricia, Aspen, and BASF. All associated honoraria are paid directly to her institution and used to support professional development activities for postgraduate students and early-career researchers.

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