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Review of evidence for the beneficial effect of fish consumption

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Öryggi, umhverfi og erfðir

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Report summary

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Titill / Title	**Review of evidence for the beneficial effect of fish consumption** / Yfirlitsgrein um jákvæð áhrif fiskneyslu		
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Ágrip á íslensku:	Þessi skýrsla inniheldur yfirlit yfir helstu innihaldsefni í fiski sem talin eru hafa jákvæð áhrif á heilsu manna. Fjöldi heilsuþátta sem tengdir hafa verið við jákvæð áhrif fiskneyslu voru skoðaðir og metnir. Mesta áherslan var lögð á að skoða og meta innihaldsefni í fiski sem eru til staðar í hlutfallslega háum styrk og því líkleg til að hafa áhrif á heilsu s.s. langar fjölómettaðar omega-3 fitusýrur, selen og D vítamín. Lögð var áhersla á að fara yfir og meta upplýsingar um jákvæð áhrif innihaldsefna í fiski á heilsu manna í nýlegum samantektarrannsóknum (en. meta-analysis), yfirlitsgreinum og álitsgreinum sérfræðinga. Skýrslan var liður í Evrópuverkefninu QALIBRA eða “Quality of Life – Integarted Benefit and Risk Analysis. Webbased tool for assessing food safety and health benefits” eða QALIBRA -Heilsuvogin á íslensku.		
Lykilorð á íslensku:	Yfirlitsgrein, jákvæð innihaldsefni, fiskur, fiskneysla, heilsuþættir		
Summary in English:	The aim of this review is to facilitate policy makers, nutritionists and other interested parties of Western societies in judging claims regarding the health benefits of fish consumption. This review focuses on the main constituents in fish that have been associated with health benefits of fish consumption. A variety of human health endpoints that may be positively influenced by fish constituents are considered and evaluated. Most attention is given to the constituents in fish that are present at relatively high levels in fish and thus are likely to influence human health. These include omega-3 fatty acids (omega-3 FAs), selenium, and vitamin D. The scope of this review is broad rather than detailed concentrating on collation and evaluation of existing information about human benefits of fish consumption from meta-analysis studies, reviews and expert opinions. This report was part of the work performed in the EU 6th Framework project “QALIBRA - Quality of life – integrated benefit and risk analysis. Web – based tool for assessing food safety and health benefits”.		
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Review of evidence for the beneficial effect of fish consumption

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Abstract

The aim of this review is to facilitate policy makers, nutritionists and other interested parties of Western societies in judging claims regarding the health benefits of fish consumption.

This review focuses on the main constituents in fish that have been associated with health benefits of fish consumption. A variety of human health endpoints that may be positively influenced by fish constituents are considered and evaluated. Most attention is given to the constituents in fish that are present at relatively high levels in fish and thus are likely to influence human health. These include omega-3 fatty acids (omega-3 FAs), selenium, and vitamin D. The scope of this review is broad rather than detailed concentrating on collation and evaluation of existing information about human benefits of fish consumption from meta-analysis studies, reviews and expert opinions. The evidence reviewed suggests that wild fish is a fairly unstable source of omega-3 fatty acids and other essential nutrients. Regular consumption of fish may, however, contribute to fewer incidences of nutritional deficiencies as well as decrease risk of several human health endpoints such as death from cardiovascular disease and stroke and onset of dementia (omega-3 FAs). In addition, some results indicate that selenium and vitamin D due to fish consumption or fortification decrease risk of colon, lung and prostate cancers. Vitamin D has also been associated with decreased risk of certain autoimmune diseases and decreased risk of falls and bone fractures in the elderly.

In addition to beneficial fish constituents, fish may also contain contaminants and other undesirable substances that potnetiallycounteract some important benefits of fish consumption. The fact that fish is neither homogenous in terms of beneficial constituents nor contaminant content, complicates advices on fish consumption. Factors such as the type of fish, season, reproductive stage and age affect the amount of nutrients and contaminants within a single species as well as between species. Therefore the exposure to these substances in human diet due to fish consumption varies considerably over time. Food policy makers need to take this variability into account before deciding whether or not measures need to be taken regarding advice to the public concerning fish consumption

Introduction

Food contains a wide range of desired substances e.g. nutrients, additives, dietary fibre as well as undesired substances e.g. environmental contaminants (heavy metals, endocrine disrupters like PCBs, and dioxins), pesticide residues, mycotoxins or excess amounts of otherwise desired components including nutrients. Food can also contain pathogenic bacteria, viruses and parasites. Decision-makers and consumers must weigh these potential risks and benefits when making regulatory decisions and dietary choices.

Governmental food policy aims at improving public health through food and supplements. This includes both regulations on food safety, food fortification and food consumption and supplement intake recommendations for the public. In this way food policy makers can direct people´s eating habits through advices or by enforcing certain supplements to be added to particular food items. Various foods and food supplements are claimed to have a wide variety of health benefits. It is therefore vital that food policy makers are provided with as good evidence as possible regarding these claims. Fish is a multicomponent food item of high nutritional value, but may also contain various undesirable substances. Food policy makers need to take both beneficial and harmful effects of fish consumption into account before deciding whether or not measures need to be taken. Food policy makers will also have to acknowledge and take into account people’s fear and possible overreaction to information about foods containing undesirable substances (1).

The aim of this review is to facilitate policy makers, nutritionists and other interested parties of Western societies in judging claims regarding the health benefits of fish consumption. The scope of this review is broad rather than detailed, concentrating on collation and evaluation of existing information about human benefits from the intake of fish constituents. Light is shed on the relevance of fish consumption on health benefits by relating effective doses to the level of constituents in fish. The focus of our literature review is on meta-analysis studies, reviews and expert opinions.

Fish constituents

Fish and fish products are a source of many essential nutrients. They contain high-quality protein, are rich in vitamin D and minerals like iodine and selenium. In addition seafood is high in omega-3 FAs and the most important source of these fatty acids and vitamin D in our diet. However, seafood also contains undesirable substances like heavy metals and persistent organic pollutants. The key undesirable constituents in fish are dioxins, dioxin-like polychlorinated biphenyls, methyl mercury and brominated flame retardants (2, 3).

Presently little is known about the relative contribution of the various desirable nutrients in fish to the beneficial effects of fish consumption. So far most beneficial effects of fish have been ascribed to omega-3 FAs; however, fish constituents include a range of other potentially desirable substances.

To achieve full benefit from fish, it may not be enough to consume only fish oil (He, 2009 = ID ref599). To explore health benefits of fish consumption it is therefore necessary to look at the nutritional value of individual fish constituents. In this review the main emphasis will be on ***fish oils (omega-3 FAs)***, ***vitamin D*** and ***selenium***, i.e. constituents that can be at relatively high levels in fish and which additional intake might be beneficial to people. Because of relation to vitamin D effect on bone health, ***calcium*** will also be discussed. Below more details about these constituents in fish and fish products will be given.

The fish constituents: ***fluorine***, ***iodine***, ***iron***, and ***vitamin B*** will only be briefly discussed, even though these substances have suboptimal intake levels in portions of Western populations. The reason is that fish is either not the major source of these compounds nor is fish consumption likely to become the most practical strategy for replenishing deficient people of these substances.

In addition to these constituents, fish is also a source of several substances that are important for human body functions, but are typically not deficient in humans of the Western World. These substances include various ***proteins*** for building of muscle mass, ***peptides*** for healthy blood pressure and cancer prevention (4), ***taurine*** for lowering high blood pressure (McCarthy, 2003=ref 162) and protection against neurodegenerative diseases (5), ***choline*** (from lecithin) for reducing cardiovascular diseases (CVDs) and enhancing memory (6, 7), ***coenzyme Q10*** (ubiquinone) for alleged cardio protective effects and slowing of Alzheimer´s and Parkinson´s disease (8, 9), ***creatine*** for added athletic performance (191), ***carnosine*** for skeletal muscle performance (11) and for anti-oxidative anti-aging properties (10), ***copper*** for the maintenance of the cardiovascular- and brain systems (12, 13) , ***phosphorus*** for heart and kidney function and healing of broken bones (14), and ***vitamin A*** for night blindness, healthy skin and cancer protection (15). Future studies may reveal additional evidence that some of these fish constituents contribute more to the health benefits of fish consumption than current knowledge infers. An example of this could be the possible role of fish proteins in reducing risk of type 2 diabetes (16). Herein this group of substances will not be discussed further.

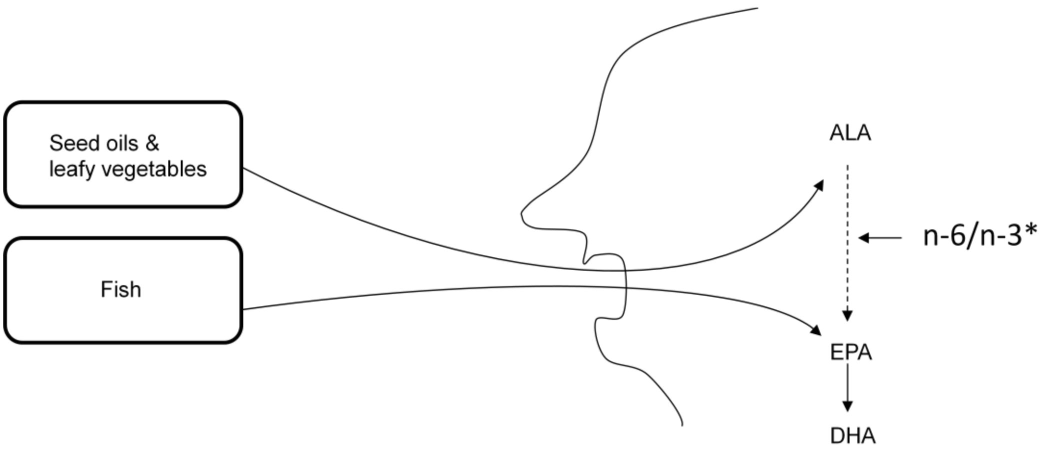
Optimal nutrition may be defined in terms of the level of a nutrient required to avoid deficiency, or the amount required to have an effect on biomarkers and functional indicators of nutrient intake, or the level of a nutrient which prevents disease (17). The amount of nutrients above the level required to avoid signs of deficiency, may give added benefits. The constituents of fish most commonly associated with human health benefits are listed in Table 1 as well as their daily requirement and amount in fish.

Table 1. Constituents of fish most commonly associated with human health benefits.

Class	Constituent	Daily requirement		C Level in 100 g fish	References
		A For avoiding deficiency	**B For added benefit**		
Oils/Lipids	Omega-3 FAs (EPA + DHA)	200-400 mg	650-800 mg	118-2000 mg	A & B: Table 2 C: 18 19
	Coenzyme Q10	n.s.			
	Choline (from lecithin) [b)]	125-550 mg		74-77 mg	A: 20 C: 21
Nitrogenous compounds	Proteins	0,66-0,87 g/kg body weight	n.a.	15-20 g	A: 22 C: 23
	Peptides	n.a.			
	Taurine			6-176 mg	C: 24
	Creatine				
	Carnosine				
Dietary minerals	Calcium (Ca)	400-1000 mg	1000 mg	250-380 mg in canned bony fish	A: 25 B: 26 C: 27
	Copper (Cu)	0,9-1,3 mg	3 mg	0,02-0,1 mg	C: 28, 29
	Fluorine (F)	1,5-4,0 mg	n.a.	0.004-0.4 mg [a)]	A: 30 C: 31, 32
	Iodine (I)	120-150 µg	n.a.	30-1270 µg per 100 g fillet	A: 25 C: 33, 34
	Iron (Fe)	3-8,1 mg	n.a.	0,36-3,3 mg	A: 22 C: 28, 35
	Phosphorus (P)	100-1250 mg	n.a.	200-400 mg	A: 14 C: 36
	Selenium (Se)	55-90 µg	200-300 µg	13,6-90 µg	A & B: 37 B: 38 C: 39, 40
Vitamins	Vitamin A	210-625 µg RE	n.a.	2-90 µg RE	A: 22 C: 36
	Vitamin B_2	0,3-1,6 mg	n.a.	0,01-0,14 mg	A: 25 C: 23
	Vitamin B_6	0,1-2 mg	n.a.	0,06-0,83 mg	A: 25 C: 23
	Vitamin D	200-800 IU	1000 IU	50-1000 IU	A: 25 B: 41 C: 42

n.a., not applicable
NE, Niacin Equivalents (1 NE = 1 mg niacin = 60 mg tryptophan)
RE, Retinol Equivalents (1 RE = 1 µg retinol) (25).
Vitamin D, 1 IU = 25 ng vitamin D (25).
a)_ Muscles of Atlantic cod, Atlantic halibut, Atlantic salmon and rainbow trout were measured to have 9-16 mg fluorine per kg dry weight (31). The dry weight is assumed to be 25% of wet weight.
b) Lecithin is normally considered to be phosphatidylcholine (6). Choline is 13% w/w of phosphatidylcholine (6) and 88% of choline chloride.

Omega-3 FAs are the best known constituents of fish. Seafood, including fish and algae are essentially the only human food sources of the long chain fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). These fatty acids can make up to one third of fat in fish muscle (43). The known effect of fish fat is ascribed to DHA and EPA. The term "fish oil" will from hereon be used for intakes of DHA and EPA based on fish consumption as well on intakes of isolated fish oil products containing DHA + EPA. DHA and EPA are very important for the human body, DHA is the most common fatty acid of the human brain (44) and in nerve endings during development (45) while the highest concentrations of EPA are found in human muscle and liver tissues (46). The human body can neither synthesize DHA nor EPA from scratch but need the precursor alpha linolenic acid (ALA) for initiating the synthesis process. ALA, DHA and EPA all belong to a so called omega-3 FAs series, because their first double bond from the tail starts at the third carbon. Figure 1, shows the sources of these fatty acids in human diet.



**Within the human body, competition for enzymes between n-3 and n-6 families results in a very inefficient formation of EPA from ALA.*

Figure 1. Sources of short (ALA) and long (EPA, DHA) omega-3 FAs.

It is a growing belief among scientists that the functional roles of omega-3 FAs are mainly based on members of the longer chains (e.g. EPA and DHA), rather than on ALA. This belief is based on two facts. Firstly, in addition to calorie intake the only known functional role of ALA in adults is to be a precursor for longer chain fatty acids such as DHA (Figure 1) (19). Secondly, a high dietary omega-6/omega-3 FAs (n-6/n-3) ratio typical for Western diets makes the ALA to DHA conversion very inefficient. The actual requirements for essential fatty acids are not known, neither for ALA or longer chain omega-3 FAs (48). Current ALA recommendations are based on estimations of the actual consumption of various population groups (48). DHA and EPA requirements have until recently been calculated as certain fraction of the estimated ALA requirement, but are now set to decrease risk of coronary heart disease (48), see table 2.

Table 2. Short (ALA) and long (EPA & DHA) omega-3 FAs intake recommendations for adults along with actual consumptions.

	Recommended (women – men)		**Consumed* (women – men)**	
	ALA (g/day)	**EPA+DHA (mg/day)**	**ALA (g/day)**	**EPA+DHA (mg/day)**
Europe	2 - 3 1)	250 1)		
Austria		-	1,1 – 1,2 1)	251 – 280 1)
France		400 – 500 1)	0,7 – 0,9 1)	350 – 420 1)
Finland		450 1)	1,8 – 2,5 1)	-
Germany			1,3 – 2,3 1)	210 – 340 1)
The Netherlands		450 1)	1,3 – 2,0 1)	80 – 100 1)
UK	1,1 – 1,6 7)	200-1500 7)		203 6)
N-America				
Canada	1,2-1,6 g/d 2)			
USA	1,1 – 1,6 1) (2-3) 3)**	650 2) ~1g 5)	(1-2) 3)†	~160 4)
Australia	2 8)	160-430 8)†	1,17 8)	162 8)
World		650-800 9)		

*Mean values.
** Recommended dose for the prevention of CHD.
† A range, not the difference between genders.
1) (49)
2) Not distinguishing between individual omega-3 FAs (50).
3) (51)
4) A fourfold increase in fish consumption is needed to achieve the recommended dose of the combined EPA and DHA in the U.S.A. (50).
5) The recommendation for patients of coronary heart disease by the American Heart Association (52)
6) Average person in UK consumes Average long chain omega-3 FAs concentration of oily fish is 2 g/100g, 0.3 g/100g white fish and 0.4 g/100g shellfish. The average adult consumes each week 50 g oily fish, 104 g white fish and 27 g shell fish. From this information the daily intake of EPA + DHA via seafood consumption was calculated (2).
7) UK Department of Health recommend: 0.2 g/day EPA + DHA
British Nutrition Foundation Task Force recommend: 1.0-1.5 g/day EPA + DHA (http://www.omega3fattyacids.co.uk/omega-3-intake-recommendations.html).
8) 53. Average consumption of people >=19 years old.
9) Dietary Recommendations for Omega-3 Fatty Acids. (http://www.omega3learning.purdue.edu/info/what-are-omega-3-fatty-acids/dietary-recommendations-for-omega-3-fatty-acids/).

In addition, humans also require linoleic acid (LA), the precursor of the n-6 series. Because LA and ALA compete for the same enzymes, the actual requirements of ALA depend on levels of LA consumed. The direct consumption of EPA and DHA can bypass the enzyme competition of LA and ALA by providing at least some of the downstream products of ALA.

Vitamin D regulates cellular growth and influences the modulation of the immune system. Vitamin D also regulates the calcium and phosphorus in the blood and promotes bone formation and mineralization (54).

Severe vitamin D deficiency leads to softening of bones (55). Vitamin D deficiency (hypovitaminosis) can also lead to muscle weakness (56) and possibly cardiovascular diseases (57). At higher levels vitamin D may potentially decrease the risk of some cancers (15).

Too much vitamin D can lead to mental retardation and kidney failure (54). Safe intake of vitamin D probably lies above 10 000 IU/day (58).

The two major sources of vitamin D are skin production in response to sunlight and dietary intake. Main dietary sources of vitamin D are fortified foods, in addition to oily fish, egg yolk, liver, and vitamin D supplements (59). Vitamin D intoxication is an extremely rare occurrence (54), while vitamin D deficiency is common all over the world (59).

Calcium, at adequate bioavailable amounts, is important in preventing osteoporosis (27). Animals store their calcium in bones. Fish eaten with bones, such as canned sardines and salmon is a relatively good source of calcium (27), especially in humans with low consumption of milk and milk products (60).

Selenium (Se) is an essential micronutrient in humans. However, too much Se in diet can cause toxicity and the gap between essential and toxic level of Se is narrow (61). Se is incorporated in many proteins and plays a role in major metabolic pathways of human cells (62).

Obvious clinical signs of human Se deficiency are rare (62). In deficiency, problems may arise with the muscles of heart and skeleton as well as weakened immune function (63).

Symptoms of Se toxicity (selenosis) include brittle hair and deformed nails and in extreme cases loss of feeling and control in arms and legs (64). The maximum save daily intake of Se lies above 600 µg (61), and probably close to 900 µg (37).

Adequate serum levels of Se have been associated with prevention of cancer and CVDs by protecting the vascular endothelium against oxidative damage. Large proportion of European populations may have suboptimal Se intake for cancer protection (65). See table 1 for adequate Se intake.

Cereal, meat and fish consumption generally contribute most to Se intakes (38, Gonzalez et al., 2006 = IDref240). There is a better correlation between human Se serum concentrations and fish or meat consumed than cereals consumed (Gonzalez et al., 2006 = IDref240). Too low Se intake is likely to contribute to morbidity and mortality in many countries of the Western world (38).

Fluorine is essential for dental health. In presence of fluorine, crystals of the mineralization of bones and teeth become more resistant to decay (30). Adequate levels of fluorine are believed to decrease risk of tooth caries and in presence of sufficient levels of calcium and vitamin D to increase bone mass and decrease incidence of bone fractures (30).

Chronic fluorine intakes of 20-80 mg/day results in fluorosis, i.e. a harmless brownish teeth enamel (30). Too much fluorine can also result in nausea, itching, diarrhea, and vomiting (30).

The main source of fluorine is natural or fluoridated drinking water (in the form of fluoride ions) and in dental products (15). Fish and tea may also supply substantial amounts (30).

Iodine forms part of the thyroid hormones, which are involved in the control of metabolic rate and necessary for the development of the nervous system in the fetus and infant (15).

Iodine deficiency is associated with enlarged thyroid gland, weight gain, poor concentration, dry skin, delayed tendon reflexes, an increased risk of miscarriage, and mental retardation in the developing fetus (15).

Symptoms of toxicity can be similar to symptoms of deficiency because both disrupt normal function of the thyroid gland (15).

Naturally fish has the highest concentrations of iodine compared to other types of food (66) and therfore is an important source of iodine in human consumption. Depending on soil, cereals, grains and cow’s milk can also be key sources of iodine (15). Globally the main source is salt fortified with iodine (66).

More than half of European school-age children may have inadequate iodine intake, which potentially affects their ability to learn (67). The United States population is generally iodine sufficient, but women at childbearing age may nevertheless be at risk of iodine deficiency (68). Normally a daily intake of 500 µg for young children and 1000 µg for adults is considered safe (25).

Iron is an essential nutrient and an important component for many enzymes. It is in a vital component of hemoglobin as it facilitates oxygen transport from the lungs to the tissues (15).

Iron deficiency is responsible for about half of the incidences of decreased levels of hemoglobin in the blood (anemia) (69). Mild symptoms of anemia include general fatigue, more severe symptoms include heart failure and increased risk of preterm delivery (69). Iron-deficiency anemia may compromise normal cognitive development (70).

High doses of iron can cause constipation, nausea, diarrhea and vomiting, while epidemiological studies have found association between high iron body levels and CVDs and cancer in the general population (15).

Sources of iron include meat, fish, vegetables and fortified foods. Lean fish and especially oily fish has been shown to increase bioavailability of iron from other sources such as from vegetables (71). A recent study has shown that oily fish may be just as good source of iron as red meat (72).

Iron deficiency affects up to one third of young women in Europe (71), while iron overload is generally not reached through oral intake of iron (15).

Vitamin B is a group of watersoluble compounds that have been grouped together due to historical reasons (73).The main reason being that they often coexist in same food sources. These vitamins are indispensible for many coenzymes involved directly or indirectly in energy metabolism, which are necessary for cell growth and oxygen transport (30). Of the eight known B vitamins, fish is a good source for at least five of them (Table 1). These are thiamine (B_1), riboflavin (B_2), niacin (B_3), pyridoxamine (B_6) and cobalamine (B_{12}). Vitamin B deficiencies are mainly due to deficiencies in vitamins B_2 and B_6 (25). Vitamin B_2 intake from Western diets are mainly from milk and milk products, even though meat and fish are also good sources (74). Vitamin B_2 deficiency may reduce metabolism of vitamin B6 (74), and in fact vitamin B_6 deficiency rarely occurs alone, but in association with a deficit in other B vitamins, like B_2 (25). Vitamin B_2 and B_6 deficiencies are associated with problems with surface of intestine and skin, neurological problems, and possibly with increased risk of cancers and CVDs (74, 25). Multiple vitamin B deficiencies are likely to occur where cereals are not fortified with micronutrients (73). Toxicity of B vitamins is normally not a problem because they are easily cleared (B_1), have limited intestinal absorption (B_2), or because signs of toxicity does not develop except at very high intakes such as above 35 mg/day for B_3, above 100 mg/day for B_6, and above 1000 µg/day for B_{12} (25).

The cardiovascular system

The interest in fish as functional food started around 1980 with publications regarding low rate of coronary heart disease (CHD) among Alaskan and Greenland Eskimos and among Japanese in Japan (75, 76, 77, 79).

Reports on the status of health in Greenland in the 1970s showed that death from ischemic heart diseases constituted only 3.5% of all deaths in Greenland Inuits (75). Blood samples from Inuits living in Greenland showed low omega-6 and high omega-3 FAs levels compared to blood samples from Danes, a difference most likely due to diet (75). The high EPA levels were shown to contribute to decreased blood aggregation and increased bleeding time (75).

The progression of CVDs. Plaques are fatty inflamed deposits that form on the inside walls of arteries (78). When the hardening (sclerosis) of arteries (arteriosclerosis) is due to the build-up of fatty materials inside the arterial lumen, the process is called atherosclerosis. Cholesterol and triacylglycerol (triglyceride) play a major causal (etiological) role in the formation of plaques in the arteries (80). About 2 percent of plaques will eventually rupture and cause a potential fatal blood clot (thrombosis) (78). A thin layer of cells called endothelium makes up the lining of blood vessels. Endothelial dysfunction can lead to inflammation and increased blood pressure (81). Both arterial plaques and a failing of the endothelium are early signs of CVDs (82). High blood pressure, or hypertension, increases the workload of the heart and can cause the heart to become weaker resulting in gradual failing of its duty to provide itself and the remaining body with enough oxygen. If the heart is not provided with enough oxygen it becomes ischemic, and irregular heartbeats can occur, such as ventricular fibrillation. Ventricular fibrillation can lead to the formation of thrombosis and result in sudden cardiac death (SCD). The progression of atherosclerotic cardiovascular disease is shown schematically in figure 2. Arterial plaques, signs of the silent progression of CVDs, are not easily detected at an early stage in living subjects. The asymptomatic nature of the early stages of CVDs does not give people incentive to seek cure in form of healthier food and life style. When CVDs becomes advanced, so do detectable signs of the disease, such as hypertension, shortness of breath, and chest pain (angina pectoris). The (potentially) deadly consequences of CVDs include myocardial infarction (heart attack), SCD which is most often caused by ventricular fibrillation, and cerebrovascular infarction (stroke).

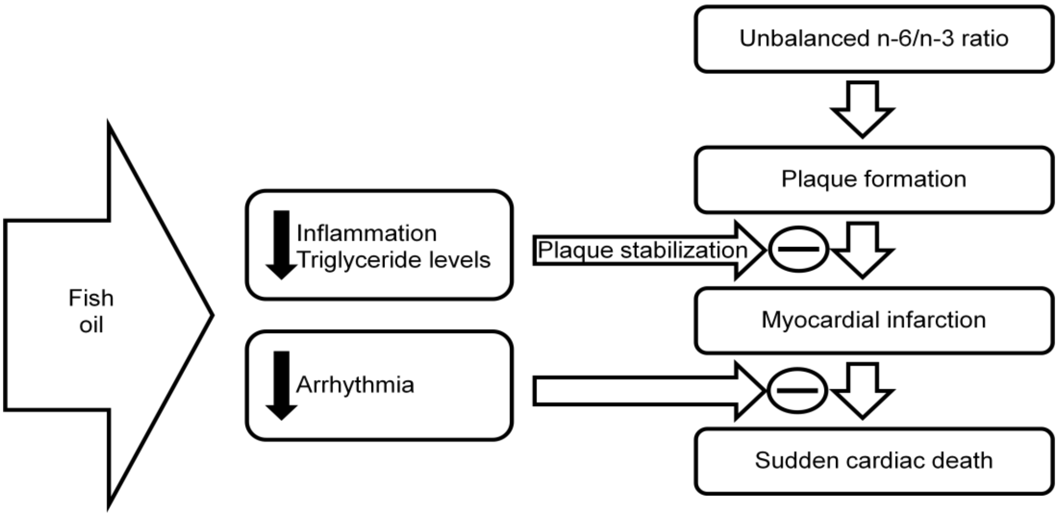


Figure 2. Progression of atherosclerotic cardiovascular disease, including possible points where fish constituents may affect the progression of the disease.

Long chain (LC) omega-3 FAs mechanism(s) of action

Hypertension, atherosclerosis, thrombosis, inflammation and arrhythmia are all conditions that influence not just CVDs but also other common chronic diseases. The decrease in EPA and DHA intake in the Western world may have contributed to the increased incidence of atherosclerosis, CHD, hypertension, metabolic diabetes, obesity, collagen vascular diseases and cancer (83). Inflammation is the main problem of many diseases including CVDs and cancer.

Omega-3 FAs may lower blood pressure (anti-hypertensive properties), delay the onset of arterial hardening (anti-atherogenic property), prevent blood clotting (anti-thrombotic property), fight inflammation (anti-inflammatory property), and stabilize heart rate (anti-arrhythmic properties).

As described above, some endpoints may occur early and others late in the progression of CVDs. This review deals with endpoints in approximately such chronological order. The emphasis will be on LC omega-3 FAs in fish oils.

Cardiovascular health endpoints.

Plaque stability (the anti-atherogenic and anti-thrombotic properties)

The cardiovascular protection by omega-3 FAs is potentially mediated to some degree by decreasing the rate of atherosclerosis (84). Thicker fibrous caps, absence of inflammation and fewer macrophages can increase plaque stability (85). Omega-3 FAs may be incorporated in plaques enhancing their plaque stability (85). However, the authors of a review on the findings of randomized, controlled trials came to the conclusion that omega-3 FAs of marine origin showed no consistent effects on plaque stabilization parameters (85).

Inflammation

Chronic inflammation is a feature of many diseases such as rheumatoid arthritis, psoriasis, asthma, inflammatory bowel disorders and CVDs (85). Studies exploring the effect of omega-3 FAs on inflammation biomarker have been inconsistent (85). Of eight randomized trials, none found significant effect of fish derived omega-3 FAs on CRP, but some observed decline in inflammatory cytokines (85).

Thrombosis

Thrombosis most often occurs in wake of plaque rupture but thrombosis may also occur if blood flow slows down. Thrombosis may lead to MI or stroke. Omega-3

FAs can inhibit the platelet aggregation and thereby prevent thrombosis. Results from randomized trials on various molecules involved in inflammation have not been consistent (85).

Glucose tolerance

Diabetes patients are more prone to CVDs than the general public. The body of diabetes patients is less able to clear glucose from the blood. Omega-3 FAs can have adverse effect on glucose tolerance at very high doses (≥10 g/day) but not at lower doses (85). Review of the findings of randomized, controlled trials shows that omega-3 FAs of marine origin show no consistent effects on the body ability to clear glucose from blood (i.e. glucose tolerance) (85).

Hypertriglyceridemia

Hypertriglyceridemia is becoming more common in western populations as the prevalence of obesity and diabetes mellitus rise (47). Strong evidence support the hypothesis that hypertriglyceridemia is an independent risk factor for cardiovascular disease, still it has been difficult to show this in intervention studies (47). A review of the findings from randomized controlled trials showed that omega-3 FAs of marine origin consistently lower elevated plasma triglyceride levels in a dose-dependent fashion, with greater efficacy at higher triglyceride levels (85).

Cholesterol

Fish oils have been shown to raise the high density lipoprotein (HDL) cholesterol (47). A review of the findings from randomized controlled trials showed that omega-3 FAs of marine may also slightly increase LDL cholesterol levels (85), which does not improve the overall cholesterol profile (86).

High blood pressure

Omega-3 FAs of marine origin can lower blood pressure (85). In view of the high dose required to lower blood pressure and the proven efficacy of other nutritional factors and of antihypertensive medications, an increased intake of omega-3 FAs has a limited role in the management of hypertension (87).

Selenium and CVDs risk

Animal studies have demonstrated that Se compounds may improve cardiac recovery from heart attack type of injuries and reduce incidence of ischemia-induced ventricular arrhythmias (88). Fatal cardiomyopathy in humans has been shown to respond to Se supplementation in areas of low Se intake in China and increased Se supplementation in Finland may have contributed to fewer heart disease mortalities (62). It has been proposed that selenium may account for some of the health benefits that have been associated with omega-3 FAs (89).

Human studies evaluating the relationship between Se and CVDs endpoints remain inconsistent (88).

Heart rate, fibrillations, fatal and nonfatal CVD

Approximately 70% of all CVDs deaths in Europe is from CHD (90). Fatal CHD has been defined as the combined fatal instances of myocardial infarction (MI) and SCD (91, 92). Irregular muscle movements (fibrillations) of the ventricle, the main pumping chamber of the heart, is most often the reason for SCD (52). High resting heart rate is associated with increased SCD risk (52). A review of randomized trials revealed fish intake is able to slow heart rate by few beats per minute (52). The evidence that EPA+DHA can reduce risk of SCD is very strong (48). Fish oils generally have larger preventive effect on fatal vs. nonfatal CVDs events (93), suggesting influence of the anti-arrhythmic properties of fish oils rather than effects on the development of CHD (52). Most meta-analysis studies (94, 95, 92) and reviews (London et al. 2007 = IDref500) support the hypothesis that fish or fish oil can reduce risk of fatal CHD but not all (96). Epidemiological studies show more consistent reductions in the incidence of nonfatal MI than do clinical trials using omega-3 FAs intakes, suggesting fish oil is only partially responsible for the effect (85).

Stroke

Stroke is a major cause of disability, dementia and death (97, 98, 99). Strokes fall into two main categories based on how they affect the blood vessels: ischemic (blockage) and hemorrhagic (leaking) (100). Approximately 70 to 90% of all strokes in the Western world are likely to be ischemic (101, 100). At levels below 1 g EPA + DHA fish oil may decrease risk of ischemic stroke (100) but potentially increase risk of hemorrhagic stroke at intake levels of 3-15 g EPA+DHA (102).

In a meta-analysis from 2005 on the effect of fish consumption on stroke risk, it was concluded that compared to no fish consumption, any fish consumption significantly reduced the risk of developing ischemic stroke (100). This was supported by a review published the year after (102).

Table 3. The effect of fish oil and selenium on human cardiovascular health, according to recent expert opinions.

Risk factor/ Endpoint	Factor	Judgment on risk factors	Reference
Unstable plaques	Fish oil	No consistent effects on plaque stabilization parameters.	85
Inflammation	Fish oil	No consistent effects on inflammation parameters.	85
Thrombosis	Fish oil	No consistent effects on thrombotic parameters.	85
Glucose intolerance	Fish oil	No consistent effects on glucose tolerance parameters.	85
Hypertriglycerid emia	Fish oil	Fish oil can decrease levels of triglycerides. It is, however not known if lowering triglycerides by fish oil will decrease risk of CVDs.	47, 85
Unfavorable cholesterol levels	Fish oil	Concomitant with lower triglyceride levels, increased fish oils result in modestly higher LDL cholesterol and HDL cholesterol levels, an effect that is consistent with other interventions that reduce triglyceride levels.	85, 86
High blood pressure	Fish oil	Fish oil can consistently lower high blood pressure, but the dose effect is too small to have importance in the prevention of CVDs.	85, 87
CVDs risk	Selenium	Current evidence is insufficient to support a protective role for selenium in cardiovascular prevention	88
Heart rate, fibrillations, fatal and nonfatal CVDs	Fish oil	The evidence are suggestive but not sufficient that dietary omega-3 FAs for the primary or secondary prevention of CVDs. It is however very likely omega-3 FAs can delay SCD by preventing ventricular arrhythmia, especially in populations that generally consume little or no fish.	48, 52, 92, 93, 94, 95, 96
Stroke	Fish oil	Fish oil may reduce risk of ischemic but not hemorrhagic stroke.	85

The neurological system (both dementia and mental diseases)
Classification of mental disorders varies between USA and Europe and even more between Western and non-Western cultures (103, 104). Cases of mental disorders often fall outside the strict definitions of disorders.

It has been suggested that the consumption of long chain omega-3 FAs reduces depression, aggression and anger while improving mental well-being (105).

A change in the pattern of dietary fat consumption in the Western World during the last 150 years may have coincided and even caused an increase in the occurrence of disorders in the central nervous system (CNS) (106). The pattern change involves the decreased consumption of LC omega-3 FAs from fish products along with increased consumption of saturated fat from domestic animals and omega-6 FAs from vegetable oils (106).

Omega-3 FAs in cell membrane phospholipids have physiological role both in CNS and cardiovascular system (107). The brain needs a continuous supply of essential fatty acids (EFA) during the entire life span (108). EFA deficiency during infancy delays brain development, while deficiency in aging will accelerate deterioration of brain functions (108).

In a recent literature systematic review, investigating the association of mental disorders and omega-3 FAs from foods and supplements, all mental disorders were included where some studies were available (109). The authors included ***affective disorders*** (e.g. mood disorders including major and dysthymic depression and bipolar disorders), ***anxiety disorders*** (including panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and phobias), ***anorexia nervosa***, ***attention deficit/hyperactivity disorder (ADHD)***, ***tendencies to harm others*** (including anger, hostility and aggression), ***alcoholism***, ***borderline personality disorder***, ***schizophrenia***, and ***autism*** (109). The authors however, excluded ***degenerative disorders*** such as Alzheimer´s disease because it had been dealt with in other recent literature reviews (e.g. 110). According to Schacter et al. (109) very little data is available, except for schizophrenia and depression and in general more research is needed before it is possible to judge if omega-3 FAs in foods can prevent psychiatric disorders or conditions.

Neurological health endpoints.

Affective disorders
Depression
Major depression is the greatest single cause of disability worldwide, but the prevalence from one country to another is large and with similar pattern as for coronary artery disease (CAD) (111). The World Health Organization (WHO) has estimated that major depressive disorder may become the second leading cause of death in the Western world by 2020 (109). The similar prevalence of major depression and CAD suggests similar risk factors (111).
Studies from 1991 and 1995 suggested that abnormal cell membrane fatty acid composition may be important in depression (112). Populations with high intake of fish have lower reported rates of depression (111).

Women of childbearing age are particularly at risk for depression (113). Depression that occurs during pregnancy (prenatal) or within a year after delivery (postpartum) is called maternal or perinatal depression. The prevalence of perinatal depression in mothers is around 13% or approximately twice the prevalence of depression in the whole population (113). The loss of omega-3 FAs in mothers over to fetus and infant during pregnancy and breast feeding may contribute to postpartum depression (109). Treatment of depressive episodes during childbearing years must be balanced between the mother´s well-being and fetal safety (113).

In a review from 2005 of epidemiological and clinical studies with regard to the association of omega-3 FAs with depression it was concluded that the evidence was good for the association of omega-3 FAs consumption with less depression (114). In a critical review of the effect of omega-3 FAs on depression in humans, 22 studies of various types were identified but these did not result in clear conclusions on whether omega-3 FAs are useful for preventing or treating depression (109). In an overview from 2006 on the evidence of omega-3 FAs efficacy on the treatment of depression and other mood disorders further studies were suggested in order to shed light on the therapeutic capability of omega-3 FAs in these diseases (106). A review from 2007 on the evidence for health benefits of omega-3 FAs, suggests supplementations of omega-3 FAs are useful in the treatment of depression in doses of 0,2-9,6 g EPA + DHA per day (115). In a meta-analytic review, published in 2007, including 10 double-blind, placebo-controlled studies on the association between depression and low dietary intake of omega-3 FAs, it was concluded more studies were needed to identify a subgroup of depressive patients and composition and dose of omega-3 FAs most efficiently treating depression (116).

Bipolar (affective) disorders (BDs)

The finding that EPA and DHA had modulating effects on cellular signal transduction similar to common mood stabilizers triggered the hypothesis that omega-3 FAs might be useful to treat BDs patients (117). Patients with BDs comprise about 3.9% of the adult USA population (117). BDs have an early onset and last the whole of life (117). Even the newest drug treatments against BDs often become either ineffective or intolerable over time (117).

A number of epidemiological reports supply a connection between dietary fish/seafood intake and protection against BD (118). A systematic literature review from 2005 on the effects of omega-3 FAs on mental health indicated that greater seafood consumption predicted lower rates of BDs (109).

Schacter et al., 2005 found 5 studies relating omega-3 FAs and the onset or treatment of BDs (109). Based on these studies, nothing could be concluded about the value of omega-3 FAs with respect to prevention or treatment of BDs (109). Doses of EPA + DHA that seem to be effective in treating BD range from 1 to >7 g of per day (117).

Attention-deficit/hyperactivity disorder (ADHD)

ADHD is the most common developmental disorder of childhood, affecting up to 15% of school-age children in the USA (119). There are no biological markers for ADHD (119). ADHD may be caused by multiple factors, both genetic and environmental, that may differ from one individual to another (119). Individuals with ADHD commonly have other problems such as dyslexia, autism, asthma, eczema and are more prone to infections (119). The fact that ADHD aggregates in families suggests common causes, one of which has been suggested to be the lack of omega-3 FA from the diet (119).

In a review of laboratory and clinical research evidence from omega-3 FAs studies it was determined that ADHD symptoms can seemingly be alleviated by EPA and DHA supplementation (119). However, available studies are few and small, further confirmation needs larger studies (119). Most of the studies used doses of 300-700 mg EPA and DHA per day, which may not be enough for optimal mental health performance (119).

Schacter et al., 2005 found 10 studies on the association of omega-3 FAs and the onset or treatment of ADHD (109). Based on these studies, nothing could be concluded about the value of omega-3 FAs to prevent or treat ADHD (109). In a review from 2006 on the effects of omega-3 FAs on ADHD and related diseases it was concluded that more large scale studies are needed to address the question of what proportion of children in the general population might benefit from increased intake of dietary omega-3 FAs (119).

Dementia

Alzheimer´s disease (AD) is the most common type of dementia in Western countries, characterized by progressive memory loss, intellectual decline, and eventually global cognitive impairment (120). An estimation suggests up to 10% of Western populations over 65 years of age and 47% above 80 years of age suffer from dementia (120). The prevalence of cognitive impairment and dementia are expected to rise due to aging of populations (121). The cause of cognitive decline and dementia are currently unknown, but according to epidemiological studies fats from fish and vegetables may maintain adequate cognitive functioning or even prevent its failure (121). AD has been associated with brain lipid defects, such as decreased levels of DHA in certain areas of the brain (120).

In a systematic review on the evidence for omega-3 FAs as a modifiable risk factor for dementia, five studies were identified (110). The evidence suggested omega-3 FAs had no effect on cognition in old age in healthy individuals but might reduce risk of dementia (110). Results from a workshop on the beneficial effects of omega-3 FAs suggest evidence of beneficial effects of EPA + DHA on cognitive decline are emerging but are not yet sufficient to support an intake level different from coronary heart disease risk reduction, i.e. 250 to 500 mg/day (48).

Cognitive development

Cognitive development can be measured using IQ scores. Very little direct information are available on the relationship between maternal omega-3 FAs intake during pregnancy and cognitive development of the fetus (122). In a meta-analytical review of eight randomized controlled trials (RCTs) on the fetal benefits of supplementing mothers or formula milk with omega-3 FAs it was concluded that for each increase in fetal DHA, corresponding to maternal additional consumption equivalent to 100 mg DHA per day, results in an increase in child IQ by 0,13 points (122). Even though this IQ gain is clinically undetectable for each individual child, the IQ gain could add up for the whole population (122).

Schizophrenia

Around 0.5% of the populations suffer from schizophrenia. It has been suggested that the genetic background of schizophrenia is an intrinsic part of being humans (123). The most common age of onset is in or just before early adulthood. There is a growing literature to suggest that schizophrenia is not just a brain disease, but associated with many body functions such as insulin metabolism, fatty acid metabolism, and inflammatory and immune processes (123). Schizophrenic patients have 2-4 times more prevalence of diabetes, and 2-3 times higher mortality rate from CHD than the general population (123). Schizophrenic patients tend to consume food of lower quality (i.e. foods high in saturated fats and sugars but low in fruits and vegetables), be physically less active, and smoke more than the general public (123). Some results suggest there are lower blood cell membrane DHA levels in schizophrenic patients (123). Low dietary intake of omega-3 FAs, smoking and other factors can lower cell membrane omega-3 FAs levels, it is therefore not known if low membrane omega-3 FAs levels has a role in the etiology of schizophrenia or is a consequence of the disease (123). It has been suggested that EPA and DHA supplementation perinatally could prevent onset of schizophrenia by preventing inflammatory neuronal damage (124).

In a systematic review of the scientific medical literature on the ability of omega-3 FAs in prevention and treatment of mental disorders Schacter et al., 2005 found 28 studies on the association of omega-3 FAs and the onset or treatment of schizophrenia (109). The results suggested short-term omega-3 FAs intervention might be beneficial in treatment of schizophrenia but more studies are needed to explore the potential of omega-3 FAs for the prevention or treatment of schizophrenia (109), including further studies with relevant animal models (125).

Table 4. The effect of fish oil on human neurological health, according to recent expert opinions.

Endpoint	Factor	Judgment on risk factors	Reference
ADHD	Fish oil	Inconclusive evidence.	109, 119
Bipolar disorders	Fish oil	Inconclusive evidence.	109, 118
Dementia	Fish oil	Evidence suggests omega-3 FAs may reduce risk of dementia but strong conclusions cannot yet be drawn.	48, 110
Depression	Fish oil	The evidence for the ability of fish oil intake to prevent or treat depression is promising but not conclusive	106, 109, 114, 115, 116
Cognitive development	Fish oil	Limited evidence suggests increased infant omega-3 FAs consumption may increase cognitive performance.	122
Schizophrenia	Fish oil	Inconclusive evidence. More studies needed on the relationship between schizophrenia and fish oil intake.	109, 125

Cancers

Cancer is a major cause of mortality in the world. Dietary factors are estimated to account for approximately one third of cancers in industrialized countries (126, 127). However, diet may also contain cancer preventive constituents. Vitamin D, omega-3 FAs and selenium are examples of fish constituents that can potentially prevent cancer.

Cancer risk and cancer mortalities

About 10 million new cancer incidences occurred globally in year 2000 and over 6 million cancer deaths (126). Of all deaths worldwide, approximately 12% are caused by cancer (128).

Results from a workshop on the available evidence for the beneficial role of long chain omega-3 FAs on chronic diseases, suggest that EPA + DHA are not able to reduce risk of cancer (48).

In a review from 2007 on epidemiological evidence for the role of trace elements on cancer risk it was suggested available evidence for selenium (Se) reducing cancer mortality was inconsistent (128).

People living at the northern most latitudes, where sunlight is sparse, are more prone to cancers of the prostate, breast, colon, ovarian, esophageal, non-Hodgkin´s lymphoma and variety of other lethal cancers (54). These people may benefit from higher dietary levels of vitamin D. Accumulating evidence suggest vitamin D may protect against cancer but evidence are still scarce (129).

An inverse relation has been found between fish consumption and most cancers, especially cancers of the alimentary tract (130). It was difficult to find expert reviews or opinions on the role of fish consumption or intake of fish constituents on the risk of some cancers, e.g. cancers of the pancreas, kidney, liver and gallbladder.

Breast cancer

Breast cancer is the second most common cancer in the world, and the most common among women (126). According to a joint WHO/FAO expert consultation report on the prevention of chronic diseases, evidence is inconclusive for the effectiveness of fish consumption or the intake of known fish constituents such as omega-3 FAs, vitamin D, or selenium in preventing common cancers, such as breast cancer (126).

In a review from 2005 (131) on epidemiological studies of vitamin D and cancer incidence and mortality it was concluded that for breast cancer, some data were promising with regard to beneficial effects from vitamin D, but the evidences are far too sparse to support a conclusion. Another review from 2006 on vitamin D, calcium, and breast cancer risk concludes that the evidence is promising but more well designed human cohort and clinical trials are still needed to confirm the potential effect of vitamin D (132). The authors of a review on epidemiological studies, published in 2007, on the association between vitamin D and breast cancer conclude there are difficulties in associating breast cancer with either vitamin D intake or vitamin blood levels (133).

Silvera and Rohan (2007) reviewed the epidemiological evidence for the role of trace elements on cancer risk and they concluded that available evidence for selenium does not support an inverse association between selenium exposure and breast cancer risk. (128).

Colorectal cancer

Colorectal cancer is the second to third most common cancer in most Westernalized countries (134).

In a review from 2006 on the effect of dietary factors on colon cancer it was stated that the evidence for preventive role of omega-3 FAs was not yet convincing, while it was possible that the potential risk-lowering effects of high n-3 to n-6 ratio of seafood diet might be important in this respect (134). A systematic review from 2006, on the cancer preventive role of omega-3 FAs concluded that there was no association between omega-3 FAs consumption and incidence of colorectal cancer (135). According to a review from 2007 on nutrition obesity and colorectal cancer, better data is needed to explain the potential benefits of diets rich in fish (136).

Vitamin D intake has been hypothesized to reduce the risk of colorectal cancer, but the likely reason dietary vitamin D is not a significant risk reduction factor for colorectal cancer in many studies is that dietary sources provide only a portion of total vitamin D (137). Nevertheless, a large number of epidemiological studies provide support for the ability of adequate vitamin D status to reduce risk of colorectal cancer (136, 138). In a meta-analysis of 18 observational studies published between 1966 and 2004 on vitamin D and prevention of colorectal studies it was concluded that intake of 1000 International units (IU)/day of vitamin D was associated with 50% lower risk of colorectal cancer (139). Another review of epidemiologic studies on vitamin D as a modifier of colon cancer risk found strong biological evidence on the protective role of vitamin D, however, such protection was likely to require higher intakes than 400 IU/day (140).

According to a review from 2007 on nutrition obesity and colorectal cancer, some forms of selenium may prove to be preventive against colorectal cancer (136). However, in a review from 2007 on epidemiological evidence for the role of trace elements on cancer risk it was concluded that available evidence for selenium reducing colorectal cancer risk was inconsistent (128).

Endometrial Cancer

In a systematic literature review and meta-analysis published in 2008 on vitamin D and calcium in relation to endometrial cancer, the existing evidence did not support relation between endometrial cancer and the ranges of dietary vitamin D examined (141).

Esophageal and stomach cancers

Cancers of the stomach are relatively uncommon in the Western world, but the rate of cancers in the upper part of the stomach (gastric cardia), next to the esophagus have been increasing in Europe and the United States (142). Obesity may contribute to this increased rate of gastric cardia cancers (142). A review from 2005 on selenium in cancer prevention suggests that selenium intake may be able to reduce risk of cancers of the stomach (i.e. in the gastric-cardia area) (65). Later reviews of human epidemiologic studies have also supported an inverse association between selenium and gastric cancer risk (128, 142).

Liver cancer
According to a review from 2005 on selenium in cancer prevention, selenium intake may be able to reduce risk of cancers of the liver (65). This opinion is based on three human Se trials from China and on animal studies, demonstrating the reduction of carcinogenic adducts in the liver in Se fed rats.

Lung cancer
Silvera and Rohan reviewed epidemiological evidence for the role of trace elements on cancer risk and concluded that available evidence for selenium appears to support a possible reduction in risk for lung cancer (128).

Non-Hodgkin lymphomas (NHL)
NHL are a heterogeneous group of malignancies arising from lymphoid tissue with unclear etiology (143). NHL are responsible for about 3.4% of cancer deaths in U.S.A (143). NHL has been inversely associated with sun exposure, alcohol use and fish consumption (143). Reviews and meta-analysis support the inverse association between sunlight and NHL (144, 145, 143) but the association is not as clear between vitamin D intake and NHL. The inverse association with fish consumption has mostly been nonsignificant (143). Further epidemiological studies have to focus on NHL subtypes (143).

Prostate cancer
Prostate cancer is the second most common cancer in human males, worldwide (146).

Giovannucci has reviewed the association between vitamin D and prostate cancer risk and concluded that available dietary studies did not support an association between vitamin D intake and lower prostate cancer risk. (131, 140).

Two reviews from 2005 on selenium in cancer prevention concluded that the evidence suggested selenium intake protected against the risk of prostate cancer (65, 147), but the selenium levels in serum probably need to be at least 147 µg/l (65). A meta-analysis was carried out to determine quantitatively if men with low selenium levels were at increased risk of prostate cancer (146). According to this meta-analysis of twenty epidemiological studies, a possible inverse association exists between selenium levels and risk of prostate cancer (146). Silvera and Rohan reviewed the epidemiological evidence for the role of trace elements on cancer risk and concluded that available evidence for selenium appears to support an inverse association between selenium exposure and prostate cancer risk (128).

Cancer of the urinary bladder
Cancer of the urinary bladder is neither among the most common nor deadliest cancers, but studies have suggested an inverse association between intake and body levels of selenium and risk of urinary bladder cancer. So far evidence is insufficient to draw a conclusion regarding such association (128, 148).

Table 5. The effect of fish oil, vitamin D and selenium on human cancer risk, according to recent expert opinions.

Endpoint	Factor	Judgment on risk factors	Reference
Cancer risk and mortalities	Fish oil	The evidence does not support the hypothesis that consumption of fish oils can prevent cancer.	48
	Selenium	Inconsistent evidence.	128
	Vitamin D	The evidence for cancer protective properties of vitamin D is suggestive but still incomplete.	129
Breast cancer	Fish oil	There is inconclusive evidence that increased consumption of fish and omega-3 FAs from fish is effective in preventing breast cancer.	126
	Vitamin D	The evidence is still inconclusive with regard to the effect of vitamin D intake to decrease risk of breast cancer.	126, 131, 132, 133
	Selenium	Selenium intake does not decrease risk of breast cancer according to current evidence.	126, 128
Colorectal cancer	Fish oil	Even though diets rich in fish are often associated with lower risk of colorectal cancer, evidence is lacking for the direct involvement of the omega-3 FAs found in fish. A correct n-3/n-6 ratio may be important.	134, 135, 136
	Vitamin D	Vitamin D intake of 1000 IU/day may be associated with lower risk of colorectal cancer.	136, 137, 138, 139, 140
	Selenium	It is possible that some forms of selenium may prevent colorectal cancer.	128, 136
Endometrial Cancer	Vitamin D	The evidence is not supportive of the association between dietary vitamin D and endometrial cancer.	141
Esophageal and stomach cancers	Selenium	Possible, but evidence is still inconclusive	65, 128, 142
Liver cancer	Selenium	Possible, but evidence is still inconclusive	65
Lung cancer	Selenium	The evidence currently available for selenium appears to support a possible reduction in risk for lung cancer.	128
Non-Hodgkin lymphomas	Vitamin D	Insufficient evidence	143
Prostate cancer	Vitamin D	The evidence is not supportive for an association between vitamin D intake and prostate cancer risk.	131, 140
	Selenium	The evidence support an inverse association between selenium exposure and prostate cancer risk	65, 128, 146, 147
Cancer of the urinary bladder	Selenium	Insufficient evidence	128, 148

Inflammatory, autoimmune and allergic diseases

Chronic inflammation is the root of chronic degenerative diseases such as heart diseases and cancers. Inflammation is also an intrinsic part of autoimmune and allergic diseases. Autoimmune diseases such as diabetes type I, ulcerative colitis and multiple sclerosis (MS) occur when the immune system becomes over reactive against the host tissue. When an over reactive response is directed against external substances the resulting disease is allergy (atopy), involving diseases such as asthma and eczema.

Allergic diseases (atopy)

Diet may have a role in the onset of allergy but strategic usage of diet may also favorably affect the immune system and help prevent allergic diseases (149). Our limited understanding of the etiology of allergy, constrains our capacity to use diet for allergic prevention (149). A recent systematic review on the effects of omega-3 and omega-6 FAs in preventing the development of allergic diseases, suggest these oils are unlikely to be useful for the primary prevention of either the development or the sensitization of allergic diseases (150).

Asthma

Breast milk contains some long chain omega-3 FAs. Breast feeding for at least six months of life may result in lower rates of asthma (151). According to a review from 2007 on the health benefits of fish oils it was concluded, despite the performance of several randomized controlled trials, that the beneficial effects of fish oils on asthma was unclear (115). A more recent review did not find any reduction of asthma risk resulting from omega-3 FAs supplementation (150).

Diabetes I

In a systematic review and meta-analysis aimed at investigating the effect of childhood vitamin D supplementation on type 1 diabetes it was shown that infants who were supplemented with vitamin D had a lower risk of developing type 1 diabetes (152). These results need to be backed up by randomized controlled trials of adequate quality (152).

Eczema

Omega-3 FAs can probably not protect against the risk of developing eczema (150). Infants with family history of eczema are less likely to suffer from eczema themselves if breast milk is their only diet during first three months of life (153). Supplementing the mother with fish oil will decrease the severity of eczema in high risk children (154), suggesting long chain omega-3 FAs in milk are at least partly responsible for this protective effect. This protection does not seem to reach to infants with no family history of eczema (153).

Inflammatory bowel disease (IBD), i.e. Ulcerative colitis & Crohn´s disease

IBD refers to two chronic diseases, ulcerative colitis and Crohn´s disease. In both these diseases parts of the intestines are inflamed. In Crohn´s disease the inflammation reaches deeper into the wall and usually affects lower parts of the intestine. Evidence for the beneficial effects of fish oils in chronic IBD is conflicting and largely inhibited by small study populations (115).

Multiple sclerosis (MS)

MS is a disease in which the immune system attacks the myelin sheaths around neuronal axons. The damage prevents communication between brain and spinal cord potentially causing various neurological symptoms.

In a review from 2007 on the role of omega-3 FAs in neurological diseases it was concluded that evidence did not support an effect of omega-3 FAs on the incidence of MS (118). Epidemiological studies suggest a link between low vitamin D status and prevalence of MS (155). In a recent review of the therapeutic potential of vitamin D in MS it was concluded vitamin D has the potential to treat and even prevent MS, this may require vitamin D serum levels >100nmol/L (155), which may correspond to 4000 IU per day (156) or high consumption of fish (Table 1).

Rheumatoid arthritis (RA)

RA is the only inflammatory condition for which there is good evidence for potential therapeutic effects of omega-3 FAs (115). Fish oils can relieve symptoms of RA but probably they cannot affect the progression of the disease (115). Amount of LC omega-3 FAs needed to relieve symptoms, i.e. a daily intake of 1-7.1 g EPA + DHA (115), requires substantial intake of fish lipids (Table 1).

Table 6. The effect of fish oil and vitamin D on human inflammatory, autoimmune and allergic diseases, according recent expert opinions.

Endpoint	Factor	Judgment	Reference
Asthma	Fish oil	Inconsistent evidence.	115, 150
Diabetes I	Vitamin D	Possible, but evidence is still inconclusive.	152
Eczema	Fish oil	Fish oil probably does not prevent onset of eczema but may decrease symptoms of eczema in children with family history of eczema.	150, 154
Inflammatory bowel disease (IBD)	Fish oil	Inconsistent evidence.	115
Multiple Sclerosis (MS)	Fish oil	No significant association between fish oil and the incidence of MS. Fish oil may however reduce the severity of the disease.	118
	Vitamin D	Vitamin D intake may potentially have a role in treating or preventing MS. Necessary intakes not achievable with fish consumption alone.	41, 155
Rheumatoid arthritis	Fish oil	Can be used for treatment at high intakes of fish oil	115

Bone health
Based on the definition of vitamin D deficiency (157) about half of the European adult population is deficient in vitamin D and large portion of institutionalized older people severely deficient (158). It has, however, not been clearly defined which clinical symptoms to be expected at various vitamin D serum levels (158). In absence of sunlight, at least 1000 IU vitamin D is required per day to maintain good health (159).

Vitamin deficiency is involved in several bone related diseases. Vitamin D deficiency in children results in rickets. In 2008 the American Academy of Pediatrics released a statement recommending 400 IU of vitamin D (corresponding to 1 table spoon cod liver oil) to all children from infancy to adolescence to prevent rickets (160). Suboptimal vitamin D body levels are thought to play a role in falls and fractures of the elderly. Older individuals, individuals living in northern latitudes with prolonged winters, and obese individuals are among those who are most vulnerable to low vitamin D levels (Bischoff-Ferrari 2007).

Vitamin D analogs have been shown to be even more protective against falls (161) and fractures (162) than natural vitamin D, but the long term effectiveness of vitamin D analogs is yet not known and people may have less problems with consuming natural vitamin D than analog vitamin D for preventive purposes.

Cross-sectional studies show that elderly persons with higher vitamin D serum levels have increased muscle strength and a lower number of falls (163).

Falls are a major problem in the elderly, causing injuries, psychological difficulties, and social isolation (164). Parallel to decreased bone strength, a loss of muscle power and performance, deterioration in gait and postural stability along with slower response times, lead to an increase in falls (165). Vitamin D deficiency can exacerbate osteoporosis (159) making bones more fragile. Falls and decreased bone mineral density increase the risk of fractures (26). People who consume fish oil or fat fish have been shown to have higher vitamin D levels (55).
Fatty fish consumption is greatest in Europe's northern most latitudes (166). Some studies have even revealed higher vitamin D serum levels at higher latitudes in Europe, despite less sunshine (158). It is therefore possible that some elderly people in these areas are avoiding vitamin D deficiency by consuming enough fatty fish or fish oils.

Falls
A systematic review published in 2003 on the effect of vitamin D on falls in older people, the results from the pooled data did not support the reduced risk of falling as a result of vitamin D supplementation alone (167). The year after, Bischoff-Ferrari and colleagues published a meta-analysis to estimate the effect of vitamin D on falls in elderly individuals (168). According to this analysis vitamin D supplementation appears to reduce risk of falls about 20%, but intake of calcium should also be considered (168). Excluding the potential effect of calcium, the results from a systematic review of the effect of vitamin D on the reduction of risk of falling suggested that vitamin D might be effective in this respect (169). In a review of meta-analysis and original studies the authors conclude there is a

statistically significant positive relationship between vitamin D supplementation and decreased risk of falls (170). According to a Cochrane systematic review of the effect of vitamin D and other interventions to decrease risk of falls in older people in nursing homes, vitamin D supplementation can significantly reduce the rate of falling (171).

Fractures

Vitamin D decreases vertebral fractures and may decrease nonvertebral fractures, according to a meta-analysis, published 2002, on the effect of vitamin D on fractures in postmenopausal women (172). In an editorial review from 2005 on the effect of vitamin D on bone health, it was suggested likely that older men and women that maintained serum vitamin D levels above 75 nmol/l 25-hydroxyvitamin D (i.e. 25(OH)D) would be at lower risk of bone fracture, but more data was needed where vitamin D was used at doses above 800 IU/d (173). A daily intake of 800 to 1000 IU vitamin D is needed to reach a serum level of 75 nmol/l 25(OH)D (173). Also in 2005, the authors of a meta-analysis of randomized controlled trials of fracture prevention with vitamin D, came to the conclusion that oral vitamin D supplementation between 700 to 800 IU/d, i.e. more than the US recommended dose of vitamin D of 400-600 IU/d, appeared to be sufficient for nonvertebral fracture prevention in ambulatory or institutionalized elderly persons (174).

In a meta-analysis published in 2007 on the effect of vitamin D on the risk of fall and fractures a trend was found for vitamin D supplementation preventing non-vertebral fractures (169). In a 2008 review on the efficacy of vitamin D in relation to bone health, the authors found inconsistent evidence for association between vitamin D serum levels and bone fractures (175). From large recent reviews on the effect of vitamin D in lowering risk of fractures in older people (176, 26), it was concluded that vitamin D supplementation at low doses (400 IU/d) can decrease the risk of fractures, but only in the presence of adequate calcium levels (1000 mg/d).

Table 7. The effect of vitamin D on human falls and fractures, according to recent expert opinions.

Endpoint	**Factor**	**Judgment**	**Reference**
Falls	Vitamin D	Studies indicate a statistically significant positive relationship between vitamin D supplementation and decreased risk of falls.	167, 168, 169, 170, 171
Fractures	Vitamin D	Frail older people may experience fewer fractures if supplemented with vitamin D along with calcium, but not with vitamin D alone.	26, 169, 172, 173, 174, 175, 176,

Summary of results in relation to relevant nutrient doses

A general estimate of the levels of nutrients in 100 g of fish is found in table 1. The following summary should be considered in the light of the level of fish consumption required to achieve benefits.

According to the evidence reviewed, fish oil is the most important fish constituent with regard to the effects on cardiovascular health endpoints. The evidence for the protective effects of fish oil consumption is strongest for SCD, ischemic stroke, and fatal or non-fatal MI. It has been suggested the effect of fish oil on SCD (antiarrhythmic effects) and on MI (antithrombotic effects) is not linear and much higher intake is needed for maximal protection against MIs (88). Fish oil consumption corresponding to about 700 mg per day seems to be protective against SCD. Fish oil is especially protective in those that have survived cardiovascular events such as MI(s) (177, 178). Fish oil at higher levels may be protective against non fatal MI, but such protection is not observed except at fish intakes corresponding to 1- 3 g EPA + DHA (179, 180). Fish consumption has also been indicated to be protective against risk of ischemic stroke, with a substantial rise in protection when fish consumption is increased from no to some fish consumption (100).

Fish oil also seems to be the most important fish constituent with regard to neurological diseases. As it may increase infant cognitive function, prevent or treat depression and reduce risk of dementia, while the effect on schizophrenia is less clear. By supplementing the pregnant mother with as little as 100 mg DHA per day child cognition may improve (122). Low omega-6/omega-3 FAs plasma ratios and high plasma omega-3 FAs levels have been associated with lower risk of depression (114). In a large Finnish survey Fish consumption corresponding to 470 mg EPA + DHA per day was not associated with the onset of depressive mood (181). However, a daily dose of 750 mg EPA + DHA per day has been suggested to be protective against the risk of depression (182). A broad range of fish oil doses has been useful in treating symptoms of depression, ranging from 200 to 9600 mg EPA + DHA (115). Fish consumption as low as one meal per week may reduce risk of dementia (48). A broad range of fish oil supplementations, as high as 18.500 mg per day, may reduce the risk of dementia in a dose dependent manner (110).

Vitamin D and selenium rather than fish oil seem to be important with regard to beneficial effects against cancer. Vitamin D intake of 1000 IU a day has potential in lowering the risk of colorectal cancer. While, selenium intake may reduce risk of colorectal cancer, lung cancer, prostate cancer and possibly cancer in the esophageal and upper part of stomach at supplementations of 200µg Se per day (37).

Fish oil and vitamin D also seem to have a positive effect on inflammatory and autoimmune diseases such as diabetes I, MS and rheumatoid arthritis. Vitamin D dose needed to reduce risk of diabetes I is unclear but may range from 400 to 2000 IU per day (152). Fish oil doses corresponding to 900 mg EPA + DHA per day may reduce symptoms of MS (Nordvik et al., 2000 = IDref697) but it is less clear if fish oil can also reduce the risk or progression of MS (118). Vitamin D doses corresponding to 4000 IU/d may be needed to treat and possibly prevent MS (155). Fish oil doses of 1000-1500 mg per day of EPA +DHA are probably needed to relieve symptoms of rheumatoid arthritis (115).

Vitamin D and calcium are important with regard to falls and bone fractures. Vitamin D intake of 800-1000 IU per day can reduce risk of falls and decreased risk of fractures can be achieved with as low vitamin D supplementation as 400 IU/d in presence of 1000 mg/d calcium.

Taking into account that fish consumption in Western countries is on average far below 100 g per day (184), it is clear from the summarization above that in order to achieve benefits from fish consumption, consumers should select fish that contains fish oil, vitamin D, and selenium in the upper range (Table 1).

Discussion

This review aims to shed a light on positive factors found in fish and which ones are likely to be main contributors to beneficial health effects of fish consumption. Despite the lack of direct proof of beneficial effects of fish consumption, the above reviewed evidence suggest that some fish constituents have a positive influence on human health at levels at or close to levels achievable by fish consumption. Just as with drugs, stability in the level of active constituents is important to estimate the effect of a given dose, however fish and seafood is neither homogenous in terms of nutrients nor contaminant content and therefore the levels of fish constituents may be highly variable. Biological factors (e.g. species, sex, spawning, and fish age) and environmental factors (e.g. nutrient availability, season, location and temperature) affect the amount of nutrients and contaminants within a single species as well as between species. These fluctuations make it difficult to establish general estimates about constituent content of individual fish species. On top of this other factors such as storage, preparation and cooking may also have a large influence on the nutrient content and bioavailability of fish consumed. Therefore policy makers need to keep in mind that recommendations regarding fish consumption can potentially be complicated as they might have to consider national or even local conditions.

Although the majority of the population living in the Western societies are in the position of consuming adequate amount of nutrients through a healthy diet available to them, Western populations continue to suffer from suboptimal intakes of several of the nutrients that fish is a very good source for, such as long chain omega-3 FAs, calcium, iodine, iron, selenium and vitamin D (Table 1).

When the consumption of certain nutrients is persistently too low, Western societies tend to solve this problem through fortification of various commonly consumed foods with the nutrients that are missing in their normal diet. Examples are fortification of iodine in table salt, iron in cereals, vitamin D in milk products, and long chain omega-3 FAs to eggs, yoghurts and bread spreads.

A complementary strategy might be to encourage increased fish consumption. In fact epidemiological studies suggest that fish consumption results in more consistent beneficial health effects on human health than fish oil alone (85, 177). In other words, epidemiological studies suggest that on average beneficial effects of fish consumption may outweigh the detrimental effects resulting from the undesirable substances in fish e.g. methyl mercury, dioxins and PCBs, even though fish is a major source of these undesirable substances in the overall exposure to humans in their daily Western lifestyle. Human exposure to methyl mercury is for example almost entirely due to consumption of fish and seafood

(185). Over 90% of human dioxin exposure is from diet, mainly animal fat (186), including fish and meat. Humans are generally not exposed to PCBs via food, but the main dietary source of PCBs are fish, especially sportfish caught in contaminated lakes or rivers and also contaminated meat and milk.

When a food or food compound is associated with both potential health risks and benefits, and particularly when the levels of intake associated with risk and benefit are close like may be the case for fish products, there is a need to define an intake range, for which the balance of risk and benefit is acceptable for risk management purposes (EFSA, 2006).

To estimate the net health effect of food consumption a risk-benefit assessment of the food or food constituents in question needs to be carried out. In order to optimise cost-efficiency and to improve transparency, a stepwise approach has been suggested (187). A risk-benefit assessment includes identification of hazard and positive health effect, characterization of hazard and positive health effect, exposure assessment, and characterization of risk and benefit which are weighed or compared to each other (187). When the risk and benefit involved are present at similar magnitude, like it might be for some fish, the risk-benefit assessment should include calculations to assess the direction and size of the net health effect (187).

Several factors are normally taken into consideration when deciding if there is a need to change or recommend a change in the current pattern of food consumption such as fish. In addition to the net health effect of fish consumption the decision maker normally also has to take social, environmental, and economical aspects into consideration.

Environmental aspects include among others the issue about the sustainability of fish sources. The World fish catch has reached its maximum for wild fish catch, which in turn affect the production of fish oil and feed derived from fish. The current recommendation to the Western population to eat three fish dishes per week of which one should be from oily fish can for example not be provided from wild fish catch. All the increase in fish supply must therefore come from aquaculture since there are few if any wild stocks that are underexploited according to (188). After growing steadily, particularly in the last four decades, it has been estimated that aquaculture presently contributes to half of the fish consumed by the human population worldwide (188).
Aquaculture of fish involves both white fish like tilapia, carp, and oily fish such as salmonids. The most limiting factor for the future development of aquaculture is the supply of feed as both fish meal and fish oil are the primary ingredients in feed for fish aquaculture.

The challenge of fish farming will be to find more sustainable sources of fish feed so that aquaculture could be the source of additional fish supply that enables authorities to recommend increased consumption of fish to increase public health.

As mentioned before, fish is not homogenous in terms of nutrients or contaminant content. Factors such as the type of fish, season, feed, life stage (e.g. reproductive stage) and age affect the amount of nutrients and contaminants within a single species and between species. Therefore the exposure to these substances due to fish consumption varies considerably over time and geographical area.

In the future, the nutrient composition of fish may become more homogeneous source of beneficial nutrients. Results show that the fatty acid composition of diets for oily fish like salmonids is reflected in the fish muscle of the cultured fish with significantly lower levels of omega-3 FAs in the muscle in fish fed diets containing plant oil (189, 190). Feeding experiments have also been carried out on farmed fish to ensure higher and more even levels of iodine in the fish (34). Thus it is possible to maximize the positive benefits of fish consumption for humans through optimization of feed composition for cultured fish. This also enables the aquaculture industry to control the quality of the cultured fish and ensure that it is a more stable and homogeneous source of omega-3 FAs and minimise the carry-over of contaminats into the human food chain. Future aquaculture therefore has to strike a delicate balance between the need to optimise the use of marine resources and the need to preserve the healthful benefits of farmed fish and this can only be achieved through feeding programs that strive to replace as much as possible of the fish meal and fish oil currently used in fish feeds with sustainable, alternative and contaminant free feed resources.

Conclusions

According to the health endpoint tables compiled above, the most likely added gain due to consumption of fish or fish constituents includes; better cognitive development (fish oil), fewer incidences of certain cardiovascular diseases (fish oil), neurological diseases (fish oil), cancers (selenium and vitamin D), inflammatory and autoimmune diseases (vitamin D), and falls and bone fractures (calcium and vitamin D).

Fish oil has traditionally been considered the main beneficial fish constituent However, additional and potentially synergistic effects of several fish constituents are likely to explain the higher benefits observed in epidemiological studies on fish consumption using fish than observed in studies using fish oil alone.

Future studies are needed in order to shed light on whether other constituents in fish, such as peptides, taurine, choline, coenzyme Q10, creatine and carnosine are of importance in scope of overall beneficial effect of fish consumption.

Based on the levels of fish oils, vitamin D, selenium, iron, iodine, fluorine, vitamin B present in 100 g of fish (Table 1) there is no risk of overdose of these nutrients in human diet through fish consumption alone. The sole risk of fish consumption is therefore related to the levels of undesirable compounds such as dioxins, PCBs, and MeHg in the fish/seafood. Epidemiological studies suggest that on average beneficial effects of fish consumption may outweigh the detrimental effects resulting from the undesirable substances in fish e.g.methyl mercury, dioxins and PCBs. Quantitative benefit-risk assessments of fish consumption is presently ongoing and the results from these studies will determine whether or not the results from the epidemiological studies can be confirmed (www.qalibra.eu ; www.beneris.eu).

Giving advice about fish consumption is further complicated by the fact that fish is neither homogenous in terms of nutrients nor contaminant content. Factors such as the type of fish, season, fisheries area, feed, life stage (e.g. reproductive stage) and age affect the amount of nutrients and contaminants within a single species as well as between species. Therefore the exposure to these substances due to fish consumption varies considerably over time and between geographical areas. Food policy makers need to take this variability into account before deciding whether or not measures need to be taken regarding advice to the public concerning fish consumption. This can be achieved by gathering more data on seasonal variation of nutrients in fish as well as the effect of cooking and processing methods in national food composition databases.

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