Invited Commentary

Invited Commentary: Dietary Polyunsaturated Fatty Acids and Chronic Systemic Inflammation—A Potentially Intriguing Link

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It remains largely unclear whether consumption of total and individual polyunsaturated fatty acids (PUFAs) is associated with chronic systemic inflammation in healthy, free-living individuals. While available evidence (stemming principally from mechanistic studies) has indicated that greater intake of n-6 PUFAs may lead to increased levels of inflammation—for instance, by their acting as precursors to proinflammatory eicosanoids and increasing levels of oxidized linoleic acid metabolites—n-3 PUFAs are precursors to some antiinflammatory eicosanoids. New human data from a Dutch prospective study, the Rotterdam Study—as presented by Muka et al. (Am J Epidemiol. 2015;181(11):846–856) in this issue of the Journal—now make an important contribution to the relatively scarce literature on the association of dietary n-3 and n-6 PUFAs with serum levels of C-reactive protein (CRP), a key marker of inflammation, in a general population. The study by Muka et al. benefitted from repeated CRP measurements, comprehensive correction for potential confounding, and wide-ranging sensitivity analyses. The findings show no significant trend regarding n-3 PUFAs but indicate an important inverse association between n-6 PUFAs and chronic systemic inflammation. This study provides support for existing dietary guidelines, which encourage consumption of a combination of n-3 and n-6 PUFAs in the diet.

C-reactive protein; inflammation; polyunsaturated fatty acids

Abbreviations: CRP, C-reactive protein; CVD, cardiovascular disease; LA, linoleic acid; PUFAs, polyunsaturated fatty acids.

Nutritional guidelines generally recommend reducing total consumption of saturated fatty acids by increasing the proportion of polyunsaturated fatty acids (PUFAs) in the diet (1, 2). The potential vascular benefits of doing so are, at least in part, believed to be a result of lipid-lowering effects of replacing saturated fatty acids with PUFAs (3, 4), since circulating lipid fractions such as low-density lipoprotein cholesterol are established risk factors for cardiovascular disease (CVD) (5, 6). However, fatty acids may also act by influencing other intermediate factors, such as blood pressure, glycemic control, and inflammation (3). Recent studies on the association of fatty acids with cardiometabolic consequences have also emphasized the importance of potentially diverse health effects of specific subtypes of fatty acids, which vary in chain length, number, and location of double bonds, and the food sources in which they are present (7–10).

In this regard, concerns have been raised about treating PUFAs as a single homogenous group of fatty acids, given the potentially heterogeneous associations of n-6 PUFAs and n-3 PUFAs with inflammation. Specifically, attention has been drawn to a supposed proinflammatory effect of n-6 PUFAs and the consequences of increasing total PUFA consumption (11). Indeed, the n-6 PUFA arachidonic acid is a precursor of various eicosanoids, some of which are proinflammatory, and high levels of these factors may give rise to an increased level of chronic systemic inflammation (12, 13). Additionally, it has been proposed that diets high in linoleic acid (LA), in combination with high levels of oxidative stress, may lead to greater CVD risk by increasing levels of oxidized LA metabolites (14, 15).

By contrast, the seafood-derived long-chain n-3 PUFAs are precursors of eicosanoids with less potent proinflammatory capacities or some antiinflammatory capacities, such as resolvins (3, 13). It has therefore been suggested that the ratio of n-6 PUFAs to n-3 PUFAs (which may be greater than 15:1 in Western diets) should be considerably reduced and may
even be more important than increasing total PUFA consumption, in order to reduce inflammation and associated disease risks (11).

However, the suspected opposing effects of n-6 and n-3 PUFAs on inflammation have largely been based on mechanistic studies, whereas evidence from human studies is scarce. Furthermore, recent studies have found that in addition to arachidonic acid serving as a precursor for proinflammatory factors, n-6 PUFAs may also exhibit antiinflammatory properties through pathways separate from cyclooxygenase (16, 17).

In this issue of the American Journal of Epidemiology, Muka et al. (18) report results from a new study of the association between dietary PUFAs and circulating levels of C-reactive protein (CRP), a key marker of inflammation, in more than 4,700 middle-aged men and women in the Netherlands. Dietary intakes of composite PUFAs, n-6 PUFAs, and n-3 PUFAs were assessed from a validated food frequency questionnaire at baseline, whereas serum CRP concentration was measured both at baseline (1989–1993) and during the third follow-up visit (1997–1999). After adjusting for a wide range of possible confounders, Muka et al. found that increasing levels of total PUFA consumption were significantly associated with lower levels of CRP (18). Interestingly, the inverse association in the current study was largely driven by n-6 PUFAs, which were also significantly and inversely associated with CRP. Neither n-3 PUFAs nor the n-3:n-6 PUFA ratio was associated with CRP following adjustment for confounding factors.

The present study contributes to the literature on dietary PUFAs importantly, with data on a known marker of inflammation in a large, free-living population (18). The prospective nature of the assessment and the collection of repeat measures of circulating CRP helped reduce within-person variability and the likelihood of reverse causation, and the detailed information obtained on dietary habits as well as potential confounding factors helped minimize the effects of residual confounding. Admirably, the investigators also conducted a range of subsidiary analyses to reinforce their findings.

So how do the results of this study compare with those from the previous literature? Few epidemiologic studies have evaluated the association of n-3 and n-6 PUFAs with inflammatory markers, and results have been heterogeneous. Inverse associations of dietary LA (an n-6 PUFA) (19) and serum total n-6 PUFAs (20) with CRP have previously been reported, though not in all studies. Pischon et al. (21) reported no association of dietary LA with CRP or any other inflammatory marker. In the same study, Pischon et al. also found a significant interaction between long chain-n-3 PUFAs and LA intake, in which the highest levels of inflammation, as measured by soluble tumor necrosis factor receptors 1 and 2, occurred in subjects with the lowest n-3 PUFA intake and the highest LA intake, but the lowest levels of inflammation were present among subjects with the highest intake of n-3 and n-6 PUFAs combined (21). In accordance with this finding, a systematic review of clinical trials also found that there was a trend towards an increased risk of death from coronary heart disease or CVD with interventions that increased only LA intake, but a reduced risk of death from coronary heart disease or CVD with mixed n-3/n-6 PUFA interventions, although this included only secondary prevention trials (15). Johnson and Fritsche (22) reported that among 15 clinical trials including healthy participants, there was no evidence for an association of dietary LA with a wide range of inflammatory markers. Although Muka et al. did not investigate a potential interaction between n-6 and n-3 PUFAs, the observed strong inverse association of total PUFA intake with CRP level lends further support for a protective effect of combined n-3 and n-6 PUFA consumption (18).

Observational evidence regarding the association of n-3 PUFAs with inflammation is mixed. For instance, Pischon et al. observed inverse associations with inflammatory markers of long-chain-n-3 PUFAs but not of intermediate-chain α-linolenic acid (21). On the other hand, both Poudel-Tandukar et al. (19) and Lopez-Garcia et al. (23) found inverse associations of α-linolenic acid with CRP. Although evidence from observational studies is highly valuable for assessing associations with habitual ranges of intake in free-living populations, clinical trial evidence may be more robust to effects from measurement error, reverse causality, and residual confounding. In a systematic review of clinical trials, Rangel-Huerta et al. (24) found that long-chain n-3 PUFAs had no association with levels of inflammatory markers in healthy participants. However, the evidence from trials carried out among patients at high CVD risk was more heterogeneous, with some (but not all) trials finding reductions in inflammation following increased long-chain n-3 PUFA intake. The authors proposed that the protective associations seen in trials of high-risk patients but not among healthy participants might be due to a greater potential to reduce inflammation at higher baseline levels of inflammatory markers and oxidative stress (24).

In summary, the reported inverse association of n-6 PUFAs with CRP is in line with the findings of various other observational studies, although protective associations are not generally reported in randomized trials. Such discrepancies between observational and trial evidence may be explained to some extent by potential effects of measurement error, reverse causality, and residual confounding in observational studies. Associations observed in clinical trials, on the other hand, may depend (for instance) on the specific type and amount of intervention, which may not necessarily reflect usual diet in free-living populations. In the current study, n-3 PUFAs were not associated with CRP levels (18), which the authors propose may be due to the high levels of α-linolenic acid contributing to total n-3 PUFA consumption in this population. Although it is true that Pischon et al. found a significant association of long-chain n-3 PUFAs but not α-linolenic acid with inflammation (21), several other observational studies found inverse associations of α-linolenic acid with inflammatory markers (19, 23). Nevertheless, the lack of association between n-3 PUFAs and CRP in a general population in the current study is in line with clinical trial evidence suggesting that n-3 PUFAs may be more potent in reducing inflammation among patients who are already at high risk of CVD (24).

A few limitations of the current study should be mentioned. First, in the association with PUFAs, serum CRP level was used as a marker of inflammation, which until recently was a biomarker of particular interest because of its strong association with various types of CVD and vascular and nonvascular mortality (25). However, a subsequent Mendelian randomization study suggested that CRP is unlikely to be
causally related to CVD (26). One of the proposed pathways through which n-3 and n-6 PUFAs may affect inflammation is the production of various eicosanoids that in turn may give rise to overall systemic inflammation (12, 24). Therefore, CRP seems to be only an “indirect” biomarker of inflammation in relation to PUFA intake. Nevertheless, despite its potential lack of a causal effect, CRP may still be a valuable biomarker of systemic inflammation in clinical practice—for instance, in predicting CVD risk (27).

As Muka et al. also note (18), some discrepancies between studies of dietary fatty acids and CRP—and, in a broader context, dietary fat and overall CVD risk—may be due to country-specific differences in food composition and dietary practices, as well as differential effects of specific fatty acid isomers. For instance, in the Rotterdam Study, correlations of specific food sources with n-3 PUFAs are somewhat different from those reported in the large pan-European population of the European Prospective Investigation into Cancer and Nutrition (18, 28), which may partly explain differences in associations between studies conducted in different countries. Large multicountry studies with data on dietary habits, intermediate risk factors, and incident CVD events should allow evaluation of the association of dietary PUFA with intermediate risk factors and disease events in a manner that investigates the potential effects of different food sources on these associations across different countries. This is particularly important, given that nutritional guidelines are dependent on the literature at hand, including studies that are often conducted in 1 country or geographical area.

Emerging evidence suggests that specific fatty acid isomers may have opposing associations with cardiometabolic risk (7–10), but intake levels of such fatty acid isomers are extremely difficult to estimate using traditional dietary assessment tools. Therefore, studies measuring objective biomarkers of fatty acid levels (such as circulating blood fatty acids) are needed to disentangle the associations of specific n-3 and n-6 PUFA subtypes with inflammation and overall CVD risk, and—in combination with extensive dietary data—may help to further establish which specific food sources may affect circulating levels of such fatty acids.

Nevertheless, the study by Muka et al. is a useful addition to the relatively scarce literature on the association of dietary PUFA with inflammation in free-living general populations, and it is particularly valuable because of its prospectively repeated measurements of CRP (18). Overall, the inverse association of n-6 PUFA with CRP levels provides further evidence in favor of potential anti-inflammatory properties of n-6 PUFA, and lends support to the existing guidelines that recommend consumption of a mixture of n-3 and n-6 PUFA in the diet.

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REFERENCES


