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BENEFITS OF SEAFOOD CONSUMPTION ON HEALTH

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1. INTRODUCTION

Fish and a variety of other organisms from the aquatic environment have been much appreciated over the ages as food by humans. In a great number of communities the beneficial properties have been recognized for many generations and have entered into folklore. Scientific research since the 1950's has been directed, with increasing emphasis, to isolating and identifying the beneficial components followed by demonstrating their effect on health and quantifying their impact. The overwhelming focus has been on the long chain n-3 polyunsaturated fatty acids (LC n-3 PUFA's) eicosapentaenoic acid (EPA) and docosapentaenoic acid (DHA) as the documented carriers of the health benefits. The first part of this background paper concentrates on these effects but it is also pertinent to note that consumption of seafood ensures supplies of several important nutrients and micronutrients (in addition to the LC n-3 PUFA's). The effects of these are summarized in the second part of the paper.

The first section reviews the evidence for benefits of seafood consumption on human health, including on cardiovascular risk factors, clinical cardiovascular outcomes, neurological outcomes, and other potential outcomes. Results of prospective cohort studies and randomized clinical trials in humans are emphasized, with attention to metabolic studies and animal-experimental evidence, when appropriate, to elucidate potential mechanisms of effect. Potential risks of seafood consumption for human health are reviewed in a separate FAO/WHO background paper and are not covered here. However, it should be emphasized that for much of the evidence cited below, the measured exposure of interest was seafood consumption, which implicitly quantifies the net overall effect, including both harm and benefit, of seafood consumption.

2. CARDIOVASCULAR RISK FACTORS

Consumption and both seafood and marine n-3 PUFA influence several cardiovascular risk factors.[1-12] Most of the effects have been demonstrated in randomized controlled trials of either seafood or fish oil consumption, with generally similar effects for each; additional confirmatory evidence is also derived from some observational studies of seafood consumption and cardiovascular risk factors. Thus, at least for these cardiovascular risk factors, the effects of seafood vs. marine n-3 PUFA appear to be relatively similar, and the terms are often used interchangeably in the sections below.

Generally speaking, many physiological effects of seafood or n-3 PUFA can be seen within weeks of changes in consumption and probably result from altered cell membrane fluidity and membrane receptor responses, following incorporation of n-3 PUFA into cell membranes,[13, 14] as well as direct binding of n-3 PUFA to cytosolic receptors that regulate gene transcription.[15] The different physiological effects appear to have varying dose-responses and time-responses of effect (Figure 1).[16] At typical dietary intakes, anti-arrhythmic effects predominate, and such effects may reduce the risk of sudden cardiac death and coronary heart disease (CHD) death within weeks. At higher doses, maximum antiarrhythmic effects appear to have been achieved, but other physiological effects may begin to modestly impact other clinical outcomes. Notably, some of these other physiological effects (such as triglyceride-lowering) may require months to years of consumption before lower risk of clinical outcomes is seen. Thus, both the dose-response and the time-for-observed-clinical-benefit may vary depending on the specific risk factor evaluated. Several relevant cardiovascular effects are reviewed below.

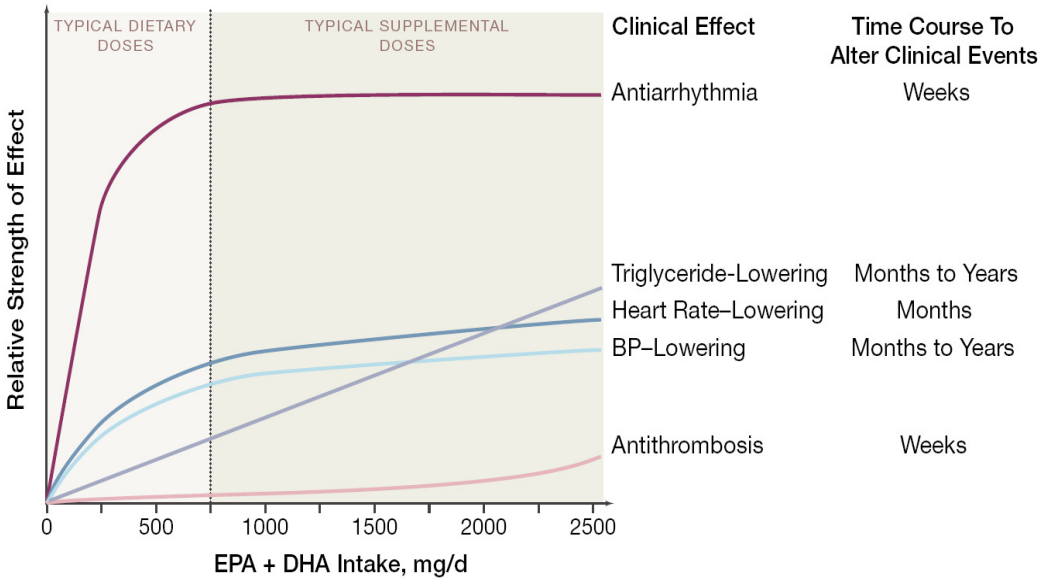

Figure 1. Schema of physiological effects of n-3 PUFA consumption. The relative strength of effect denotes the relative impact of n-3 PUFA consumption on the physiological effect (e.g., triglyceride-lowering). The time course to alter clinical events denotes the expected duration of consumption for the physiological effect to alter disease outcomes. For example, the dose-response for anti-arrhythmic effects appears to be initially steep with a subsequent plateau, and effects on disease outcomes may occur within weeks, whereas the dose-response for triglyceride-lowering is more gradual and monotonic, and effects on disease outcomes may require months or years of intake. Potentially important effects of n-3 PUFA on endothelial, autonomic, and anti-inflammatory responses are not shown because the dose- and time-responses of these effects are not well-established. Physiological effects are not necessarily exclusive: e.g., anti-arrhythmic effects may be partly mediated by effects on blood pressure (BP) or heart rate. *Reproduced from Mozaffarian & Rimm, JAMA 2006;296:1885-99.*

2.1. BLOOD LIPIDS

Marine n-3 PUFA consumption lowers serum triglyceride concentrations by 25-30%,[17-19] within the range of efficacy of other triglyceride-lowering drugs. The potential cellular mechanisms for this effect have been previously reviewed.[20] The dose-response appears to be fairly linear[19]: little triglyceride-lowering is seen with dietary doses or low-dose (<1 g/d) supplementation, while higher doses (3-4 g/d) appreciably lower triglyceride levels (Figure 1). With demonstrated efficacy, few contraindications, and no serious side effects, n-3 PUFA is an FDA-approved pharmological therapy for hypertriglyceridemia.[21] However, the n-3 PUFA doses required to lower triglycerides appreciably are several-fold higher than the doses that reduce coronary mortality (see below). Additionally, the clinical benefits of lowering elevated plasma triglyceride levels, by any pharmological means, have not yet been convincingly demonstrated. Thus, triglyceride-lowering per se is unlikely to account for benefits of low-dose n-3 PUFA (<2 g/d or

less) for reducing CHD death, although such effects may contribute over time to modest risk reductions in other clinical outcomes (e.g., nonfatal MI).

Particularly in patients with hypertriglyceridemia n-3 PUFA raises LDL-C concentrations (+5%) and lowers the proportion of small dense LDL-C particles;[22-24] this latter effect may in part account for the higher LDL-C concentrations. Given the frequently coexisting relationship of high triglycerides, low HDL-C, and small dense LDL particles in many individuals, the effects of n-3 PUFA to lower triglycerides, raise HDL-C, and decrease the proportions of small dense LDL particles appear concordant.

2.2. BLOOD PRESSURE AND SYSTEMIC VASCULAR RESISTANCE

In a meta-analysis of 36 randomized, placebo-controlled trials, fish oil consumption (median dose 3.7 g/d, median duration 8 weeks) among adults >age 45 lowered systolic BP by 3.5 mm Hg ($p<0.01$) and diastolic BP by 2.4 mm Hg ($p<0.01$).[6] In younger healthy adults (<age 45), the BP-lowering effects were less pronounced.[6] At the fish oil doses used in these trials (one trial 0.2 g/d, others ranging from 1.0 to 15 g/d), the BP-lowering did not appear to be dose-dependent.[6] Conversely, observational analyses suggest that, at lower dietary doses as consumed from seafood, the effects are similar but the dose-response may be more linear.[8] Animal-experimental studies[25] and observational studies in humans[8] indicate that the BP-lowering effect of seafood or n-3 PUFA consumption results from a reduction in systemic vascular resistance (i.e., lower arteriolar resistance), with unchanged cardiac output. In vitro studies demonstrate that n-3 PUFA induce nitric oxide production,[26] modulate endothelial activation[27] and modify the location and function of cell membrane caveolae proteins including eNOS.[28, 29] In short-term trials in humans, n-3 PUFA consumption increases biomarkers of nitric oxide production,[30] mitigates peripheral vasoconstrictive responses to norepinephrine and angiotensin II,[4, 5, 31] improves arterial wall compliance,[32] and enhances vasodilatory responses.[31] These effects, separately or in sum, could account for lowering of systemic vascular resistance. Thus, overall, the evidence indicates that n-3 PUFA consumption lowers systolic BP by ~3-5 mm Hg and diastolic BP by ~2-3 mm Hg, due to reductions in systemic vascular resistance, with a dose-response that appears graded at lower (dietary) doses, and plateaus at higher (supplement) doses (Figure 1). Heart Rate.

In a meta-analysis of 30 randomized, placebo-controlled trials, fish oil consumption (median dose 3.5 g/d, median duration 8 weeks) significantly reduced resting heart rate (HR) by 1.6 bpm (95% CI=0.6-2.5, $p=0.002$).[7] The effect appeared to vary with duration of consumption: in trials of <12 weeks duration, HR was reduced by 0.7 bpm ($p=0.27$), whereas in trials of ≥12 weeks duration, HR was reduced by 2.5 bpm ($p=0.001$). Similar to BP-lowering effects, the HR-lowering did not appear to be dose-dependent at the fish oil doses used in these trials (range 1 to 15 g/d),[7] but in observational analyses of fish consumption did appear to be dose-dependent at lower (dietary) doses,[8] with a threshold effect at ~250 to 300 mg/d EPA+DHA[33] (Figure 1). Resting HR is determined by intrinsic sinus node function, vagal and sympathetic activity, and systolic and diastolic cardiac function. Experimental studies in isolated rat myocytes, exercising dogs, and non-human primates confirm that n-3 PUFA lowers resting HR and suggest that this could result from direct cardiac electrophysiological effects.[1, 2, 34] For instance, membrane n-3 PUFA may alter myocardial ion channel function[1, 2] to modulate sinus node automaticity or responsiveness. Marine n-3 PUFA may also lower HR by more indirect effects, such as by improving left ventricular diastolic filling (see below) or augmenting vagal tone.[35] Given the relationship of higher resting HR with risk of CHD death and sudden cardiac death,[36-42] the HR-lowering effect of fish oil – approximately a 3 bpm reduction – may in part account for, or at least be an indication of, clinical benefits of seafood consumption.

2.3. HEART RATE VARIABILITY

Heart rate variability (HRV) is influenced by underlying resting HR, autonomic function, circadian rhythms, and underlying cardiac health. Experimental trials evaluating fish oil and HRV have been inconsistent,[35, 43-51] possibly due to small sizes (n=10 to 84), variable doses used (3-6 g/d), relatively short durations of intake (weeks to months), or limited periods of HRV assessment (often 60 min or less). In a small observational study,[52] granulocyte membrane DHA levels were associated with time-domain HRV in a subset of subjects (n=43) with type 1 diabetes, but only crude (unadjusted) results were presented. In 291 patients undergoing coronary angiography,[53] tissue EPA and DHA levels correlated with time-domain indices HRV in multivariable-adjusted analyses. In a large population-based study of 4,263 older adults, habitual consumption of fish and dietary marine n-3 PUFA was associated with specific components of HRV after multivariable-adjustment (including adjustment for differences in resting HR), suggesting favorable effects of seafood consumption on vagal activity, baroreceptor responses, and sinoatrial node function.[54]

2.4. CARDIAC RELAXATION AND FILLING

Left ventricular diastolic filling consists of two phases: an early phase of active (energy-dependent) relaxation, and a second phase of more passive (compliance-dependent) filling (with a final brief phase due to atrial contraction). Abnormalities of early relaxation are among the earliest signs of ischemic heart disease, while abnormal passing filling (reduced compliance) often results from long-standing hypertensive heart disease or ischemic heart disease. In non-human primates, 24 months of fish oil consumption improved left ventricular diastolic filling, increasing both end-diastolic volume and stroke volume, and improved myocardial efficiency.[3, 55] In a small experimental trial in healthy adults, 7 weeks of fish oil (4 g/d) improved the early phase of diastolic filling ($p<0.02$).[56] This relatively acute improvement suggests a functional or metabolic, rather than structural, effect on energy-depending filling. Marine n-3 PUFA may also improve the second (compliance-dependent) phase of diastolic filling by augmenting or preventing decline in ventricular compliance. In hypertensive rats, fish oil consumption reduced left ventricular hypertrophy.[57] In a cohort study of older adults, habitual modest fish consumption was associated with a trend toward lower electrocardiographically-defined left ventricular mass ($p=0.07$), a measure of left ventricular size and hypertrophy, and with a higher E/A ratio ($p=0.004$), a measure of more normal diastolic filling.[8] N-3 PUFA do not appear to directly impact cardiac systolic function.[8, 55, 56] N-3 PUFA consumption does increase cardiac stroke volume in experimental trials in nonhuman primates[3, 55] and observational studies of habitual modest fish consumption in humans.[8] However, the higher stroke volume appears to be due to slower resting HR (increasing filling time) and enhanced diastolic filling, rather than changes in contractility.[3, 8, 55]

2.5. ARRHYTHMIC RISK

In animal-experimental and in vitro studies, n-3 PUFA directly affect atrial and ventricular myocyte electrophysiology, mediated at least in part by effects on myocardial membrane ion channels[1, 2, 58] and possibly cell-cell connexins.[59, 60] In isolated rat myocytes, particularly ischemic cells that are partially depolarized, both EPA and DHA reduce myocyte excitability and reduce cytosolic calcium fluctuations via inhibition of membrane Na^+ and L-type Ca^{++} ion channels.[1, 2, 58] However, similar effects were also seen with n-6 PUFA,[61, 62] which in humans have neither comparable strength nor specificity of associations with CHD death and sudden cardiac death as do n-3 PUFA.[63] (Indeed, capsules containing n-6 PUFA have been used as an inert control drug in clinical trials of n-3 PUFA.) The lack of specificity in these experiments for n-3 PUFA makes it difficult to ascertain the relevance of these in vitro experimental effects to observed clinical benefits of n-3 PUFA in humans. Confirmation of direct anti-arrhythmic effects of n-3 PUFA on hearts in humans is limited by the absence of any reliable and easily obtainable biomarker of

such effects. Nevertheless, the strong relationships of n-3 PUFA consumption with incidence of CHD death or sudden cardiac death (and possibly also atrial fibrillation) in both observational studies and clinical trials (reviewed below), together with documented effects of seafood and fish oil consumption on heart rate (and likely also heart rate variability), indicate that n-3 PUFA have effects on cardiac electrophysiology that, either directly or indirectly, are likely to reduce the risk of arrhythmias.

2.6. INSULIN SENSITIVITY

n-3 PUFA do not have major effects on biomarkers of glucose metabolism or insulin sensitivity. In a pooled analysis of 3 prospective cohort studies, higher marine n-3 PUFA consumption was associated with modestly higher incidence of type 2 diabetes mellitus, with relative risks of 1.00, 1.05, 1.17, and 1.24 in quintiles 2-5, vs. quintile 1 (p trend=0.001).[64] Similarly in this analysis, individuals consuming fish 5+ servings/week, compared to <1/month, had modestly higher incidence of diabetes (RR=1.22, 95% CI=1.08-1.39). In experimental studies, n-3 PUFA modestly increase hepatic glucose production, without alterations (either improvements or worsening) in peripheral insulin resistance. Thus, it seems plausible that seafood and n-3 PUFA consumption may increase the nominal diagnosis of diabetes by increasing circulating concentrations of glucose, but without causing the other adverse metabolic abnormalities (insulin resistance, high triglycerides, and low HDL cholesterol) that result in increased health risks related to diabetes. In any case, these effects on glucose appear to be small. In a meta-analysis of 26 randomized trials, fish oil consumption (2 to 22 g/d) slightly raised fasting glucose levels among noninsulin-dependent diabetics and significantly lowered fasting glucose levels among insulin-dependent diabetics.[22] However, n-3 PUFA did not significantly affect hemoglobin A1c levels.[22] Thus, the effects of n-3 PUFA on fasting glucose levels are either too small to impact long-term glycemia or are counterbalanced by a small effects on postprandial glucose levels. Given beneficial effects of n-3 PUFA on several markers of the metabolic syndrome, including lowering triglycerides, increasing (slightly) HDL-C and LDL particle size, lowering BP, and lowering inflammation (see below), it is unlikely that n-3 PUFA consumption adversely affects glucose-insulin metabolism to any appreciable extent.

2.7. COAGULATION AND THROMBOSIS

High doses of n-3 PUFA (3-15 g/d) increase bleeding time,[65] but this has not been associated with higher rates of clinical bleeding. In a review of 9 randomized trials among 2,612 participants, including persons taking aspirin or warfarin, no consistent associations were seen between fish oil use or dose and bleeding risk.[66] For example, in one trial among 610 patients undergoing coronary bypass surgery who received 4 g/d of fish oil for 1 year, together with either aspirin or warfarin, neither bleeding time nor numbers of bleeding episodes were significantly affected.[67] n-3 PUFA suppress platelet activating factor in experimental in vitro studies, but in human trials significant effects of fish oil consumption on platelet aggregation are not reliably seen.[19] Consistent changes in fibrinogen, factor VII, or factor VIII are also not identified in controlled trials.[19] Thus, at least at doses up to 4 g/d (and likely higher), clinically apparent effects of n-3 PUFA on bleeding risk are not evident. Effects on platelet function do not appear to be a major pathway for lower risk of cardiovascular outcomes, although subtle effects cannot be excluded as a possible contributing mechanism.

2.8. INFLAMMATION AND ENDOTHELIAL FUNCTION

Potential anti-inflammatory effects of n-3 PUFA have received much attention in review articles and the lay press, given the role of EPA and DHA as precursors to specific eicosanoids and other inflammatory mediators. However, production and breakdown of these inflammatory metabolites is highly regulated, and thus it is not clear that changes in substrate due to consumption of EPA or DHA (from diet or supplements) have any major effects on these

pathways in humans. Controlled trials have generally not detected significant effects of fish oil intake on C-reactive protein levels.[19, 68] Conversely, fish oil consumption does appear to inhibit production of some cytokines, including interleukin-1beta and tumor necrosis factor-alpha.[69] However, to achieve these effects, relative high doses (>2 g/d) of n-3 PUFA may be necessary, and it is not clear that lower doses typically consumed in most nations produce substantial anti-inflammatory effects. Several, although not all, randomized trials in humans have demonstrated that fish oil consumption also lowers circulating markers of endothelial dysfunction, such as E-selectin, vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1).[68, 70]

3. CARDIOVASCULAR OUTCOMES

Cardiovascular disease encompasses a diverse range of outcomes, including CHD, various ventricular and atrial cardiac arrhythmias, ischemic and hemorrhagic stroke, congestive heart failure, valvular heart diseases, and peripheral arterial disease. CHD can be further subdivided into components of chronic progression of stable atherosclerotic plaque, plaque instability and acute plaque rupture, thrombosis and coagulation, and secondary cardiac arrhythmia. While several risk factors for these conditions are shared (e.g., high blood pressure is a risk factor for chronic progression of atherosclerosis, acute plaque rupture, ischemic stroke, atrial fibrillation, and congestive heart failure), each of these conditions also has distinct etiologic and physiological determinants. Thus, just as varying dose- and time-responses are seen for effects of seafood and fish oil consumption on risk factors, the effects of seafood consumption on clinical events also varies considerably, depending on the specific cardiovascular outcome considered.

3.1. ATHEROSCLEROSIS

One randomized trial did not detect significant effects of fish oil consumption (6 g/d for 2.3 years) on the progression of coronary atherosclerosis.[71] although this study was small (n=59) and may have been underpowered. A second randomized trial (n=223) evaluated the effects of fish oil consumption (1.65 g/d for 2 years) on progression of coronary and carotid atherosclerosis.[72, 73] Significant effects on carotid atherosclerosis were not seen; however, individuals randomized to fish oil had modestly less progression in the coronary arteries (p=0.04). The latter findings are consistent with an observational analysis among 229 women, in whom modest dietary n-3 PUFA consumption from seafood was associated with less progression of coronary stenoses and fewer new lesions during 3.2 years follow-up.[74] A third open-label randomized trial evaluated the effects of EPA (1.8 g/d for 2.1 years) on progression of carotid atherosclerosis in 81 Japanese patients with type 2 diabetes.[75] Individuals randomized to EPA had less progression of both mean and maximal intimal medial thickness. Although confirmation in additional studies is warranted, together these few studies suggest that seafood or fish oil consumption may modestly reduce chronic progression of stable arterial plaque.

3.2. CORONARY ARTERY RESTENOSIS FOLLOWING ANGIOPLASTY

Several clinical trials have evaluated the effect of fish oil consumption on coronary artery restenosis following angioplasty, with mixed results.[76] A meta-analysis of 12 randomized controlled trials indicated a trend toward modestly lower risk of restenosis with fish oil intake (RR= 0.87, 95% CI=0.73-1.05), but this did not achieve statistical significance.[76]

3.3. NONFATAL MI AND ACUTE CORONARY SYNDROMES

Nonfatal myocardial infarction (MI) and acute coronary syndrome (ACS) result from chronic progression of atherosclerosis, followed by plaque instability and acute rupture, followed by acute thrombosis. Thus, benefits of seafood or fish oil on any or all of these processes could

reduce risk of nonfatal MI/ACS. As described above, a limited number of studies suggest that n-3 PUFA consumption may modestly reduce the chronic progression of stable arterial plaque; in contrast, appreciable effects on thrombosis are not seen until very high levels of supplementation are reached. Effects of n-3 PUFA on plaque instability are not well-established; in one randomized controlled trial among 188 patients undergoing carotid endarterectomy, fish oil consumption (1.4 g/d for median 42 days) resulted in fewer plaques with thin fibrous caps and signs of inflammation and more plaques with thick fibrous caps and no signs of inflammation.[77] Thus, limited evidence suggests that fish oil intake may modestly reduce atherosclerosis progression and plaque instability. The dose- and time-responses of effects of n-3 PUFA on risk factors for atherosclerosis progression and plaque rupture, such as triglyceride and blood pressure levels (Figure 1), suggests that higher doses and prolonged duration of consumption may be necessary to lower risk of nonfatal MI/ACS appreciably.

Observational and clinical trial data support this. At modest levels of dietary marine n-3 PUFA consumption (<1 g/d), benefits for nonfatal MI/ACS are equivocal, with some but not all studies suggesting modest benefit.[63, 78-85] In contrast, evidence from Japan suggest that high levels (>1 g/d EPA+DHA) and prolonged consumption (years) of n-3 PUFA from seafood or supplements lowers risk of nonfatal MI/ACS. In a prospective observational study among 41,578 Japanese men and women free of cardiovascular disease, individuals in the highest quintile of dietary n-3 PUFA (median 2.1 g/d) had 67% lower incidence of nonfatal coronary events (95% CI=37-83%) compared with those in the lowest quintile (median 0.3 g/d), after adjustment for other risk factors.[86] In a randomized open-label trial among 18,645 Japanese men and women with hypercholesterolemia (3,664 with established CHD) treated with statins, prolonged EPA supplementation (1.8 g/d for 4.6 years) reduced major coronary events by 19% (p=0.01).[87] In both studies, benefits of n-3 PUFA were largely attributable to reduced nonfatal coronary events, rather than reduced CHD death, consistent with the very low rates of CHD death in Japan due to very high background seafood consumption.[88] Thus, growing evidence suggests that prolonged consumption (years) of relatively high levels of marine n-3 PUFA (>1 g/d) may reduce the risk of nonfatal MI/ACS; the required doses and durations of intake require further investigation.

3.4. CHD DEATH AND SUDDEN CARDIAC DEATH

CHD death and sudden cardiac death are clinically defined events that physiologically overlap and often share the final common pathway of ventricular arrhythmia, often ischemia-induced ventricular fibrillation. Consistent evidence from 19 prospective cohort studies and randomized trials indicates that consumption of marine n-3 PUFA from either fish or fish oil supplements lowers the risk of CHD death and sudden cardiac death.[63, 79-84, 86, 89-102] In contrast to the apparent graded dose-response for nonfatal CHD events, the dose-response for CHD death and sudden cardiac death appears nonlinear: compared with little or no intake, modest consumption (~250-500 mg/d EPA+DHA) lowers relative risk, and higher intakes do not substantially further lower CHD mortality. A pooled analysis of these studies demonstrates this nonlinear effect for CHD death, with a 36% risk reduction up to 250 mg/d EPA+DHA and then little additional lowering of risk at higher doses (Figure 2).[16] Results were very similar when restricted to prospective cohort studies of seafood consumption in generally healthy (primary prevention) populations.[103] Thus, overall benefits of fish or fish oil consumption for CHD death appear very similar in prospective cohort studies of fish consumption in generally healthy populations (i.e., primary prevention) vs. controlled trials of fish oil in individuals with established heart disease (i.e., secondary prevention). The time-course of benefit appears relatively early; in a large trial among patients with recent MI, fish oil consumption reduced mortality within 3 months due to fewer sudden cardiac deaths.[104] Effects did not appear to vary whether or not patients were receiving antiplatelet medications, beta-blockers, ACEI-inhibitors, or statins.[105]

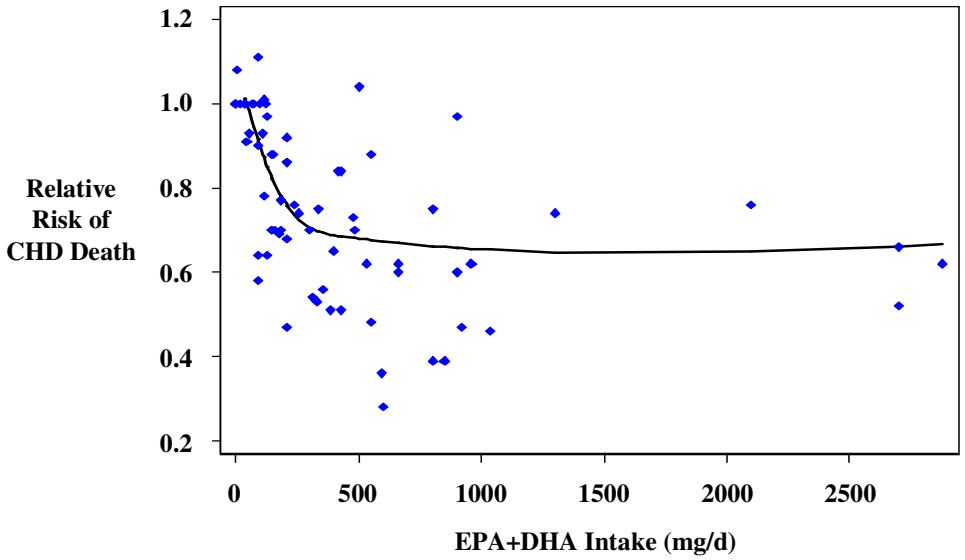

Figure 2. Pooled analysis of evidence from 15 prospective cohort studies and 4 randomized controlled trials of n-3 PUFA consumption from seafood or supplements and multivariable-adjusted relative risk of CHD death. At intakes up to ~250 mg/d, the relative risk of CHD death was 14.6% lower (95% CI=8-21%) per each 100 mg/d EPA+DHA, for a total risk reduction of 36% (95% CI=20-50%). At higher intakes, little additional risk reduction was present (0.0% change per each 100 mg/d, 95% CI=-0.9-0.8%). Results were very similar when restricted only to prospective cohort studies of seafood consumption in generally healthy (primary prevention) populations.[103] *Reproduced from Mozaffarian & Rimm, JAMA 2006;296:1885-99.*

3.5. TOTAL MORTALITY

In a meta-analysis of randomized controlled trials, fish oil consumption reduced total mortality by 17% (RR=0.83, 95% CI=0.68-1.00, p=0.046).[16] Because the effects of modest fish oil consumption on mortality are mainly to reduce CHD death/sudden cardiac death, the magnitude of the effect on total mortality would depend on the proportion of CHD deaths/sudden cardiac deaths in the population being examined. In this meta-analysis, most of the trials were performed in subjects with known CHD or at high risk of CHD,[16] in whom up to half of all deaths may be from CHD.[81] Based on a 36% reduction in CHD death (Figure 2) and 50% of all deaths being from CHD, the predicted effect on total mortality in such individuals is very similar to the actual observed result: i.e., a 36% risk reduction in CHD death x 50% CHD deaths = 18% lower risk of total mortality, or very similar to the actual finding of 17% lower risk in the meta-analysis. A proportionally smaller effect on total mortality would be anticipated in generally healthy populations in whom a lower proportion of total deaths would be attributable to CHD, e.g. in the general population of middle-aged adults in whom approximately one quarter of deaths are typically due to CHD.[106]

3.6. RECURRENT VENTRICULAR TACHYARRHYTHMIAS

Three small clinical trials (n=200 to 546) evaluated whether fish oil consumption (1.8 to 4 g/d) affected recurrent ventricular tachyarrhythmias during 1-2 years follow-up in patients with pre-existing ventricular tachyarrhythmias and implantable cardiodefibrillators.[107-109] Findings were mixed, with two studies showing no significant effect[107, 109] and one showing reduction in risk;[108] these relatively small trials may have been underpowered. In many cases, the pathoetiology of recurrent (ectopic or reentrant) ventricular tachyarrhythmias will be different from primary (often ischemia-induced) ventricular fibrillation that causes CHD death and sudden cardiac death. Thus, the mixed results of these small trials have little bearing on the far larger and more consistent body of evidence relating to the effects of fish or fish oil consumption on cardiac death in generally healthy individuals and those with established CHD (reviewed above).

Modest dietary n-3 PUFA consumption was associated with 35% lower incidence of atrial fibrillation (AF) in a prospective cohort study among older adults.[110] Conversely, significant associations between fish consumption and risk of AF were not seen in two subsequent observational studies.[111, 112] In a small (n=160) open-label randomized trial among patients undergoing cardiac surgery, consumption of n-3 PUFA (2 g/d) from 5 days pre-operatively until hospital discharge, reduced the incidence of post-operative atrial fibrillation from 33.3% to 15.2% (p=0.01).[113] Experimental studies in vitro and in animal models also suggest that n-3 PUFA may reduce myocardial vulnerability to atrial fibrillation,[114-117] possibly by means of effects of n-3 PUFA on connexins.[59, 115, 118] Ongoing small clinical trials are evaluating the efficacy of n-3 PUFA to prevent recurrence of atrial fibrillation in individuals with paroxysmal atrial fibrillation or following cardioversion. Atrial fibrillation is a clinically heterogeneous disorder, with incidence possibly related to autonomic activity and changes in cardiac dimensions in younger adults and athletes, similar acute changes and possible superimposed ischemic-recovery in the post-operative setting, and increased vascular stiffness and reduced ventricular compliance in older adults; furthermore, risk factors for first onset may be different than those for recurrence. Thus, seafood consumption may prevent atrial fibrillation in some settings but not others, and careful further investigation is required.

3.7. CONGESTIVE HEART FAILURE

As described above, seafood and fish oil consumption improve several cardiovascular risk factors that are known risk factors for congestive heart failure (CHF), including heart rate, vascular resistance and tone, cardiac relaxation and filling, systemic inflammation, endothelial function, and possibly autonomic function. By means of these effects and also potentially direct effects on the myocardium, n-3 PUFA may also improve left ventricular efficiency and diastolic function. In a prospective cohort study among older US adults, higher consumption of fish was associated with lower incidence of CHF.[120] After adjustment for other risk factors, individuals consuming fish 3-4 times/week had 31% lower risk (RR=0.69, 95% CI=0.52-0.91), compared to intake <1/month. In a second prospective cohort study in Rotterdam, estimated dietary intake of EPA+DHA was associated with a nonsignificant trend toward lower incidence of CHF (extreme-quintile RR=0.89, 95% CI=0.69-1.14), with greater tendency toward lower risk in women (RR=0.75, 95% CI=0.54-1.04) and diabetics (RR=0.58, 95% CI=0.32-1.06).[121] In a third prospective cohort of Swedish men, estimated dietary n-3 PUFA consumption was associated with lower incidence of CHF in the third quintile of intake (RR=0.67, 95% CI=0.50-0.90), but without significant lower risk in the fourth (RR=0.89, 95% CI=0.68-1.16) or fifth (RR=1.00, 95%=CI 0.77-1.29) quintiles, compared with the first.[122] Thus, overall, evidence for benefits of seafood consumption on CHF can be considered emerging, but further investigation is required to confirm this relationship.

3.8. STROKE

Results of ecologic and retrospective case-control studies of seafood consumption and stroke risk have been conflicting,[123-128] and most did not separately evaluate ischemic vs. hemorrhagic strokes. Some ecological and experimental studies suggested that high intake of marine n-3 PUFA might increase the risk of hemorrhagic stroke, possibly due to inhibition of platelet function.[123, 129, 130] However, n-3 PUFA intake in these studies was markedly higher than in typical diets,[131] and as reviewed above, n-3 PUFA appears to affect bleeding times only at high doses (3-15 g/d).[65] No significant differences in stroke risk have been reported in randomized trials of fish intake[79, 100] or fish oil consumption (1-2 g/d),[81, 87] but these trials were designed to evaluate CHD events and were not adequately powered to assess stroke. Prospective cohort studies, which generally better control for confounding and bias compared with ecologic or retrospective case-control studies, have generally observed inverse associations between modest seafood intake and incidence of stroke. In a meta-analysis of 9 prospective studies (including 3,491 incident strokes among 200,575 individuals), modest fish consumption was associated with lower incidence of ischemic stroke; no significant associations were seen for hemorrhagic stroke.[74]

4. EARLY NEUROLOGICAL DEVELOPMENT

DHA is preferentially incorporated into the rapidly developing brain during the last trimester of pregnancy and the first two years of infancy, concentrating in brain gray-matter and retinal membranes (Figure 3).[131, 132] Although infants can convert shorter-chain n-3 fatty acids to DHA to a greater extent than adults,[133] it is not known whether such conversion is adequate for optimal brain development in the absence of adequate maternal DHA intake.[134, 135] Both observational studies and randomized controlled trials have assessed the relationships of maternal DHA consumption with early brain development. Multiple observational studies have demonstrated independent beneficial associations of maternal DHA levels or fish consumption during pregnancy with behavioral attention scores, visual recognition memory, and language comprehension in infancy and childhood.[136-139]

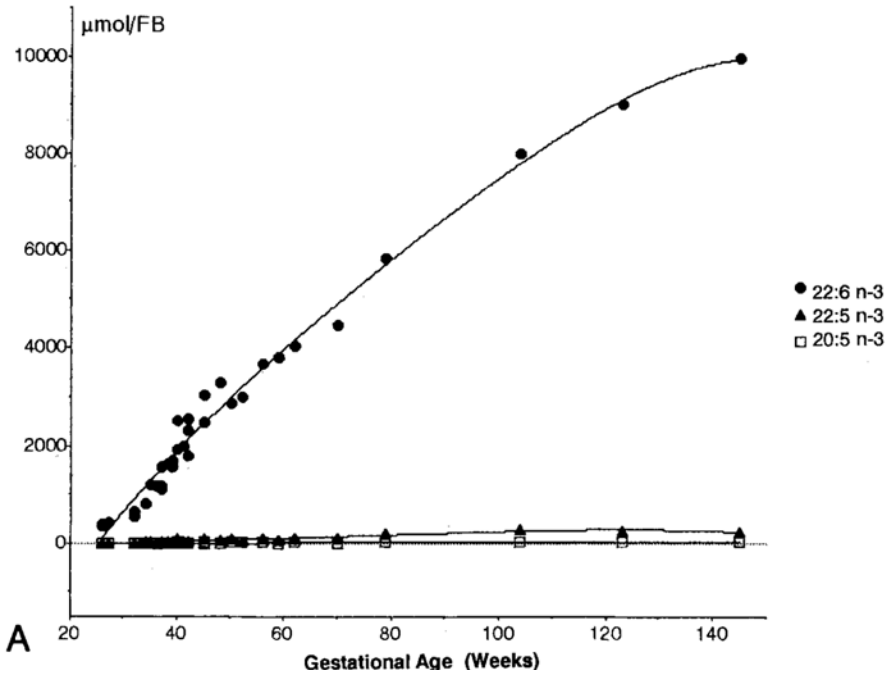

Figure 3. Accumulation of marine n-3 PUFA in the forebrain (FB) during human brain development. The dramatic accumulation of DHA (22:6n-3), compared with EPA (20:5n-3) or DPA (22:5n-3), is seen in these 34 infants, including both preterm and postnatal normally fed infants up to 2 years of age. *Reproduced from Martinez, J Pediatr 1992;120:S129-38.*

These observed benefits are consistent with findings of randomized controlled trials. Although the timing of DHA intake (gestational vs. nursing), the specific neurological outcomes assessed (visual acuity vs. global cognition vs. specific neurological domains), and the timing of the neurological assessment (late infancy vs. childhood) have varied, pooled quantitative analyses demonstrate significant benefits. In meta-analysis of 14 randomized controlled trials, DHA supplementation improved childhood visual acuity in a dose-dependent manner.[141] Results for cognitive testing have been less consistent, possibly due to differences in the specific neurological domains evaluated.[133, 136, 142] Nevertheless, in a quantitative pooled analysis of 8 randomized controlled trials, increasing maternal DHA intake by 100 mg/d was calculated to increase child IQ by 0.13 points (95% CI=0.08-0.18).[143] Most of these trials evaluated the effects of maternal DHA intake during nursing, rather than during pregnancy. In a trial among pregnant women, treatment with cod liver oil from week 18 of pregnancy until 3 months postpartum increased cord blood DHA by 50% and raised mental processing scores, a measure of intelligence, at 4 years of age.[144] Consistent with this, a recent prospective analysis indicated significantly higher incidence of suboptimal verbal development in children whose mothers had consumed lower amounts of dietary n-3 PUFA from seafood during pregnancy (Figure 4).[140] Thus, although specific dose-responses and full neurological effects require additional elucidation, consistent evidence from both observational studies and controlled trials demonstrates that higher maternal consumption of n-3 PUFA (particularly DHA) during pregnancy and nursing improves early brain development in children.

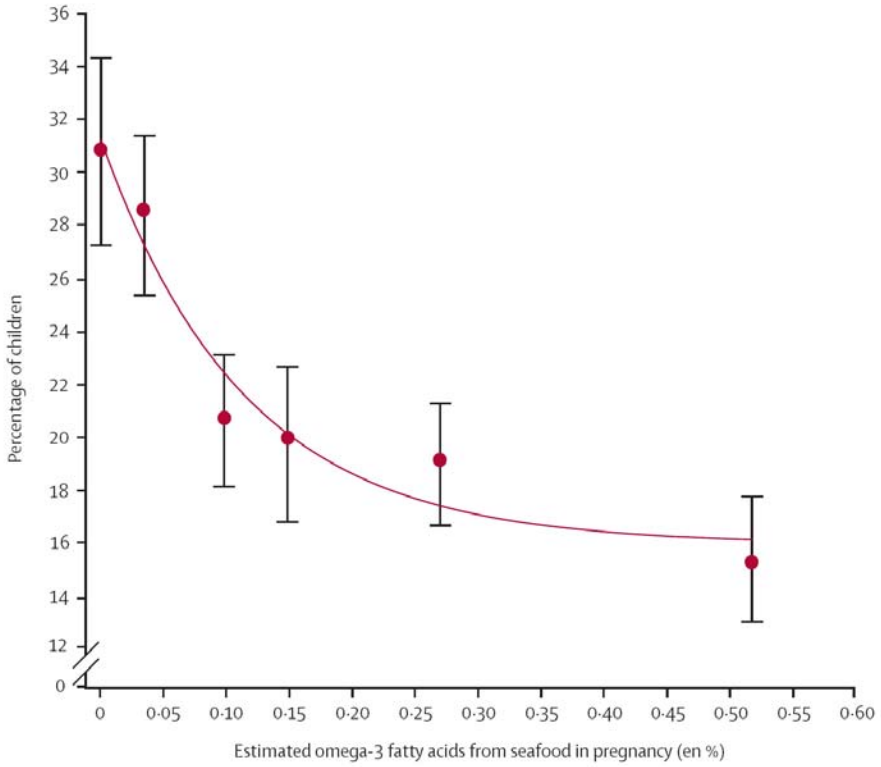

Figure 4. Prevalence of children with low verbal IQ according to mothers' dietary omega-3 fatty acid consumption during pregnancy. Estimated maternal consumption is expressed as percent of total calories (en%). The prevalence (●) and 95% CIs (⎮), and the best curve fit of these data, are shown for six different categories of maternal omega-3 fatty acid consumption. *Reproduced from Hibbeln, Lancet 1992;369:578-85.*

5. OTHER NEUROLOGICAL AND CLINICAL OUTCOMES

Emerging evidence suggests that seafood and marine-3 PUFA consumption may also benefit other clinical outcomes, but these effects are not as well-established as benefits for CHD death and early neurodevelopment. Thus, benefits for these potential outcomes listed below should be considered as emerging or possible, with perhaps the most promising evidence to-date for benefits on mood/depression, at least in certain circumstances (e.g., pregnancy).

5.1. COGNITIVE DECLINE AND DEMENTIA. [145]

5.2. MOOD AND DEPRESSION. [146, 147]

5.3. INFLAMMATORY DISEASES (ASTHMA, ARTHRITIS, PSORIASIS, ALLERGY). [11, 148]

5.4. CANCER

No probable or convincing effects; see the World Cancer Research Fund (WCRF) Second Expert Report 2007.

5.5. BONE HEALTH

In animal models, diets high in EPA+DHA have attenuated bone loss in ovariectomized animals, compared to diets enriched in n-6 PUFA.[149, 150] Potential mechanisms include proposed effects of n-3 PUFA on factors influencing bone formation and resorption, including prostaglandins, calcium, and cytokines.[150, 151] However, studies in humans are relative few and show mixed results. Small intervention trials in postmenopausal women with fish oil supplementation have yielded mixed results.[152, 153] In cross-sectional studies, consumption of seafood, n-3 PUFA, or a lower n-6/n-3 PUFA ratio has been associated with greater bone mineral density (BMD) in some[154-157] but not all[158] studies. In a Japanese case-control study, moderate fish consumption was associated with lower hip fracture risk.[159] In prospective studies, serum long-chain n-3 PUFA, especially DHA, have been positively associated with bone mineral accrual and peak BMD in young men.[160] Consumption of dark meat (oily) fish was associated with lower incidence of hip fractures in the Nurses' Health study,[161] but no association between fish consumption and incidence of bone fracture was seen in either a Japanese cohort[163] or the EPIC-Oxford cohort.[162]

6. HEALTH BENEFITS OF OTHER NUTRIENTS FROM FISH

As demonstrated above the association between seafood consumption and risk of CHD has been extensively studied. Although, as recorded above, the results are inconsistent, the majority of studies are in favour of cardio protective effects of seafood consumption. There is little doubt that LC n-3PUFAs in fish are key nutrients responsible for the benefits and are important for CHD prevention. Although seafood is valued as a source of these fatty acids, it also provides other nutrients that may also have cardio protective effects. It is likely that the beneficial effects on the risk of CHD are the synergistic result of these nutrients, and the integrative effects reflect the interactions between nutrients and contaminants in fish.

It has been frequently suggested that the nutritional impact of fish consumption is greater than the sum of its parts, if they are consumed separately[164]). On a wet weight basis, the 'non-n-3 compounds' usually contribute 95-99.5% of the edible portion of seafood. In the past 20 years, a number of scientists have speculated on the likelihood that such non-n-3 compounds also contribute to the documented cardioprotection and neuroprotection that results from a low to moderate fish consumption[163, 165-172]. Many of the effects demonstrated here are reviewed by Undeland *et al.* (2009)[173] and this section draws on the information in that monograph.

A review conducted in 2006[164] concluded that LC n-3 PUFA alone do not have a clear effect on total mortality, combined cardiovascular events, or cancer. However, positive effects on these end-points were seen when only the studies that were based on intact fish were taken into account. It has been suggested that the effect was due to the heavy influence of the so-called DART II study[174], where LC n-3 PUFA intake did not lead to reduced cardiovascular mortality in humans.

Despite the indications that non-n-3 compounds from seafoods might affect certain diseases in a positive way, it is obvious from the literature that clear evidence for such effects is lacking. Most indications are derived from simplistic *in vitro* models, from animal studies that are hard to extrapolate to humans or in the best cases, randomized clinical studies in humans but with, an insufficient number of subjects to have the power for statistical analysis. This section of the background paper concentrates on available evidence for possible health benefits of whole seafood (mainly fish muscle) and the components that are not LC n-3 PUFA's. The focus is on fish as a prime supplier of vitamin D, proteins, peptides, amino acids and selenium. While the biological activity of some of these compounds is the same whatever the source, seafood has been shown to be a good source. There are other compounds, such as seafood proteins and particularly LC n-3 PUFA's where seafood is the prime (or only) source.

6.1. VITAMIN D

Fatty fish are one of a very few dietary sources of vitamin D. The need for dietary vitamin D varies with the season since vitamin D is synthesised in the skin from 7-dehydrocholesterol by exposure to sunlight. Sun deprivation is common during wintertime in high latitudes and among the elderly population[175]. The capacity to synthesise vitamin D decreases with age and darker skin, and dietary vitamin D is particularly important for these groups. Deficiency and insufficiency of vitamin D have been reported recently to be common in epidemiological studies from Nordic countries such as Denmark, the Netherlands, Sweden and Norway. There is also an ongoing debate on the definition of deficiency (today commonly set at c-25-hydroxyvitamin D < 20 nmol/l)[176]. Circulating levels of 25-hydroxyvitamin D over 75nmol/l or 30ng/mL have been suggested to be required to maximise the beneficial health effects of vitamin D. To achieve this, in the absence of sun exposure, a daily intake of 800-1000 international units (25 µg/day) of vitamin D may be needed[177].

6.1.1. Bone health

Vitamin D deficiency causes rickets in infants and children and osteomalacia in adults. These diseases are associated with decreased bone mineralisation and bone weakness, caused by malabsorption of dietary calcium. The malabsorption of calcium causes hypocalcaemia, which stimulates the secretion of parathyroid hormone. Therefore, vitamin D deficiency is associated with secondary hyperparathyroidism[177] .

6.1.2. CHD and metabolic syndrome related diseases

Vitamin D insufficiency has also been related to CHD and type 2 diabetes mellitus[175, 178]. Observational studies in populations with moderate to high risk for CHD have found an inverse relationship between vitamin D and the extent of vascular calcification[178, 179] but the association with CHD, stroke and congestive heart failure must be confirmed in further studies[180]. Inverse association between vitamin D status and several risk factors for CHD such as BMI, blood pressure, blood glucose and TAG have been found[181].

A relatively consistent association between low vitamin D/calcium status and prevalent type 2 diabetes mellitus and the metabolic syndrome has also been reported from observational studies[180]. The evidence from intervention studies with supplementation with vitamin D and/or calcium supplementation is very weak, mainly because of the lack of long-term studies. The combination of vitamin D and calcium supplementation might prevent type II diabetes in subjects with glucose intolerance[178].

6.1.3. Cancer

Epidemiological studies have shown that vitamin D prevents several forms of cancer such us colorectal, colon, breast, ovarian, endometrial, prostate and lymphoma cancer[182]. The strongest correlation has been shown for colorectal cancer[183]. Cancer at other sites has also been related to higher death rates in subjects with inadequate vitamin D, although the beneficial effects of vitamin D on cancer need to be further evaluated in prospective studies[184].

6.1.4. Pregnancy

Vitamin D deficiency is proposed to be a risk factor for maternal pre-eclampsia. The explanation could be the beneficial effects of vitamin D on the elastic wall of blood vessels[180]. Adequate vitamin D concentrations are also necessary during pregnancy to ensure appropriate maternal responses to the calcium demands of the foetus and neonatal handling of calcium[185]. Whether vitamin D supplementation could improve maternal weight gain and foetal growth in women with a high risk of vitamin D deficiency is inconclusive[185].

6.2. CONSUMPTION OF SEAFOOD-DERIVED PROTEINS, PEPTIDES, FREE AMINO ACIDS AND TRACE ELEMENTS

The nutritional value of proteins from different food sources, including seafood, has been extensively reviewed[186]. Fish muscle protein is generally rich in lysine, the sulphur-containing amino acids and threonine, which are the limiting amino acids in the cereal-based diets of developing countries, especially for children. Therefore, increasing the proportion of fish in the diet of people where cereals are the main protein source is an effective way to enhance the nutritional value of food and improve the nutritional status. Recently there has been an increasing focus on the more specific role of seafood proteins in human health; both intact proteins and manufactured protein hydrolysates, prepared chemically or enzymatically. As dietary proteins are enzymatically and chemically hydrolysed *in vivo* during gastrointestinal (GI) digestion the health effects from seafood peptides could potentially be from whole fish. However, seafood peptides and seafood proteins have rarely been tested in animal or human models in completely lipid-free forms. Thus, it cannot be fully excluded that some of the reported effects of seafood proteins/peptides originate from the LC n-3 PUFA.

6.3. FISH PROTEINS

6.3.1.Uptake of dietary proteins

A significant proportion of dietary fish intake is made up of protein. This is especially true of lean, white fish such as for instance cod. Measurements of proximate composition of cod show values of 15-17% protein and 1-2.5% fat depending on the season[187].

Proteins are partially or fully denatured by normal cooking temperatures, but hydrolysis to small peptides and component amino acids is largely undertaken by stomach acid and digestive enzymes. Animal studies[188] have shown that both whole proteins and large polypeptides survive degradation in the stomach. Similarly, systemic exposure to proteins and peptides derived from food are the basis for antibody mediated food allergies[189]. Therefore, there is potential for the uptake of bioactive proteins and peptides directly from the diet.

6.3.2.Effects on cardiac risk factors - high blood pressure

The positive health effects of a diet containing purified fish protein have been documented in animal models of CHD. Commercially prepared, virtually fat-free fish protein lowered blood pressure in hypertensive rats[190, 191].

6.3.3.Effects on obesity, metabolic syndrome and type II Diabetes

In addition to obesity being a major risk factor for atherosclerosis and high blood pressure, which both contribute to the development of CHD, obesity is strongly associated with metabolic syndrome and type II diabetes. The metabolic syndrome is a complex condition including changes in circulating lipids, reduced glucose tolerance and increased insulin resistance. Unchecked metabolic syndrome can develop into type II diabetes, characterised by high levels of circulating lipids, high blood glucose and complete insensitivity to insulin. Arterial disease, cardiac hypertrophy and reduced heart function are well-characterised complications of type II diabetes. Animal studies and one human study have shown that fish protein, as a major component of the diet, might have the potential to improve health in metabolic syndrome and contribute to the prevention of type II diabetes[168, 192-194].

A comparison of the effect of cod proteins with other animal proteins (beef, pork, veal, egg, milk), with regard to their effect on insulin sensitivity in insulin-resistant human subjects, showed that cod proteins significantly improved insulin sensitivity and had a strong tendency to cause better β-cell function[168]. Cod proteins could thereby contribute to prevention of type II diabetes by reducing the metabolic compliance related to insulin resistance.

In animal model studies in which the dietary protein source was freeze-dried, defatted cod fillets, the animals showed improvements in glucose and lipid metabolism[195], improved glucose tolerance and insulin sensitivity [192, 196] and improved insulin signalling leading to glucose uptake[170, 197]. When studying rats fed on a high-fat diet, it was found that the use of casein and soy protein as protein sources caused development of severe whole body and skeletal muscle insulin resistance[193]. However, feeding defatted cod protein fully prevented this development of insulin resistance. No reduction in body weight gain, adipose tissue accretion, or expression of TNF-α in fat and muscle were seen in these rats. A review[198] of 15 randomised, controlled trials into the effects of high-protein diets on body weight and cardiovascular risk factors showed a close association between both total protein intake and type of protein consumed and weight control. High-protein diets, especially non-meat derived proteins, promote weight loss, improve plasma lipid status and have beneficial effects on insulin sensitivity.

Taken together, these results indicate that a diet rich in lean fish protein has the potential to reduce cardiac risk factors and improve metabolic function both indirectly by aiding in the control of obesity and directly via one or several active components of fish protein.

6.3.4.Selected amino acids in fish

It is generally accepted that the relative concentration of essential amino acids is the major factor determining the nutritional value of food proteins. Seafood muscles are rich in water-soluble components; among which are free amino acids: the main non-protein nitrogenous components that influence the taste of food significantly. The major free amino acids of seafood muscle are taurine, glutamine, proline, glycine, alanine and arginine. Cooking or thermal processing cause loss of water-soluble compounds and so the positive health effects of such components (free amino acids, minerals and trace elements) are likely to be greater when consuming minimally processed foods. The effects on human health of two amino acids, arginine and taurine, when consumed in amounts obtainable from the diet, are highlighted below.

6.4. ARGININE

Fish (and meat) proteins contain relatively high amounts of arginine (1-1.2 g/100g muscle) (FAO 1970). In shellfish, even higher levels are found (1.4-1.8g/100g). Arginine, which is found both in the free (mainly shellfish), and bound amino acid pool, is an essential precursor for the synthesis of proteins and other molecules with biological importance. Arginine administration has been suggested to be important in many pathophysiological conditions in humans[199]. When consumption of fish protein (grilled cod) was compared to meat (beef) in a limited number of healthy humans (6 males), an enhanced increase in plasma arginine was demonstrated[200]. A reduced secretion of postprandial insulin was also recorded in this experiment.

The possible effects of activating the l-arginine-nitric oxide pathway have been reviewed[201]. Synergistic effects of LC n-3 PUFAs on eicosanoid balance and the l-arginine-nitric oxide pathway have been suggested to provide additional cardioprotective effects[202].

6.5. TAURINE

Differences in muscle osmolality between marine and non-marine animals are mainly due to nitrogenous solutes such as certain free amino acids, among them taurine[203]. Seafood, especially invertebrates such as molluscs and crustaceans are high in taurine (300-800 mg per 100 g edible portion)[204-207].

Humans have a limited ability to biosynthesise taurine and it may be regarded as conditionally essential as its physiological concentration can be partly regulated endogenously[208]. Taurine is synthesised from cysteine via the sequential actions of cysteine dioxygenase (CDO), which gives rise to cysteine sulphinate, and cysteine sulphinate decarboxylase (CSD), which decarboxylates cysteine sulphinate to hypotaurine. Hypotaurine is further oxidised to taurine. The capacity for

taurine biosynthesis varies between species. As an example, compared with the *in vitro* CSD activity found in rat, the activity in man, primates and the cat are very low, which is believed to be the rate-limiting enzyme responsible for the formation of taurine from cysteine[209].

Taurine is thus an end product of sulphur amino acid metabolism and considerations of the need for supplementation or dietary changes have to include consumption data on methionine and cysteine. Methionine is the only essential sulphur amino acid (SAA) and can provide sulphur for cysteine and taurine synthesis. Animal protein is generally considered to be a better source of SAA than vegetable protein. There is apparent consensus concerning normal SAA requirements. The classical experiments of Rose[210] have been used and reproduced by WHO (FAO/WHO/UNU 1985)[211] and several other authors[212] and an SAA intake of 13 mg/kg per 24 h for healthy adults is still recommended.

Fish muscle consumption is reported to result in increased concentrations of serum taurine when compared with beef and chicken muscle[213]. Humans on a diet high in seafood are reported to be high in serum taurine[207, 214, 215] whereas humans on diets relatively low in seafood are reported to be low in serum taurine [171, 216]. Human urinary excretion of taurine is also known as a marker for seafood consumption[215, 217].

6.5.1.Effects of taurine on CHD and CHD risk markers

The beneficial effects of dietary supplementation with taurine, in animal and human models, have been reviewed[218]. A reduced CHD risk through taurine, alone or in combination with LC n-3 PUFA in seafood has been put forward in several papers[219-223] which have been reviewed by Yamori *et al.* [224]. One of the well-documented biological activities of taurine is bile salt formation. Taurine (and glycine) conjugates with cholesterol derivates to form taurocholate (and glycocholate). Taurocholate is the major bile salt that extracts cholesterol from plasma in humans and a decreased taurine content is associated with a lower cholesterol extraction and subsequent accumulation and increased risk of atherosclerosis. The anti-atherosclerotic effects of taurine have been studied in different hypercholesterol-aemic and hyperlipidaemic animals, but the exact mechanism of action is still unclear. Reviewed human trials (supplemented with high amounts 3-6 g per day) and animal intervention trials have also demonstrated that taurine alone has beneficial effects on serum lipids in rats, mice, rabbits and humans[218]. In contrast, a recent human intervention trial with supplementation of 1.5 grams taurine/day[216] showed no effects on blood lipids in overweight men with a genetic predisposition for type II diabetes mellitus.

Recently, a human intervention study on the combined effects of LC n-3 PUFA and taurine has been performed. Healthy volunteers, a total of 80 individuals, were recruited and divided in two groups to attend a seven-week double-blind and parallel intervention trial. One group received fish pâté enriched with n-3 (1.1g per day) and the second an identical pâté enriched with both LC n-3 PUFA and taurine (425mg/day), both levels comparable to a diet high in seafood. Total cholesterol, LDL-cholesterol and Apo B decreased significantly more in the LC n-3 PUFA+taurine compared to the LC n-3 PUFA group. Also a significant within group enhancement of HDL-cholesterol was demonstrated in the LC n-3 PUFA+taurine group[171].

6.5.2.Taurine and mental health

Taurine is regarded as important in membrane stabilisation and in the development of the central nervous system and the retina[209]. Recently, a paper on foetal neurodevelopment as being affected by seafood has also been published[225]. These kinds of effect have to date been attributed to LC n-3 PUFA alone, pinpointing the need for further research on human subjects to clarify the possible contribution of marine 'non omega-3 compounds'.

6.6. SELENIUM

Several review papers have addressed the beneficial health effects of selenium (Se) in relation to CHD, oxidative stress conditions, the immune system, viral infections, reproduction, thyroid function, mood and cancer [226-229]. The positive interactions between mercury and selenium have been reviewed[230], while other authors[231] have questioned how selenium might moderate the toxic effects of mercury in freshwater fish. Positive effects on immune system stimulation and reductions of cancer incidence/cancer mortality have been obtained in some cases where the Se intake has been above those levels supposed to be required for synthesis of the seleno enzymes. Excluding cereals, seafood is one of the food commodities relatively rich in Se (0.2-0.5 mg Se/kg fish muscle tissue). The Se content in farmed fish is at the lower end (0.2 mg/kg fish muscle tissue) but data are scarce. The contribution of fish to the total food intake of Se is approx. 15-20%, depending on soil content in the area. Se is an essential element and forms a part of at least eleven seleno-proteins in two groups of seleno-enzymes in the human body: glutathione peroxidases (GPx) and iodothyronine deiodinases. Se is beneficial at low concentrations, whereas at higher concentrations it becomes toxic. The range between deficiency, essentiality and toxicity, however, is rather narrow. The Scientific Committee on Food (SCF) from the European Commission (2000) recommended that Se intake should not exceed 300 µg Se per day. The Dietary Reference Intake established by the National Academy of Sciences (2000)[232] in USA is 55 µg Se/day for adult men and women. A so-called Population Reference Intake (PRI) of 55 µg Se/day was established by the SCF (1993)[233]. However, in some European countries different PRI values are recommended varying from 30-150 µg Se/day[173].

6.6.1.Bioavailability of Se from fish

The bioavailability and metabolic fate of Se from dietary fish in humans have not been studied extensively. A cross-sectional study[234] among coastal fishermen and inland men from Latvia (in total 68 men, 24-79 years) was carried out in order to investigate the relationships between fish intake and different markers of Se status and thyroid hormone function. The number of fish meals per month was correlated with plasma Se, selenoprotein P and GPx. The mean plasma Se level in the subjects with high fish intake was 81% higher than in those with the lowest intake.

An intervention study[235] was carried out to measure the bioavailability of Se from trout, yeast and selenate. The study had a parallel, randomised, reference substance controlled design and was carried out with 35 volunteers in the Netherlands and United Kingdom. Apparent absorption of Se from cooked or salted enzymatic ripened trout (88 ± 5% respectively 90 ± 3%) was similar to selenate (93 ± 4%). It also showed that there was no difference between the two fish processing methods used. Apparent absorption of yeast Se (54 ± 7%) was significantly lower than from Se in trout and selenate. However, Se retention from trout (86%) was significantly higher than selenate (60%). The retention of Se from yeast (59%) was lower.

In another study[236], wheat, garlic and cod intrinsically labelled with Se-77 or Se-82 stable isotopes were consumed in random order by 14 adults. The minimum wash-out period was six weeks between each test meal. Se absorption was significantly higher from wheat (81 ± 3%) and garlic (78 ± 14%) than from cod (56 ± 4%). The form of Se, and the food constituents with which it appears are suggested to be key determinants of post-absorptive metabolism.

6.6.2.Speciation of selenium in fish

From a nutritional and health point of view, it is important to know the chemical form in which Se is present in the edible part of the fish. The chemical form determines the degree of bioavailability and bioactivity after absorption. Although the methodologies for speciation trace element analysis have improved over the last ten years the speciation of Se in fish is still not optimal. Poor extraction recovery of Se from the raw material is one of the obstacles in this analysis.

6.6.3.Effects on cancer

Prospective studies of Se and cancer in humans[237], showed that in approximately 50 out of 72 studies, a lower cancer risk was associated with higher Se intake. The strongest evidence for a beneficial effect of Se appears to be related to lung cancer, oesophageal and gastric-cardia cancers and, most notably, prostate cancer.

The strongest evidence of the efficacy of Se as a cancer prevention agent, particularly for prostate cancer, is provided by the Nutritional Prevention of Cancer trial[238]. Subjects with a history of non-melanoma skin cancer were treated for 4.5 years with yeast-Se (200 µg Se/day) and the follow-up time was 6.5 years. Fifty percent lower total cancer mortality was found and 37% lower total cancer incidence.

Further randomised clinical trials using defined Se compounds are needed for confirmation of the above-mentioned clinical results.

7. SUSTAINABILITY

Although there is no association between resource sustainability and health a note is included below on the issue of sustainability, which must be considered if proven health benefits lead to greatly increased demand. With the wide range of benefits from seafood consumption documented in the foregoing, it is germane to consider whether increased production is possible and if there are sustainability issues that must be taken into account. For the last 20 years global landings from capture fisheries have been stagnant, at around 82-84 million tonnes from marine waters and 7-9 million tonnes from freshwater. Even with the widespread failure to manage fishery resources properly, which has resulted in a situation that some 28% of stocks are overexploited, there is general scientific agreement that significantly more cannot be produced from wild fish populations.

However, despite the stagnation in capture fisheries, total global fish production has continued to rise, amounting to about 140 million tonnes in 2007 (FAO 2009)[239]. The balance is made up by production from aquaculture, which now amounts to 50 million tonnes, comprising 44% of all fish for human consumption.

Global fish consumption has gradually increased, regardless of the increasing world population and stood at 17.0 kg of fish (live weight equivalent) per capita, per year, in 2007[239]. FAO databases show that the countries with the highest fish consumption are in the range of 100 to 200 kg per capita, per year, whereas some countries have an extremely low consumption of only 0.1 to 1 kg per capita, per year. Developed countries on average consume 24.0 kg per capita/year and developing countries 14.4 kg. One of the biggest challenges in the world's food production is the increasing demand for meat, i.e. animal proteins in general. This not only consumes large amounts of plant material but rearing animals is a very significant producer of greenhouse gases, particularly from ruminants. Fish proteins presently constitute 15.6% of all animal proteins consumed by humans.

A widespread recognition of the benefits of seafood consumption would inevitably lead to additional demand. If we speculate that the recommendations of two meals of 140 g of fish per week (Food Standards Agency 2004)[240] is widely adopted then per capita consumption would have to rise to 23.3 kg. (instead of the 17.0 that it was in 2007).This translates into an additional production that would have been needed in 2007 of 42.2 million tonnes, rising to 84 million tonnes in 2050.

Aquaculturists are optimistic that far more fish can be produced, but there are issues of nutritional quality using land based feeds. LC n-3 PUFA's would have to be incorporated into the feeds. Intensive research is required on how this could be achieved, including production from

hydrocarbons by yeast fermentation, extraction from algal sources[241,242] and genetic modification of plants to become LC n-3 PUFA producers.

8. CONCLUSION AND FUTURE IMPLICATIONS

The following table summarises the **evidence for the beneficial effects of seafood on health as well as indicating the strength of that evidence demonstrated by studies and trials.**

Endpoint	***Clinical Effect***	***Strength of the Evidence***	***Comment***
Cardiovascular Risk Factors			
Serum Triglycerides	*↓ 25-30%*	*Convincing*	*Linear dose-response effect, requires very high dietary intakes or supplement doses for clinically appreciable reduction.*
Serum HDL-C	*↑ 3%*	*Convincing*	*Small effect.*
Serum LDL-C	*↑ 5%*	*Convincing*	*LDL-C concentrations increase slightly, but this is due to increased size rather than number of the LDL particles.*
Blood Pressure	*Systolic: ↓ 3-5 mm Hg.* *Diastolic: ↓ 2-3 mm Hg*	*Convincing*	
Heart Rate	*↓ 2-3 bpm*	*Convincing*	
Heart Rate Variability / Autonomic Function	*↑ HRV indices, ↑ vagal activity*	*Possible*	*Inconsistent small experimental trials; several observational studies demonstrating positive relationships.*
Cardiac Relaxation and Filling	*↑ left ventricular efficiency, ↑ diastolic function*	*Probable*	*Consistent effects in animal-experimental studies, small human trials, and limited larger observational studies.*
Arrhythmic Risk	*↓ 25-50%*	*Probable*	*Probable based on in vitro studies, animal experiments, and associations with clinical cardiovascular outcomes (below)*
Insulin Sensitivity	*No effect*	*Probable*	*No effect on insulin sensitivity, but likely small effect to increase hepatic glucose production.*
Coagulation and	*No strong*	*Convincing*	*Only increased bleeding time at very high*

Thrombosis	*effects*		*doses of fish oil (3-15 g/d); no effects on clinical bleeding, although subtle effects cannot be excluded.*
Inflammation	*↓ cytokine production*	*Possible*	
Endothelial Function	*↑*	*Possible*	
Cardiovascular Outcomes			
CHD Mortality –			*Probable threshold of effect – most risk reduction occurs with modest intake (~250 mg/d EPA+DHA), with little additional benefit with higher intakes (see Figure 1).*[63, 79-84, 86, 89-102]
CHD Death	*↓ ~35%*	*Convincing*	
Sudden Death	*↓ ~50%*	*Convincing*	
Ischemic Stroke	*↓ ~30%*	*Probable*	*Strong evidence from prospective cohort studies;*[164, 165] *no RCTs.*
Nonfatal CHD –			
Nonfatal MI / ACS	*? Modest benefit*	*Possible*	*Possible benefits at very high intakes (~2 g/d n-3 PUFAs).*[86, 101]
Progression of Atherosclerosis	*? Modest benefit*	*Possible*	*Mixed results in cohort studies*[74] *and RCTs.*[71-73]
Post-Angioplasty Restenosis	*? Modest benefit*	*Possible*	*Possible benefits in a meta-analysis of RCTs.*[76]
Recurrent Ventricular Tachyarrhythmias in Patients with Implantable Cardiodefibrillators	*? Modest benefit*	*Insufficient*	*Mixed results in three small RCTs.*[107-109]
Atrial Fibrillation	*↓ ~30% +*	*Possible*	*Mixed results in two cohort studies;*[110, 111] *benefit in a small pilot RCT of post-surgical patients.*[113]
Congestive Heart Failure	*↓ ~30%*	*Possible*	*Benefits in one prospective cohort study;*[120] *trends toward benefit in two others.*[121, 122]
Neurological			

Early Neurodevelopment	*Convincing*	
Cognitive Decline and Dementia	*Possible*	
Mood and Depression	*Possible/ Probable*	
Other		
Inflammatory Diseases (Asthma, Arthritis, Psoriasis, Allergy)	*Possible*	
Cancer	*Insufficient/ Possible*	*See WCRF report.*
Bone Health	*Insufficient*	

RCT=randomized clinical trial.

With regard to future implications it is to be hoped that food safety authorities will continue to insist on a scientific approach to balancing the risks and benefits of seafood consumption at different life stages.

9. REFERENCES

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