

# **TABLES ON THE HEALTH EFFECTS OF FISH**

**For BENERIS**

**Benefit-risk assessment for food: on iterative value-of-information approach**

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## Introduction

The health effects of fish have been extensively studied on various fields of interest. The main aim of the work presented here was to provide a general overview on the amount and quality of existing data on the health benefits of fish.

The benefits were examined by reviewing the meta-analyses indexed in Medline on fish, omega-3 fatty acids and vitamin D. Furthermore the search was extended on the indexed reviews on selected topics, if meta-analyses had not been conducted on the specific area of interest. The work was based on altogether 51 articles, among which there were five Cochrane reviews and four AHRQ publications. The main references for each area of health are listed after the tables.

The following themes were found as major areas of interest in scientific literature on health benefits of fish:

- All-cause mortality
- Cardiovascular health
- Cancer
- Brain function and mental health
- Autoimmune diseases, infections and immunonutrition
- Diabetes and blood glucose
- Development and infancy
- Bone health
- Nutrition

After defining the abovementioned areas of health, the amount of exciting data was collected in tables. The data was classified based on different type of studies (ecological, descriptive and cross-sectional; cohort and case-control and furthermore interventions) and the amount of data for each type of studies was presented using the following symbols:

- No data
- + Initial findings
- ++ Replicate studies

+++ Plenty of data

It must be noted that these symbols in tables were not to indicate the efficiency or effectiveness but the amount of data. In addition, the compiled tables indicate, whether the existing studies refer on intake of fish, fish oil, omega-3 fatty acids or vitamin D. Statements, if any, on the quantifiability of data can be found in the Comments-column.

Altogether there is still much to be learned on the health effects of fish and the current evidence can be somewhat contradictory. For example the cohort studies suggest that omega-3 protects against death whereas meta-regression of RCT's does not suggest a relation between mortality and omega-3 consumption. Several studies have been examining the protective effects of fish and fish oil in cardiovascular disease but data on positive effects on brain function and mental health is also accumulating. Fish oil does not seem to have a major role in the development of cancer or regulation of blood glucose and there is insufficient evidence to draw any conclusions on the role of fish consumption in cancer. Furthermore fish is a significant source of several nutrients like vitamin D and selenium at population level in Europe. The vitamin D in fish may have an important role in maintaining the vitamin D intake at optimal level for the well being of bone health. Finally fish or fish oil may also have a role in the prevention or treatment of various autoimmune diseases like asthma, psoriasis, rheumatoid arthritis of inflammatory bowel disease.

Table 1. Evidence on the effects of fish on all-cause mortality.

	Ecological, descriptive and cross-sectional studies	Cohort and case-control studies	Exposure data from cohort and case-control studies	Interventions	Exposure data from interventions	Comments
<b>All-cause mortality</b>	++	+++	Fish and fish oil	+++	Fish oil	Recent meta-regression of RCT's did not suggest a relation between mortality and the dose of long chain omega-3 fatty acids whereas cohort studies suggest that omega-3 protects against death (RR 0,65, 95 % CI 0,48-0,88, I <sup>2</sup> =36 %). Interventions on the effect of fish oil on all-cause mortality have mainly been conducted among subjects with CVD present already at the baseline.

- No data, + Initial findings, ++ Replicate studies, +++ Plenty of data

Table 2. Evidence on the cardiovascular health effects of fish. There is quantifiable data on all of the cardiovascular effects mentioned in the table. Therefore for example the American Heart Association recommends at least two weekly portions of fish for cardio-protective effects. Certain measurable cardiovascular health related endpoints like TIA, reconstructive vascular surgery, angioplasty, Intermittent claudication and amputation were not included in the table since quantifiable data is limited.

	Ecological, descriptive and cross-sectional studies	Cohort and case-control studies	Exposure data from cohort and case-control studies	Interventions	Exposure data from interventions	Comments
<b>CVD mortality</b>	+++	+++	Fish and fish oil	++	Fish oil	Interventions on cardiovascular mortality are secondary prevention trials. Only few interventions have been conducted with fish and there is hardly any data on various fish species. Evidence from fish interventions is limited as treatments generally consist of multiple lifestyle changes. <b>Quantifiable</b> data on protective effects of fish consumption in primary prevention is limited to cohort and case-control studies.
Sudden cardiac death	+++	+++	Fish and fish oil	++	Fish oil	
Ischemic heart disease mortality*	+++	+++	Fish and fish oil	++	Fish oil	
Non-fatal myocardial infarction	+++		Fish and fish oil	++	Fish oil	The above applies.
Stroke, both fatal and non-fatal	+++	+++	Fish and fish oil	++	Fish oil	The above applies. Figures for the incidence of non-fatal strokes generally presented combined with the fatal strokes.
<b>Risk markers</b> (blood pressure, serum lipids, thrombosis, arrhythmia)	+++	+++	Fish and fish oil	+++	Fish and fish oil	Majority of studies are done with fish oils, not fish. There is <b>quantitative</b> meta-analysis data on dose-response readily available on the effect of fish oil on blood pressure and lipids. Meta-analysis on heart rate shows that fish oils reduce heart rate but there is no evidence on clear dose-response effect.

\* Including myocardial infarction/ coronary heart disease

- No data, + Initial findings, ++ Replicate studies, +++ Plenty of data

Table 3. Evidence on the effects of fish on cancer.

	Ecological, descriptive and cross-sectional studies	Cohort and case-control studies	Exposure data from cohort and case-control studies	Interventions	Exposure data from interventions	Comments
<b>Tumor incidence/ death of cancer</b>	++	++	Fish and fish oil	+	Fish oil	No significant association between omega-3 fatty acids and cancer. No large-scale interventions with fish oil on cancer as primary outcome have been conducted. However, some of the large-scale interventions on CVD have reported the overall cancer incidence or mortality. Meta-analysis found no evidence on the effect of fish on cancer incidence or death of cancer.
Breast, colorectal, lung, prostate	+	++	Fish and fish oil	-		No significant association between omega-3 fatty acids and cancer incidence
Stomach	+	++	Fish	-		Preservation (salt) or preparation (frying, grilling) method of fish may play an important, exposing role in the etiology of stomach cancer
Thyroid	++	+++	Fish	-		No significant association between fish consumption and cancer incidence
<b>Cancer treatment</b>	N.A.	N.A.		++	Fish oil	No effects compared to placebo on post operative complications, hospital length of stay, nutritional parameters or mortality
<b>Tumor behavior</b>	-	-		-		Studied only in animal models or cell cultures, omega-3 enrichment might play a favorable role in the inhibition or prevention of tumor growth in animal models

- No data, + Initial findings, ++ Replicate studies, +++ Plenty of data

Table 4. Evidence on the effects of fish on brain function and mental health. Data for most of the conditions is insufficient for drawing conclusions on efficacy or dose-response effect. This is due to limited number of studies.

	Ecological, descriptive and cross-sectional studies	Cohort and case-control studies	Exposure data from cohort and case-control studies	Interventions	Exposure data from interventions	Comments
<b>Cognitive function in ageing</b>	+	+	Fish	-		Fish consumption tends to be inversely associated with cognitive impairment and cognitive decline ( <b>Quantifiable</b> data among healthy elderly is limited to results in one Dutch cohort).
<b>Dementia/ Alzheimer 's disease</b>	++	++	Fish and omega-3 fatty acids	+	Omega-3 fatty acids	In epidemiological studies consumption of ~3 portions of fish/week has been associated with 47 % decrease in the incidence of dementia.  Two clinical trials on-going, results expected 2008. Cochrane review concluded that there is a growing body of evidence from biological, observational and epidemiological studies that suggest a protective effect of omega-3 fatty acids against dementia. However, until data from RCT's becomes available no good evidence to support the use of omega-3 PUFA for the prevention of dementia.
<b>Psychiatric diseases</b>						
Depression/ Bipolar disorder	++	++	Fish and fish oil	+++	Omega-3 fatty acids	Evidence on both prevention (cohorts, case-control) and treatment (RCT). Epidemiological data, even <b>quantifiable</b> data, supports protective role of fish consumption, but no meta-analyses on the dose-response are readily available. 4/6 RCT's have reported therapeutic benefit from omega-3 consumption. In treatment the effective dose is likely to be above what might be gained via fish consumption

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Table 4 continues

Schizophrenia	+	+	N.A.	++	Omega-3 fatty acids	Evidence from observational studies is on the disturbances in the fatty acid metabolism, not on differences in intake of fish. 5/6 RCT's have reported therapeutic benefit from omega-3 consumption. However, most studies used fish-oil as adjunctive treatment, not as monotherapy, which makes <b>quantification</b> difficult.
<b>Attention deficit / hyperactivity disorder (ADHD)</b>	+	+	Omega-3 fatty acids	+	Omega-3 fatty acids	Current evidence does not support the use of omega-3 fatty acids as primary treatment of ADHD (¼ trials found positive effect with a treatment cocktail that contained 480 mg/d of DHA and 16 mg/d of EPA. ¾ trials found no effect with respective or lower dosages). Epidemiological data indicates that there are notable differences in membrane fatty acid composition between healthy and subjects with ADHD.
<b>Eyesight/ vision</b>						
Pre-term infants	++	++	Omega-3 fatty acids	++	Omega-3 fatty acids	Supplementation of pre-term-infant formula with long chain fatty acids may improve the development on vision in pre-term infants. However the evidence is not convincing as several null findings also exists. No conclusions can be made on dose-response.
Macular degeneration	++	++	Fish and omega-3 fatty acids	-		Epidemiological data on fish intake and AMD suggest a trend toward protective relation. Three studies have found reduced risk of ADM or progression of ADM when consuming fish two of more times/ week. One study group suggested a protective effect even at the consumption level of 1-3 servings/ month. Meta-analyses are not readily available on the subject. One RCT with fish-oil is on-going.

- No data, + Initial findings, ++ Replicate studies, +++ Plenty of data



Table 5. Evidence on the effects of fish on autoimmune diseases, infections and immunonutrition. There are relatively many studies conducted on these health conditions, but data for most of the conditions is insufficient for drawing conclusions on efficacy or dose-response effect. This is due to heterogeneity of these diseases and furthermore very limited evidence on comparable endpoint measurements between various studies on certain condition.

	Ecological, descriptive and cross-sectional studies	Cohort and case-control studies	Exposure data from cohort and case-control studies	Interventions	Exposure data from interventions	Comments (Population based studies are on the incidence or risk of the disease, interventions on the treatment.)
<b>Rheumatoid arthritis</b>	++	+	Omega-3 fatty acids	+++	Fish oil	Endpoints in interventions: Tender joints, morning stiffness, use of NSAID/corticosteroids Results promising, at least 3 meta-analyses have <b>quantified</b> the effect
<b>Asthma</b>	++	+	Fish	++	Fish oil	The results from epidemiological studies suggested that fish consumption is beneficially associated with lung function and prevalence of asthma, but currently there is no readily available data estimating the dose-response effect. In clinical trials supplementation does not consistently improve severity of symptoms, lung functions, airway responsiveness or medication use in asthmatic patients.
<b>Atopic dermatitis</b>	++	+	Fish	++	Fish oil	Recent meta-analysis found no evidence on the effectiveness of supplementation in the treatment of AD. Epidemiological data suggests preventive effect, but currently the data is likely to be insufficient for estimating dose-response effect.
<b>Biomarkers of inflammation</b> (TNF- $\alpha$ , IL-1, IL-6, eicosanoids)	++	+	Fish, omega-3 fatty acids	++	Fish oil	Quantifiable data from controlled trials exists both on healthy individuals and patients. However quantifying the clinical significance of the changes in inflammatory markers is a complicated task.

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Table 5 continues

	Ecological, descriptive and cross-sectional studies	Cohort and case-control studies	Exposure data from cohort and case-control studies	Interventions	Exposure data from interventions	Comments (Population based studies are on the incidence or risk of the disease, interventions on the treatment.)
<b>Inflammatory bowel disease</b>						
Crohn's disease	+	+	Fish	+	Fish oil	End points in interventions: clinical and endoscopic score, relapse
Ulcerative colitis	+	+	Fish	++	Fish oil	Endpoints in interventions: Clinical and endoscopic score, relapse/ remission, requirement for immunosuppressive agents
<b>Nephrology</b>						
Kidney transplantation	N.A.	N.A.		++	Fish oil	Endpoints in interventions: mortality, graft survival, lipid metabolism
Ig A nephropathy	N.A.	N.A.		++	Fish oil	Endpoints in interventions: end stage renal failure, serum creatinine level, proteinuria, renal tissue damage
<b>Psoriasis</b>	+	-		+	Fish oil	In interventions fish oils have been use as primary treatment or as concomitant therapy
<b>Systemic inflammatory response</b> (in surgery, trauma or critical illness)	N.A.	N.A.		++	Fish oil	Only little data on hard endpoints like mortality or length of hospital stay, most of the data on biomarkers

- No data, + Initial findings, ++ Replicate studies, +++ Plenty of data

Table 6. Evidence on the effects of fish on diabetes and blood glucose.

	Ecological, descriptive and cross-sectional studies	Cohort and case-control studies	Exposure data from cohort and case-control studies	Interventions	Exposure data from interventions	Comments
<b>Glycemic control in diabetes</b>	N.A.	N.A		+++	Fish oil	1-2 g of fish oil/day has no effect on glycemic control in diabetes, whereas higher intake may cause adverse effects on glycemic control
<b>Development of diabetes</b>	++	++	Fish	+	Fish	Data insufficient for drawing conclusions on efficacy  Interventions have been carried out among subjects with impaired glucose tolerance or metabolic syndrome and the treatment has consisted also other life style related changes besides increased fish consumption
<b>Cardiovascular disease among diabetic subjects</b>	-	+	Fish	-		Even though evidence on diabetic subjects is limited, the cardiovascular health of diabetic subjects is likely to benefit on fish consumption at least at the same level as general population

- No data, + Initial findings, ++ Replicate studies, +++ Plenty of data

Table 7. The effects of fish in development and infancy.

	Ecological, descriptive and cross-sectional studies	Cohort and case-control studies	Exposure data from cohort and case-control studies	Interventions	Exposure data from interventions	Comments
<b>IQ of children</b>	-	+	Fish	++	Fish oil and MeHg	Recent meta-analyses have calculated that increasing maternal docosahexaenoic acid (DHA) intake by 100 mg/day increases child IQ by 0.13 points whereas prenatal MeHg exposure sufficient to increase the concentration of mercury in maternal hair at parturition by 1 microg/g decreases IQ by 0.7 points.  Cohort study on child development outcomes and prenatal exposures to MeHg from maternal consumption of a diet high in fish found no consistent pattern of associations between these variable.
<b>Prevention of pre-eclampsia</b>	-	+	Omega-3 fatty acids in erythrocytes	++	Fish oil	Current evidence does not support the use of fish oil supplements for the prevention of preeclampsia
<b>Prevention of pregnancy induced hypertension</b>	?	?		++	Fish oil	At least six trials have examined the effect of fish oil supplementation on pregnancy induced hypertension none of them has provided evidence to support the use of fish oil supplements for the prevention of pregnancy induced hypertension
<b>Retinal function</b>	?	?		++	Long chain PUFA	The effect of long chain PUFA supplementation of formula on visual acuity of infants born at term has been studied in at least seven RCTs. No constant findings on benefits exists, but supplementation appears to be relatively safe. Maternal supplementation increases the DHA concentration of milk in lactating mothers.

- No data, + Initial findings, ++ Replicate studies, +++ Plenty of data, ? No profound search done, some data may exist

Table 8. The effects of fish on bones.

	Ecological, descriptive and cross-sectional studies	Cohort and case-control studies	Exposure data from cohort and case-control studies	Interventions	Exposure data from interventions	Comments
<b>Bone mineral density</b>	+	+	Fish	-		There is firm evidence on the importance of vitamin D on bone formation and metabolism and even prevention of osteoporosis. Fish is the most important dietary source of vitamin D when excluding fortified food items. However direct evidence on the effects of fish on bone mineral density or osteoporosis is limited to few observational studies among women in Japan
<b>Osteoporosis</b>	+	+	Fish	-		

- No data, + Initial findings, ++ Replicate studies, +++ Plenty of data

Table 9. The average contribution (% of the overall daily intake) of fish and fish dishes to intakes of energy and selected nutrients in United Kingdom, Sweden, Denmark and Finland. Only those vitamins and minerals for which fish is a significant dietary source at population level in Europe (contribution of at least 5 % of daily intake) is are included in table.

	United Kingdom <sup>a</sup> (%)	Sweden <sup>b</sup> (%)	Denmark <sup>c</sup> (%)	Finland <sup>d</sup> men (%)	Finland <sup>d</sup> women (%)
<b>Energy yielding nutrients</b>					
Energy	3	3	2	3	3
Protein	7	7	6	7	6
Carbohydrates	-	1	0	1	1
Total fat	3	4	2	4	5
SAFA	2	2	1	3	3
MUFA	4	4	2	5	5
PUFA	14 (cis n-3) 4 (cis n-6)	8	4	8 18 (cis n-3)	7 17 (cis n-3)
<b>Cholesterol</b>	-	9	-	9	8
<b>Minerals</b>					
Sodium	-	8	-	9	8
Sodium chloride	-	-	-	9	8
Phosphorus	5	4	3	5	4
Iodine	11	-	14	9	8
Selenium	-	23	15		
<b>Vitamins</b>					
Vitamin D	25	23	32	45	44
Vitamin E	5	7	5	8	6
Vitamin B3	6	6	6	9	8
Vitamin B12	18	23	18	-	-

<sup>a</sup> Figures based on intake from fish and fish dishes

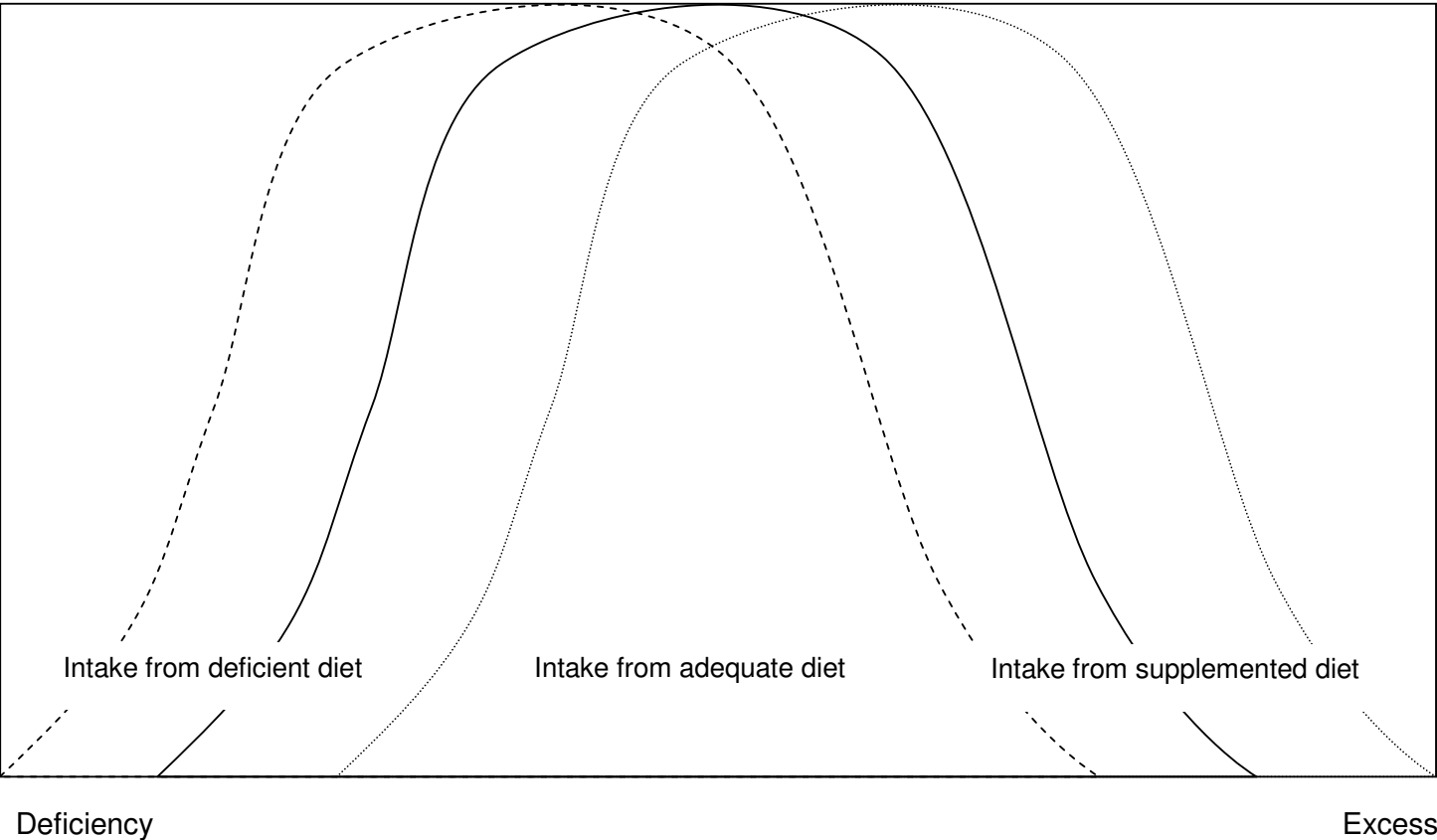
<sup>b</sup> Figures based on intake from fish and crustaceans

<sup>c</sup> Figures based on intake from fish

<sup>d</sup> Figures based on intake from fish dishes

Optimal nutritional/ health status

Malnutrition/ Disease



Healthy individual or subject whose sickness does not alter the need of nutrient/ food item. —————  
Subject with decreased requirement/ tolerance (e.g. children/ renal insufficiency patients) for a specific nutrient or food item. - - - - -  
Subject with increased requirement/ excess loss (e.g. patients with short bowel syndrome/ osteoporosis) for a specific nutrient or food item. . . . .

**Figure 1.** Age, physiological status or sicknesses effect the requirements of nutrients or food items for optimal nutritional status and health. Therapeutic effect from supplementation might be limited to correcting the nutritional deficiency or high doses of nutrient might have medicinal properties.

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### **All-cause mortality**

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