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Seafood Long-Chain n-3 Polyunsaturated Fatty Acids and Cardiovascular Disease:

A Science Advisory From the American Heart Association

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Abstract

Since the 2002 American Heart Association scientific statement "Fish Consumption, Fish Oil, Omega-3 Fatty Acids, and Cardiovascular Disease," evidence from observational and experimental studies and from randomized controlled trials continues to emerge to further substantiate the beneficial effects of seafood long-chain n-3 polyunsaturated fatty acids and cardiovascular disease. A recent American Heart Association science advisory addressed the specific effect of n-3 polyunsaturated fatty acid supplementation on clinical cardiovascular events. This American Heart Association science advisory extends that review and offers further support to include n-3 polyunsaturated fatty acids from seafood consumption. Several potential mechanisms have been investigated, including antiarrhythmic, anti-inflammatory, hematologic, and endothelial, although for most, longer-term dietary trials of seafood are warranted to substantiate the benefit of seafood as a replacement for other important sources of macronutrients. The present science advisory reviews this evidence and makes a suggestion in the context of the *2015–2020 Dietary Guidelines*

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for Americans and in consideration of other constituents of seafood and the impact on sustainability. We conclude that 1 to 2 seafood meals per week be included to reduce the risk of congestive heart failure, coronary heart disease, ischemic stroke, and sudden cardiac death, especially when seafood replaces the intake of less healthy foods.

Keywords

AHA Scientific Statements; diet; fatty acids, unsaturated; seafood

In 2002, the American Heart Association (AHA) published a scientific statement on n-3 fatty acids from seafood (including marine and freshwater finfish and shellfish) and supplements in relation to cardiovascular disease (CVD).[1] This review included a summary of observational studies and randomized trials. Also summarized were studies of n-3 polyunsaturated fatty acid (PUFA) intake as assessed with biomarkers in plasma, serum, or adipose tissue. Since 2002, more evidence has been published about the health benefits and risks of consuming seafood and supplements, the major sources of n-3 PUFAs. In 2007, these issues were addressed by the National Academies of Science, Engineering, and Medicine in *Seafood Choices: Balancing Benefits and Risks*.[2] In 2016, an update of 2004 reviews[3,4] on the topic was released, "Omega-3 Fatty Acids and Cardiovascular Disease: An Updated Systematic Review,"[5] conducted under the auspices of the Agency for Healthcare Research and Quality. An AHA science advisory on the topic of n-3 PUFA supplements, "Omega-3 Polyunsaturated Fatty Acid (Fish Oil) Supplementation and the Prevention of Clinical Cardiovascular Disease: A Science Advisory From the American Heart Association,"[6] was recently released. The purpose of this AHA science advisory is to summarize the health effects of seafood and the effects of dietary n-3 PUFAs from seafood on the primary and secondary prevention of CVD.

The long-chain (LC) n-3 PUFAs, eicosapentaenoic acid (20:5n3) and docosahexaenoic acid (22:6n3), are the LC n-3 PUFAs most closely associated with lower CVD risk.[7] More recently, some evidence has emerged for cardiovascular benefits of circulating or tissue levels of docosapentaenoic acid (22:5n3), another LC n-3 PUFA present in seafood and influenced more directly by metabolism.[8] The content of LC n-3 PUFAs is variable in seafood. Cold-water oily fish such as salmon, anchovies, herring, mackerel (Atlantic and Pacific), tuna (bluefin and albacore), and sardines have the highest levels of LC n-3 PUFAs. In contrast, shrimp, lobster, scallops, tilapia, and cod have lower levels (Appendix Table A1).[9] Although a growing number of foods such as eggs, peanut butter, orange juice, margarine, bread, yogurt, and milk are being enriched with LC n-3 PUFAs, seafood remains the primary dietary source of these fatty acids and is the only class of foods for which there is a substantial research base that includes hard clinical end points. For this reason, this science advisory is limited to seafood.

In 2010, the AHA Goals and Metrics Committee of the Strategic Planning Task Force issued 2020 Impact Goals to improve the cardiovascular health of all Americans by 20% while reducing deaths caused by CVDs and stroke by 20%.[10] The dietary goals were framed in the context of a dietary pattern that is consistent with a DASH (Dietary Approaches to Stop

Hypertension)–type eating plan and included a specific recommendation to consume at least 1 to 2 fish servings (3.5 oz per serving), preferably oily fish, per week.

This dietary recommendation is consistent with the AHA 2006 Diet and Lifestyle Recommendation.[11] In addition, the *2015–2020 Dietary Guidelines for Americans* and the *Scientific Report of the 2015 US Dietary Guidelines Advisory Committee* recommend at least 2 servings per week to provide an average of 250 mg eicosapentaenoic acid plus docosahexaenoic acid per day in place of other animal sources of protein.[12,13] The *2015–2020 US Dietary Guidelines for Americans* provide information about how to incorporate seafood into the healthy US-style eating pattern and the healthy Mediterranean-style eating pattern.

In 2012, the average seafood intake in the United States was ≈1.3 servings per week, a modest increase from 1.1 servings per week in 1999 but still well below the current recommendations.[14] In 2015, the top 5 species of seafood consumed in the United States were shrimp (4.0 lb per capita per year), salmon (2.9 lb per capita per year), canned tuna (2.2 lb per capita per year), tilapia (1.4 lb per capita per year), and pollock (1.0 lb per capita per year).[15] The LC n-3 PUFA content for commonly consumed seafood species is available in the US Department of Agriculture–Agricultural Research Service National Nutrient Database for Standard Reference, release 28[16] (abstracted from the *Dietary Guidelines for Americans, 2010*[9] and summarized for common species in Appendix Table A1). One fatty fish serving per week (4 oz) such as salmon provides the recommended daily intake of LC n-3 PUFAs (≈250 mg/d), whereas multiple servings of lean fish such as cod are required to achieve the recommended intake.

In the following sections, we summarize the available evidence on the effects of LC n-3 PUFAs from seafood on cardiovascular health. We selected those clinical markers, conditions, and hard clinical outcomes that have the greatest CVD health impact in the United States and for which LC n-3 PUFAs from seafood could provide the greatest opportunity for the prevention of CVD.

SEAFOOD AND PROPOSED INTERMEDIATE MARKERS OF CVD RISK

LC n-3 PUFAs are incorporated into the phospholipids of cellular membranes and have a wide range of demonstrated physiological effects. Seafood-derived LC n-3 PUFAs have electrophysiological effects such as favorable changes to cardiac ion channel function, β-adrenergic and other receptors, cell signaling pathways, and gap junction communication, as well as increased membrane fluidity.[17,18] Greater consumption of seafood has also been associated with other electrophysiological indexes, including lower heart rate, slower atrioventricular conduction, lower likelihood of abnormal repolarization (prolonged QT), and optimal values of several heart rate variability components. These effects are associated with a lower risk of developing ventricular arrhythmias[19,20] and sudden cardiac death.[21]

Increased dietary LC n-3 PUFA intake has been shown to enhance arterial elasticity by increasing endothelium-derived vasodilators,[22] including nitric oxide, 3-series prostacyclin, and endothelium-dependent hyperpolarizing factor.[23] Flow-mediated dilation is a measure of

brachial artery after shear stress that induces nitric oxide–dependent responses and resultant vasodilatation.[24] Low flow-mediated dilation of the brachial artery is predictive of endothelial dysfunction in the coronary arteries[25] and is thought to be an early predictor of the onset of symptomatic coronary heart disease (CHD).[26] A recent meta-analysis of 16 randomized controlled trials concluded that LC n-3 PUFA supplementation, mainly in capsule form, significantly improved endothelial function. Whether similar effects could be achieved at levels of LC n-3 PUFAs from dietary sources has yet to be determined,[27] although observational studies have found concordant associations between dietary intake of LC n-3 PUFAs from nonfried seafood and biomarkers of endothelial activation and inflammation, specifically C-reactive protein, interleukin-6, and matrix metalloproteinase.[28] LC n-3 PUFAs may exert transcriptional control of several endothelial proinflammatory genes, including those that code for endothelium adhesion molecules and cytokines.[29] Patients with diagnosed CHD fed diets high in LC n-3 PUFAs (salmon) had increased plasma LC n-3 PUFA levels and decreased vascular adhesion molecule-1, interleukin-6, and tumor necrosis factor-α markers, as well as serum triglyceride concentrations.[30] Other novel mediators resulting from LC n-3 PUFA supplementation include resolvins and protectins, and they may provide additional anti-inflammatory actions,[31] although evidence is lacking on such effects of LC n-3 PUFAs from seafood intake.

Seafood has been reported to have a cardioprotective effect on platelet-monocyte aggregation, a sensitive marker of platelet activation associated with the initiation and progression of atherothrombosis.[32] A correlation between LC n-3 PUFA intake and lower atherosclerotic plaques and arterial stiffness has been observed in multiple cohorts, including the ARIC study (Atherosclerosis Risk In Communities) and the Rotterdam Study.[33–35]

Dietary LC n-3 PUFAs from fish have been shown to reduce serum triglyceride concentrations in hypertriglyceridemic individuals,[36] likely as a result of increased clearance and decreased hepatic very low-density lipoprotein production rates.[23] Fatty fish intake has been reported to increase high-density lipoprotein particle size in subjects with coronary artery disease.[37] These effects are consistent with findings of randomized trials of LC n-3 PUFAs from supplements.

BLOOD PRESSURE

The biological effects of seafood on blood pressure are thought to be the result of the vasodilatory effects of prostaglandin metabolites of LC n-3 PUFAs, primarily from fish oil. To date, a large number of trials have demonstrated blood pressure–lowering effects of fish oil supplements in individuals with and without hypertension. Fewer trials have examined the blood pressure effects of seafood or other foods rich in LC n-3 PUFAs. In a recent meta-analysis of LC n-3 PUFAs from both supplements and food, Miller and colleagues[38] identified 70 trials with 93 intervention contrasts, 11 of which examined the short-term (<2 months) effects of foods rich in fish oil (seafood and foods enriched with fish oil together). None of the 6 trials that tested the effect of seafood significantly lowered blood pressure (Table 1),[39–43] and the overall effect was nonsignificant.

In sum, the available evidence is consistent with a beneficial role of dietary LC n-3 PUFAs on triglycerides, cardiac electrophysiology, endothelial function, and possibly blood pressure and inflammation, although the evidence for each of these end points is more limited for dietary as opposed to supplement sources. Larger well-controlled clinical trials of longer duration are warranted.

SUDDEN CARDIAC DEATH

Diets high in seafood have been more strongly associated with lower risk of fatal than nonfatal CHD events. For example, in the Physicians' Health Study, there was no significant relationship between dietary n-3 intake or blood n-3 PUFA levels and nonfatal myocardial infarction, despite the strong inverse association with sudden cardiac death.[44] Similar findings have been seen in multiple other prospective cohorts. This observation was attributed in part to the antiarrhythmic properties of the LC n-3 PUFAs. Higher seafood intakes have been associated with greater myocyte electric stability,[44] reduced vulnerability to fatal and nonfatal ventricular arrhythmias,[45,46] lower heart rate, and improved heart rate variability, each of which is a risk factor for arrhythmic cardiac death.

In healthy adults from other US-based population studies, seafood or LC n-3 PUFA intake was associated with lower sudden cardiac death risk.[21,47–49] In general, there is a dose-response association between very low to moderate intake and lower risk of sudden cardiac death but not between moderate and much higher intake. Consuming ≈1 to 2 fatty fish meals per week is associated with a 50% lower risk of sudden cardiac death compared with little or no seafood intake after adjustment for potentially confounding factors.[47,48] In most studies, no further reduction was reported with higher intake. Like CHD, the benefits of LC n-3 PUFA intake on sudden cardiac death may depend on the choice of seafood and the preparation method. Compared with <1 serving per month, consumption of ≥3 servings per week of seafood (not breaded or fried) was associated with a 68% lower risk of sudden cardiac death.[1] In contrast, fried fish was not associated with a lower risk of sudden cardiac death.[50] The excess risk in this study may be the result of the consumption of commercially prepared seafood breaded and deep-fried in partially hydrogenated oils containing *trans* fat and the low content of LC n-3 PUFAs in fried fish (typically white fish).

In contrast to studies conducted in the United States, higher seafood and LC n-3 PUFA intakes have not been associated with a lower risk of sudden cardiac death in Japanese populations.[51,52] In Japan, the background dietary seafood intake is 3 to 4 times higher than in the United States,[53] and 95% of adults eat seafood >1 time per week.[54] Hence, the lowest median quintile of LC n-3 PUFA intake is above the median of intake from US-based studies. Taken together, this evidence suggests that for apparently healthy individuals, the association between LC n-3 PUFAs from seafood and risk of sudden cardiac death is not linear but rather has a threshold effect. Modest consumption of seafood (≈1–2 servings per week) is associated with lower rates of sudden cardiac death compared with little or no seafood intake, and there is little additional benefit in risk reduction with a higher intake.

CONGESTIVE HEART FAILURE

Only a few prospective cohort studies have examined the association between seafood intake and risk of congestive heart failure, with heterogeneity in findings. Cardiovascular Health Study investigators reported a lower risk of heart failure with higher intakes of dietary LC n-3 PUFAs.[55] These findings have been confirmed in some[56,57] but not all cohort studies.[58–60] The Rotterdam Study[58] and the Cohort of Swedish Men[56] found no significant association between seafood consumption and the incidence of congestive heart failure. Four other large cohorts[55,57,59] reported an association between frequent consumption of seafood and a lower risk of heart failure (Table 2). Data from the Cardiovascular Health Study[55] and Women's Health Initiative[59] suggest that in contrast to baked or broiled seafood, fried seafood is associated with a higher risk of congestive heart failure. These data are consistent with the Physicians' Health Study, which showed a positive graded association between the frequency of fried food consumption and the risk of congestive heart failure.[61] If the positive association with fried seafood is causal, it suggests that the true effect size estimated for total seafood intake with congestive heart failure risk might be underestimated in studies that fail to account for preparation methods.

Few studies have used biomarkers of LC n-3 PUFAs to examine potential relationships with congestive heart failure. Although 1 study found no association,[60] 2 prospective cohorts[62,63] reported a significantly lower risk of heart failure in a comparison of the highest and lowest categories of serum or phospholipid eicosapentaenoic acid and docosahexaenoic acid.

There have been no randomized clinical trials of seafood and incident congestive heart failure, but evidence summarized in a recent AHA advisory report, "Omega-3 Polyunsaturated Fatty Acid (Fish Oil) Supplementation and the Prevention of Clinical Cardiovascular Disease," suggests that patients with congestive heart failure with reduced ejection fraction may benefit from LC n-3 PUFA supplementation to lower their risk of congestive heart failure–related hospitalizations and death.[6] No data are available on LC n-3 PUFAs from dietary sources and CVD outcomes in patients with congestive heart failure.

CORONARY HEART DISEASE

Individual large prospective studies and several systematic reviews and meta-analyses have reported inverse associations between seafood and dietary LC n-3 PUFAs and the risk of incident CHD among healthy populations.[5,64] In a systematic review restricted only to those studies in which participants reported seafood intake, participants who consumed seafood ≥4 times a week had a 22% lower risk of CHD compared with participants who consumed seafood less than once a month.[64] Restricting results to only the highest-quality prospective studies did not appreciably change the risk estimates. The benefit for seafood consumption (compared with nonconsumption) remained significant at levels of 1 to 4 servings per month. In a recent Agency for Healthcare Research and Quality review of prospective observational studies, mixed results were identified between individual LC n-3 PUFAs or total LC n-3 PUFAs and incident CHD.[5] An overall summary estimate across a wide range of intake was not significant. When a spline knot was added to separate lower and higher

intake, the inverse dose response was stronger but was not significant in the 100- to 400-mg/d range.

Systematic reviews of seafood intake and CHD risk have several strengths but also important limitations. Most important, they allow the calculation of pooled risk estimates with tighter overall confidence intervals across a broader range of intake than any 1 individual study estimate. In addition, recent efforts have established strict guidelines for undertaking these reviews; inclusion and exclusion criteria are predefined, and measures of quality and publication bias are required. Limitations should also be noted, especially for meta-analyses of a dietary component such as seafood.[65] First, meta-analyses usually rely on published categories of intake that are not identical across studies. This error is exacerbated by differences in the quality of the dietary assessment tool to quantify intake accurately. Furthermore, few studies use identical definitions of fatal and nonfatal CHD, which is particularly important for seafood because of the suggested benefit for sudden cardiac death and possibly congestive heart failure versus other CVD end points. Meta-analyses also generally cannot capture the potential effects of food substitution in the diet.[65] An individual's risk of CHD would be substantially lowered if he or she increased seafood consumption to 2 meals per week by substituting seafood for processed meat, but the estimated risk reduction may be substantially less (or not at all) if the 2 seafood meals per week were substituted for healthy vegetarian meals. In a recent analysis of 2 large US cohorts, substitution of 3% of total protein calories in processed meat with 3% of total protein calories from seafood was associated with 31% lower risk of cardiovascular mortality.[66] Future individual studies and systematic reviews should consider using substitution models as a more precise method to estimate risks and benefits of seafood consumption in relation to specific alternatives.

In summary, since the 2002 AHA scientific advisory on seafood intake and CHD,[1] a growing body of literature, mostly from prospective cohort studies, supports the conclusion that seafood intake or dietary intake of LC n-3 PUFAs is associated with a modestly lower risk of CHD. The benefit is likely greatest when an individual increases intake from 0 seafood meals per week to 1 to 2 seafood meals a week and could be greater if seafood replaces the intake of unhealthy foods.

STROKE

Although initial cohort studies focused on the associations between seafood intake and LC n-3 PUFA intake and total stroke,[67,68] studies since the 2002 AHA statement on seafood intake and CVD have examined the associations with ischemic stroke and hemorrhagic stroke separately. Results from the Nurses' Health Study and Health Professionals Follow-up Study indicate that intake of seafood was associated with a lower risk of thrombotic (ischemic) stroke but not with (either a lower or higher) risk of hemorrhagic stroke.[69,70] In the Cardiovascular Health Study, consumption of tuna or other broiled and baked fish was associated with a 40% lower risk of ischemic stroke among older adults; however, intake of fried fish or fish sandwiches was associated with a higher risk of ischemic stroke.[50] Whether the type of fish (lean fish low in n-3 PUFAs) or the method of preparation (frying in partially hydrogenated oils) accounted for this difference could not be determined. The association of

seafood intake and stroke mortality was examined in a combined analysis of 2 large cohort studies of men and women of Chinese ancestry. In that analysis, the risk of mortality from ischemic stroke was lower among those who consumed saltwater fish and had a higher intake of LC n-3 PUFAs.[71]

This was further summarized in a recent meta-analysis of cohort studies that suggested that compared with no or infrequent consumption of seafood, consumption of 1 serving of seafood a week was associated with a 14% lower risk of ischemic stroke with little or no association with hemorrhagic stroke.[72] Taken together, evidence from prospective studies supports the incorporation of regular seafood consumption to lower the risk of ischemic stroke.

SECONDARY PREVENTION OF CVD

A number of prospective observational studies have evaluated how seafood LC n-3 PUFAs, assessed largely with circulating biomarker levels, are associated with recurrent events among patients with prevalent CHD (Table 3).[63,73–80] Clinical end points varied from all-cause mortality to cardiac death to major adverse cardiovascular events. Most of these studies were small, typically with <100 and often <50 events. The heterogeneity in the end points evaluated, covariates, and methods for categorizing exposure (eg, quartiles, tertiles, continuously) makes it difficult to directly compare the findings across these studies. Generally, all studies suggested a trend for inverse associations between total eicosapentaenoic acid or docosahexaenoic acid intake (diet and supplements) and risk of recurrent events, although these relationships were not statistically significant.

A randomized trial[81,82] evaluated whether advice to consume fish reduces CHD in male patients with prevalent disease. This was an open-label, dietary advice trial in the United Kingdom. Men (n=2033) with recent myocardial infarction (mean, ≈1.5 months) were randomized in factorial fashion to advice to eat 2 servings of fatty fish per week, to reduce total fat to <30% calories and increase the ratio of polyunsaturated to saturated fat to 1.0, or to increase cereal fiber to 18 g/d.[81] Approximately 20% of the subjects randomized to fish advice chose to take fish oil instead (1.5 g/d). After 2 years, compared with the control group, no significant effects were seen in the dietary fat or cereal fiber groups. Patients randomized to fish advice experienced significantly lower total mortality (relative risk [RR], 0.73; 95% confidence interval [CI], 0.56–0.95) and CHD mortality (RR, 0.68; 95% CI, 0.51–0.91). A follow-up 15 years after the trial was completed found that participants who were still alive and initially randomized to fish advice reported still eating more fish, albeit much less.

DART 2 (Diet and Reinfarction Trial 2) recruited men with presumed stable angina based on physician impression and prescription without requiring electrocardiographic, stress exercise, imaging, or angiographic confirmation.[82] This trial likely was composed of a mixed population, including some with clinical angina and others with angina-like conditions (eg, esophageal spasm, heartburn, musculoskeletal discomfort). Patients were randomized in a factorial design to consume ≥2 oily fish servings per week or 4 to 5 servings of fruits and nonstarchy vegetables per day, 1 serving of orange juice per day, and

oats (servings not specified). There was also a control group receiving “sensible eating” advice (details not specified). About one third of the subjects randomized to fish advice chose to take fish oil instead (3 g/d). After 3 to 9 years, control subjects provided sensible eating advice experienced outcomes similar to or better than those of either intervention group. In post hoc analyses, subjects who chose to take fish oil rather than to eat fish had a higher risk of cardiac death and sudden death. Several design and implementation limitations (Table 3) make it difficult to interpret the findings of this trial.

INTERACTION WITH N-6 PUFA AND MERCURY

Interaction With n-6 PUFA

Concerns have been raised that high n-6 PUFA intake may attenuate the health benefits of seafood-derived LC n-3 PUFAs. Several prospective studies have addressed this issue and found no significant evidence of an interaction between n-3 and n-6 PUFA intake. In the Health Professionals Follow-up Study, ≥250 mg/d of n-3 PUFA was associated with a 40% to 50% lower risk of sudden cardiac death in men with either low (RR, 0.52; 95% CI, 0.34–0.79) or high (RR, 0.60; 95% CI, 0.39–0.93) n-6 PUFA intake (*P* for interaction=0.13).[83] In the Nurses’ Health Study, women in the highest tertile of both dietary n-6 and n-3 PUFA intake had a 54% lower risk of sudden cardiac death compared with women in the lowest tertile of both PUFAs (RR,0.46; 95% CI, 0.32–0.64; *P* for interaction=0.82).[21]

Mercury

Certain species of large predatory fish (shark, swordfish, tilefish [golden bass], king mackerel, bigeye tuna, marlin, and orange roughy)[84] are a significant source of methylmercury, which may have neurotoxic effects in the fetus[85] and reduce cognition in young children.[86] The existing evidence does not support significant adverse effects of mercury on CVD end points. Hair and toenail mercury levels are the best long-term integrated biological markers for intake of mercury,[87,88] whereas blood levels are more indicative of recent mercury ingestion. In 2 large prospective cohorts, higher concentrations of mercury in toenails were not associated with a higher risk of hypertension or CVD.[89,90] In a Finnish study of 1857 men and 91 sudden cardiac death events, a 0.5% increase in blood LC n-3 PUFAs was associated with a 23% lower risk of sudden cardiac death among men with low hair mercury (RR, 0.77; 95% CI, 0.64–0.93) but no significant effect among men with high hair mercury (RR, 1.02; 95% CI, 0.95–1.09; *P* for interaction=0.01).[91] If mercury in fish has an unfavorable effect on CVD risk, the available evidence suggests that the benefits of 1 to 2 servings a week outweigh the risks, especially if a variety of seafood are consumed.

TRIMETHYLAMINE N-OXIDE

Recently, concern has been raised about fish as a source of dietary trimethylamine N-oxide (TMAO) or its precursors[92] with respect to potential paradoxical adverse effects on CVD risk. Supporting data come mostly from secondary prevention studies that suggest that elevated blood levels of TMAO increase CVD risk.[93] Similar concerns have been raised about other sources of TMAO such as dairy, eggs, and red meat. This is an area that should

be further explored because the potential for diet to affect circulating TMAO is further complicated by differences in TMAO levels by species of fish and in other foods and the complex role that the composition of gut bacteria could have on metabolizing dietary sources of L-carnitine, choline, and betaine to produce TMAO.[94,95]

SUSTAINABILITY

Farmed Fish

The recent 2015 US Dietary Guidelines Scientific Advisory Report (2015 Dietary Guidelines Advisory Committee[13]) directly addressed environmental sustainability of dietary guidelines for greater consumption of LC n-3 PUFAs from seafood. For some species such as salmon or trout, LC n-3 PUFA levels are higher in farm-raised species, whereas other low-trophic fish such as catfish or crawfish have lower LC n-3 PUFAs.[12,13,16] The capture of wild-caught species has leveled off worldwide, but the productivity of worldwide aquaculture (farmed fish) continues to grow.[96] This growth in production should be monitored to ensure that farming systems are sustainable and environmentally appropriate and that their fish have LC n-3 PUFA content similar to that of wild-caught fish. It is important to note that the AHA recommendations to consume on average 250 mg/d is sustainable and can be met by consuming fish 1 to 2 times per week, including farmed fish, [13] in place of other animal protein sources.[12] Increased seafood intake can be achieved by choosing a wide variety of seafood that includes oily fish harvested from diverse geographic locations.

CONCLUSIONS

A large body of evidence supports the recommendation to consume nonfried seafood, especially species higher in LC n-3 fatty acids, 1 to 2 times per week for cardiovascular benefits, including reduced risk of cardiac death, CHD, and ischemic stroke. Evidence is more limited for congestive heart failure and mixed for blood pressure because of limited data. A greater seafood intake is generally not associated with either further benefit or harm. In addition to the primary CVD benefits of LC n-3 PUFA, inclusion of seafood may result in the displacement of other less healthy foods. This summary is consistent with the AHA 2020 Impact Goals to include seafood as part of the healthy dietary pattern goals[97] and the 2015 AHA Diet and Lifestyle recommendations.[98] In the *2015–2020 Dietary Guidelines for Americans*[12] and the associated 2015 Dietary Guidelines Advisory Committee Report,[13] 8 oz of seafood or 2 servings per week can be sustainable and environmentally friendly and is recommended as a good source of protein, vitamin D, vitamin B_{12}, and LC n-3 PUFAs. The *2015–2020 Dietary Guidelines for Americans* include seafood as a component of the healthy US diet, the DASH diet, and the Mediterranean diet. Others such as the Nordic diet, the Prudent diet, and the Alternative Healthy Eating Index also have seafood recommendations (or LC n-3 PUFAs), and all have been consistently linked to lower risk of CHD. In sum, the current scientific evidence strongly supports the recommendation that seafood be an integral component of a heart-healthy dietary pattern.

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APPENDIX

Table A1.

Seafood Long-Chain Polyunsaturated Fatty Acid Composition of Commonly Consumed Seafood Varieties

Common Seafood Varieties	EPA+DHA, mg/4 oz
Salmon: Atlantic, Chinook, coho	1200–2400
Anchovies, herring, and shad	2300–2400
Mackerel: Atlantic and Pacific (not king)	1350–2100
Tuna: bluefin and albacore	1700
Sardines: Atlantic and Pacific	1100–1600
Oysters: Pacific	1550
Trout: freshwater	1000–1100
Tuna: white (albacore) canned	1000
Mussels: blue	900
Salmon: pink and sockeye	700–900
Squid	750
Pollock: Atlantic and walleye	600
Crab: blue, king, snow, queen, and Dungeness	200–550
Tuna: skipjack and yellowfin	150–350
Flounder, plaice, and sole	350
Clams	200–300
Tuna: light canned	150–300
Catfish	100–250
Cod: Atlantic and Pacific	200
Scallops: bay and sea	200
Haddock and hake	200
Lobsters: Northern and American	200
Crayfish	200
Tilapia	150
Shrimp	100
Shark	1250
Tilefish: Gulf of Mexico	1000
Swordfish	1000
Mackerel: king	450

DHA indicates docosahexaenoic acid; and EPA, eicosapentaenoic acid. Abstracted from the 2010 US dietary guidelines report.[9]

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Penny M. Kris-Etherton	Pennsylvania State University	None	None	None	None	None	Seafood Nutrition Partnership (unpaid)*	None
Dariush Mozaffarian	Tufts University Friedman School of Nutrition Science & Policy	NIH/ NHLBI†	None	None	None	None	Pollock Communications*	None

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David S. Siscovick	New York Academy of Medicine	None	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
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Kevin P. Davy	Virginia Polytechnic Institute and State University	None	None	None	None	None	None	None
Angela M. Devlin	University of British Columbia (Canada)	None	None	None	None	None	None	None

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Table 1.

Summary of 5 Trials That Tested the Effects of Fish Consumption on BP

Authors, Year	Country	Intervention Regimen		Control	n	Duration, d	Net Mean Difference (95% CI), mm Hg	
		Intervention Type	DHA+EPA, g/d				Systolic BP	Diastolic BP
Von Houwelingen,[39] 1987	Netherlands	Mackerel paste (100 g/d)	4.7	Meat paste	82	42	−0.30 (−3.07 to 2.47)	−1.60 (−3.84 to 0.64)
Cobiac,[40] 1991	Australia	Salmon and sardines (142 g/d)	4.5	Mixed vegetable oil	18	35	−1.4 (−9.44 to 6.64)	−0.30 (−6.77 to 6.17)
Lindqvist,[41] 2009	Sweden	Baked herring (150 g/d, 3 d/wk)	1.2	Baked lean pork and chicken	35	42	2.10 (−3.21 to 7.41)	0.80 (−2.87 to 4.47)
Hallund,[42] 2010	Denmark	Marine trout (150 g/d)	3.2	Chicken	68	56	−2.00 (−7.55 to 3.55)	−3.00 (−7.33 to 1.33)
Ramel,[43] 2010	Iceland, Spain, Ireland	Cod (150 g/d, 3 d/wk)	0.3	Sunflower oil	139	56	2.0 (−0.7 to 4.7)	−0.50 (−3.02 to 2.02)
		Salmon (150 g/d, 3 d/wk)	2.1	Sunflower oil	139	56	−0.2 (−3.13 to 2.73)	−0.5 (−3.02 to 2.02)

BP indicates blood pressure; CI, confidence interval; DHA, docosahexaenoic acid; and EPA, eicosapentaenoic acid.

Table 2.

Dietary Total and Fried Fish Consumption and Risk of Heart Failure in Prospective Cohorts

Authors (Year), Study Name	Region	Sample Size, n	CHF Events, n	Follow-Up, y	Mean Age, y	Exposure	Adjusted RR (95% CI)
Fish intake and risk of heart failure							
Mozaffarian et al[55] (2005), Cardiovascular Health Study	US	5888	955	12	73	<1/mo	1.0
						1–3/mo	0.84 (0.67–1.06)
						1–2/wk	0.80 (0.64–0.99)
						3–4/wk	0.69 (0.52–0.91)
						5+/wk	0.68 (0.45–1.03)
Levitan et al[56] (2009), Cohort of Swedish Men	Europe	39 367	597	7	59	Never	1.0
						<1/wk	0.93 (0.72–1.21)
						1/wk	0.88 (0.68–1.13)
						2/wk	0.99 (0.73–1.33)
						3+/wk	0.97 (0.61–1.55)
Dijkstra et al[58] (2009), Rotterdam Study	Europe	5299	669	11.4	68	0	1.0
						1–19 g/d	1.15 (0.96–1.39)
						20+ g/d	0.96 (0.78–1.18)
Levitan et al[57] (2010), Swedish Mammography Cohort	Europe	36 234	651	9	61	Never	1.0
						<1/wk	0.86 (0.67–1.10)
						1/wk	0.80 (0.63–1.01)
						2/wk	0.70 (0.53–0.94)
						3+/wk	0.91 (0.59–1.40)
Belin et al[59] (2011), Women's Health Initiative	US	84 493	1858	10	64	<1/mo	1.0
						1–3/mo	1.03 (0.89–1.18)
						1–2/wk	0.89 (0.77–1.02)
						3–4/wk	0.99 (0.80–1.21)
						5+/wk	0.70 (0.51–0.95)
Wilk et al[60] (2012), Physicians' Health Study	US	19 097	695	12	66	<1/mo	1.0
						1–3/mo	0.70 (0.52–0.94)

Authors (Year), Study Name	Region	Sample Size, n	CHF Events, n	Follow-Up, y	Mean Age, y	Exposure	Adjusted RR (95% CI)
						1/wk.	0.73 (0.55–0.97)
						2+/wk	0.72 (0.54–0.96)
Fried fish and risk of heart failure							
Mozaffarian et al[55] (2005), Cardiovascular Health Study	US	5888	955	12	73	<1/mo	1.0
						1–3/mo	1.02 (0.82–1.19)
						1+/wk	1.35 (1.12–1.62)
Belin et al[59] (2011), Women's Health Initiative	US	84 493	1858	10	64	<1/mo	1.0
						1–3/mo	1.06 (0.95–1.19)
						1+/wk	1.48 (1.19–1.84)

CHF indicates congestive heart failure; CI, confidence interval; and RR, relative risk.

Table 3.

Prospective Cohort Studies and Randomized Controlled Trials of Dietary Omega-3 PUFAs From Seafood and Secondary Prevention of Cardiovascular Events

Study	Population	Exposure or Intervention	Duration of Follow-Up	Outcomes (n events)	RR (95% CI)
Prospective cohort studies					
Erkkila et al,[73] 2003	415 Patients with prior MI, revascularization, or unstable angina in Finland	Dietary fish consumption, cholesteryl ester EPA and DHA	5 y	All-cause mortality (34) Total CHD death (16) CVD (44)	Fish <57 vs 0 g/d: 0.37 (0.14–1.00) 0.45 (0.19–1.09) 1.04 (0.25–4.31)
					EPA T3 vs T1: 0.33 (0.12–0.93) 0.76 (0.33–1.79) 0.31 (0.08–1.14)
					DHA T3 vs T1: 0.31 (0.11–0.87) 0.55 (0.24–1.29) 0.48 (0.12–1.93)
Aarsetoey et al,[74] 2008	265 Patients with acute MI in Norway	Red blood cell EPA+DHA	1 d	Acute ventricular fibrillation within 6 h of symptom onset (10)	EPA+DHA per 1%: 0.52 (0.28–0.96)
Aarsetoey et al, [75] 2009	460 Patients with troponin-confirmed ACS in Norway	Red blood cell EPA+DHA	2 y	All-cause mortality (102) Cardiac death or ACS (158)	EPA+DHA Q4 vs Q1: 0.86 (0.46–1.63) 0.83 (0.49–1.41)
Lee et al, [76] 2009	508 Patients with acute MI in Korea	Plasma phospholipid EPA +DHA	1.3 y	All-cause mortality (36)	EPA per 1%: 0.29 (0.12–0.67)
					DHA per 1%: NS (not reported)
Pottala et al,[77] 2010	956 Patients with stable CHD in the United States	Red blood cell EPA+DHA	5.9 y	All-cause mortality (237)	EPA+DHA>median: 0.74 (0.55–1.00)
Ueeda et al,[78] 2011	146 Patients with acute MI in Japan	Serum EPA	1.5 y	Major adverse cardiac events (40)	logEPA inverse association (P=0.018)
De La Fuente et al,[79] 2013	572 Patients with chest pain and suspected ACS in Argentina	Red blood cell EPA+DHA	3.6 y	All-cause mortality (100) Cardiac death (54) Sudden death (35)	EPA+DHA Q4 vs Q1: 0.98 (0.50–1.94) 0.65 (0.25–1.70) 0.78 (0.22–2.80)
Harris et al,[80] 2013	1144 Patients with acute MI in the United States	Red blood cell EPA+DHA	2 y	All-cause mortality (135)	EPA T3 vs T1: 0.27 (0.07–0.55)
					DHA per 1 SD: 0.81 (0.66–0.94)
Hara et al,[63] 2013	712 Patients with acute MI in Japan	Serum EPA and DHA	3 y	All-cause mortality or heart failure hospitalization (80)	EPA T2+3 vs 1: 0.59 (0.37–0.95)

Study	Population	Exposure or Intervention	Duration of Follow-Up	Outcomes (n events)	RR (95% CI)
					DHA T2+3 vs 1: 0.60 (0.37–0.97)
Randomized controlled trials					
DART,[81] 989	2033 Men with recent MI (average, ≈1.5 mo) in the United Kingdom	Advice to consume fatty fish 2 servings/wk (or choose to take fish oil 1.5 g/d) vs usual care	2 y	All-cause mortality (224) Total CHD (276) CHD death (194)	0.71 (0.54–0.92) 0.84 (0.66–1.07) 0.68 (0.49–0.94)
Burr et al,[82] 2003 (DART 2) *	3114 Men with presumed angina based on physician impression and prescription in the United Kingdom	Advice to consume oily fish 2 servings/wk (or choose to take fish oil 3 g/d *) vs sensible eating advice	3–9 y	Total mortality (525) Cardiac death (319) Sudden death (120)	1.15 (0.96–1.36) 1.26 (1.00–1.58) † 1.54 (1.06–2.23) †

ACS indicates acute coronary syndrome; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; DART, Diet and Reinfarction Trial; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MI, myocardial infarction; NS, nonsignificant; PUFA, polyunsaturated fatty acid; Q, quartile; RR, relative risk; and SD, standard deviation.

*Several design and implementation limitations were evident, including lack of a prespecified primary outcome, lack of participant blinding, midtrial revision of randomization procedures to switch from subject choice to take fish advice or fish oil to a subgroup randomization to fish advice versus fish oil, inadequate funding that led to interrupted and delayed recruitment over 7 years, little follow-up to reinforce dietary advice or to evaluate long-term compliance, and no evaluation of changes in medications or other behaviors. Ultimately, about one third of subjects in the fish advice group elected to take fish oil (Maxepa 3 g/d).

†In post hoc analyses, higher risk was evident only in the subset of the fish advice group who choose to take fish oil instead of following dietary advice to eat oily fish.