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Health aspects of regular consumption of fish and omega-3-fatty acids

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Health aspects of regular consumption of fish and omega-3-fatty acids

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Summary

Fish are valuable health foods due to their content of polyunsaturated omega-3-fatty acids (n3-FA) as well as essential amino acids, vitamins and minerals. Nevertheless, fish consumption is still significantly lower than meat consumption in Germany. Though there are indications that a regular, moderate consumption of fish or n3-FA might help reducing cardiovascular risk factors (e.g. hypertension, hyperlipidemia, hyperglycemia, inflammation) and positively influencing the risk for certain tumor diseases. This article provides a current overview on the health effects of a high fish or n3-FA consumption.

Keywords: fish, n3-FA, cardiovascular disease, hypertension, hyperlipidemia, inflammation, diabetes mellitus type 2, atherosclerosis, cancer

Introduction

In Germany, fish is eaten significantly less than meat. According to the federal statistic office the per-capita fish intake was around 14.4 kg in 2012 (measured as round weight) [1]. The German Nutrition Society (DGE) recommends a weekly consumption of 80–150 g low-fat fish (e. g. cod, redfish, saithe) and 70 g high-fat fish (e. g. herring, mackerel) (◆ Figure 1) [2]. This equals a per-capita-intake of 15 kg low-fat and 7.3 kg high-fat fish as measured by the round weight [3]. Thus, the Germans did not reach the recommended dosage on average.

The great importance attributed to fish in the people's diet is based on its nutritional values. Fish are, depending on their genus and species, rich in the polyunsaturated n3-FA eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as well as easily digestible proteins, which contain all essential amino acids (◆ Figure 2). In addition, fish contributes to the supply of vitamin A and D and the trace element iodine. The quantity of these nutrients correlates partially with the fat content of the fish. For example, high-fat fish (e. g. herring, mackerel, sardines, tuna, and wild salmon) provide more n3-FA and vitamin A and D than low-fat fish (e. g. cod, redfish). Higher amounts of iodine are, however, mainly found in sea fish (e. g. saithe, cod, redfish) [4]. Currently, the beneficial health effects of fish are particularly attributed to marine n3-FA. In several epidemiological studies, where a correlation between an abundant fish consumption and a reduced risk for cardiovascular diseases was observed, this effect was explained with the contained polyunsaturated fatty acids (PUFA) EPA and DHA [5, 6]. Especially in Germany, where cardiovascular diseases are amongst the leading causes of death [7], regular fish consumption might possibly help people to reduce symptoms of metabolic diseases and improve the overall cardiovascular health.

This article introduces the latest data concerning the effect of a regular fish or n3-FA-intake on biomarkers of selected lifestyle diseases (hypertension, hyperlipidemia, atherosclerosis, diabetes mellitus type 2) and cancer and evaluates the benefits of a frequent fish or n3-FA-consumption for health.

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Fish/n3-FA-consumption and cardiovascular risk factors

Hypertension

Hypertension (systolic: ≥ 140 mmHg, diastolic: ≥ 90 mmHg) is an important cardiovascular risk factor, as people with hypertension have a 17 % increased risk for cardiovascular diseases compared to people with normal blood pressure (BP) [8]. The development of hypertension should be avoided in particular to prevent sequelae.

Most intervention studies were conducted with the marine n3-FA DHA and EPA, because those FA are the most promising regarding a hypotensive effect [9–13]. Especially DHA is said to exert a preventive hypotensive effect, because its intake led for example to a dose dependent reduction of the arterial blood pressure in mice [14]. Furthermore, an inverse association between the DHA intake and the diastolic BP as well as the resting heart rate was observed in healthy and hypertensive people [15]. But DHA can partially be retroconverted into EPA in the human organism, as to why it is unclear, which of these n3-FA is mainly responsible for the vasodilatative effect. In addition, only few studies used fish (e. g. salmon) for the intervention [12, 16].

As seen in ◆ table 1, some studies have demonstrated a hypotensive effect of fish or fish oil on people, who already had a previous illness (chronic kidney disease, overweight) or a high risk for hypertension. For example, a supplementation of 4 g/d of fish oil over the period of 8 weeks resulted in a significant reduction of the BP in patients with renal insufficiency (systolic: -1.7 mmHg; diastolic: -1.0 mmHg) [11]. In Addition, the meta-analysis of Geleijnse et al. (2002) showed that a significant reduction of the BP can be achieved by a regular consumption of an average of 3.7 g/d of fish oil (systolic: -2.1 mmHg; diastolic: -1.6 mmHg). Both the age of the subjects as well as the blood pressure before the start of the intervention appear to be crucial to this effect. Thus, the hypotensive effect was more pronounced if the subjects were older (> 45 years) and had a higher blood pressure at the beginning of the intervention [10].

Furthermore, the quality of the fish oil needs to be taken into account. Although a vasodilatory effect was repeatedly demonstrated for EPA and DHA [12, 14, 15], it is still questionable why some studies did not observe a hypotensive effect. There are indications that the commonly in supplements used ethyl ester derivatives of these FA are metabolized and absorbed less efficiently by the human body compared to the naturally occurring triglycerides (TG) of DHA and EPA and are thus maybe less effective [17, 18]. However, this observation is still controversial and requires further investigations, because there are also statements about these derivatives being absorbed and taking effect in a similar way to the natural n3-FA [19]. Nevertheless, the difference in the efficiency of the metabolism could be an explanation for the ineffectiveness of fish oil supplements in some studies. For example, Wu et al. (2014) observed no hypotensive effect after regular consumption (1.5 g/d, 8 weeks) of marine n3-FA in participants with hypertension [20]. In contrast, Ramel et al. (2010) have shown that an intervention with fish oil (1.3 g/d EPA and DHA) or a consumption of salmon (2.1 g/d EPA and DHA) resulted in a significantly greater reduction of the diastolic BP (salmon: -2.71 mmHg; fish oil: -2.48 mmHg) than an intervention with cod (0.3 g/d EPA and DHA), which was attributed to the different intake-levels of n3-FA [12]. There is also evidence for a hypotensive effect of fish in people with normal BP [16], but this was not confirmed by every study [21].

The majority of recent studies described a hypotensive effect by high intake levels of n3-FA from fish or fish oil in people with hypertension. However, the usual uptake level of n3-FA through food is not sufficient to obtain antihypertensive effects according to the current evidence based guidelines on fat consumption of the German Nutrition Society (DGE) [22]. Moreover, it needs to be clarified by further studies, if and how healthy people can prevent

Abbreviations

AA	arachidonic acid
CRP	C-reactive protein
DHA	docosahexaenoic acid
DMT2	diabetes mellitus type 2
EPA	eicosapentaenoic acid
FFQ	food frequency questionnaire
FMD	flow-mediated dilatation
HDL-Cholesterol	high-density-lipoprotein-cholesterol
ICAM-1	intercellular adhesion molecule-1
IL-6	interleukin-6
LDL-Cholesterol	low-density-lipoprotein-cholesterol
MeS	metabolic syndrome
MUFA	monounsaturated fatty acids
n3-FA	omega-3-fatty acids
PUFA	polyunsaturated fatty acids
RR	relative risk
TC	total cholesterol
TG	triglycerides
TNF α	tumor necrosis factor α
VCAM-1	vascular cell adhesion protein-1

Fig. 1: **The German Nutrition Society (DGE) recommends a weekly consumption of 80–150 g low-fat fish, e. g.:**
1 cod (*Gadus morhua*)
2 redfish (*Sebastes norvegicus*)
3 saithe (*Pollachius virens*)

hypertension through a regular fish consumption.

Hyperlipidemia

Hyperlipidemia (trigylcerides [TG] ≥ 150 mg/dL and/or LDL-cholesterol ≥ 140 mg/dL; total cholesterol [TC] ≥ 200 mg/dL) is an important risk factor for cardiovascular diseases [23]. Hence, it should be treated or better preventively averted.

In recent years, beneficial effects of n3-FA on blood lipid fractions were observed by several intervention studies, using either fish or fish oil in both healthy individuals and individuals with hyperlipidemia (◆ table 2). The currently best studied effect in this context is the TG-lowering effect of EPA and DHA. Thus a daily consumption of salmon (125 g/d, 4 weeks) [16] or marine n3-FA (3–14 g/d) [11, 21, 24–27] in various studies led to a significant reduction of TG levels in the blood up to 25 %. This beneficial effect was positively associated with the absorbed amount of n3-FA and the initial values of TG in the blood: The TG blood level was more strongly reduced, the more n3-FA consumed or the higher their share in the blood and the higher the TG baseline level [21, 28, 29]. Based on current knowledge it is assumed that EPA and DHA exert this effect through different mechanisms of action. They can positively influence the lipid metabolism in their function as PPAR-Agonists, for example by promoting the fatty acid oxidation and the inhibition of lipogenesis, resulting in a reduction of the formation of VLDL and TG [30, 31]. Further mechanisms by which the n3-FA ultimately affect the lipid metabolism remain to be clarified.

Regular fish consumption may also lead to an improvement of the HDL cholesterol value, which is negatively associated with the TG concentration in the blood [32]. Thus, some studie-participants exhibited not only a reduction of the TG concentration in the blood, but also increased HDL cholesterol values after the consumption of DHA and EPA (overview in [33]). Even healthy people and people with metabolic syndrome had a significant increased HDL cholesterol level after a regular consumption of 100–150 g fatty fish (3 x/week) [34] or 125 g/d salmon [16]. These effects were attributed to a promotion of the reverse cholesterol transport by EPA and DHA [34]. On the other hand, moderate dosages of n3-FA (1–3 g/d of EPA and DHA) often led to no or just a slight increase in HDL cholesterol [27, 35].

The effect on further blood lipid fractions (LDL-cholesterol, VLDL cholesterol, TC) is, however, discussed controversially. Some studies observed significantly improved blood levels of TC, LDL- and VLDL-cholesterin with a regular intake of EPA and DHA [16, 26, 35–37] and even two meta-analyses confirmed an association between a regular consumption of EPA and DHA and a significant reduction of the VLDL-cholesterol [26] or the LDL-cholesterol and TC, respectively [35]. In contrast, rather moderate intake levels (2–4 g/d EPA or DHA) seem to have no or only a minor influence on the blood levels of those lipid fractions [24, 25, 28].

4

5

and 70 g high-fat fish, e. g.:

4 **herring (*Clupea harengus*)**

5 **mackerel (*Scomber scombrus*)**

The results of recent studies show that a regular consumption of fish or marine n3-FA can contribute to the reduction of elevated TG levels in healthy people as well as individuals with hyperlipidemia and thus possibly counteract the pathogenesis of hyperlipidemia.

Inflammation

Subliminal, inflammatory processes may contribute to the development of cardiovascular diseases, with an inflammation of the blood vessels often being associated with oxidative stress and endothelial dysfunction [38]. The consequences of these changes include the loss of flexibility of the vessels, a decreased sensitivity of endothelial cells for dilatory messengers (nitric oxide [NO]) and the deposition of oxidized lipoproteins into the blood vessel walls, which can lead to thrombus formation. To assess the individual risk of atherosclerotic-related, cardiovascular diseases, different inflammatory (tumor necrosis factor α [TNFα], C-reactive protein [CRP], interleukin-6 [IL-6]) and endothelial biomarkers (E-selectin, intercellular adhesion molecule-1 [ICAM-1], vascular cell adhesion protein-1 [VCAM-1]) are used.

Long-chain n3-FA are essential for the maintenance of normal endothelial functions. Firstly, they reduce the amount of proinflammatory n6-FA (arachidonic acid [AA]) in cell membranes (e. g. erythrocytes) and tissues [38]. Secondly, n3-FA compete in the body with n6-FA (AA) for the enzyme cyclooxygenase (COX) [39] and in this way inhibit the formation of proinflammatory eicosanoids (prostaglandin E2 [PGE2]), cytokines (TNFα, IL-6) and other in-

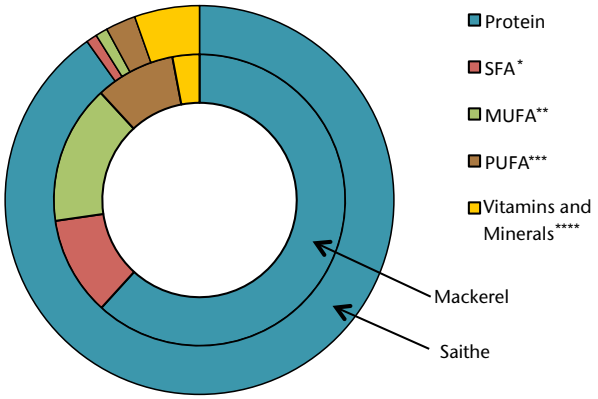

Fig. 2: **Ratio of nutrients of mackerel and saithe in fresh mass %** (mod. after [4]).

* SFA = saturated fatty acids

** MUFA = mono unsaturated fatty acids

*** PUFA (poly unsaturated fatty acids): eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA]

**** vitamines: A, E, D, B_1, B_2, B_6, B_{12}, Niacin
minerals: sodium, potassium, calcium, magnesium, phosphorus, ferrum, selenium, iodine

Author [Source]	Participants	Parameters	Results
Epidemiological Studies			
Liu et al. [15]	265 men and women (healthy or hypertensive)	measurement BP and plasma-DHA/EPA	DHA inverse associated with diastolic BP
Animal Study			
Hoshi et al. [14]	FVB/NJ mice	3 µM DHA intravenous once	dose-depending reduction of the arterial BP
Intervention Studies			
Cazzola et al. [21]	155 men	0; 1.35; 2.7 or 4.05 g EPA/day, 12 Weeks	n. C.
Dokholyan et al. [9]	103 men and women with hypertension	0.48 g EPA + 0.12 GLA per day (placebo: olive oil), 12 weeks	n. C.
Lara et al. [16]	48 men and women	125 g/d wild salmon, 4 weeks	BP ↓ (systolic: –4.6 mmHg, diastolic: –3.0 mmHg)
Mori et al. [11]	47 men and women with chronic kidney disease	4 g/d n3-FA capsules (EPA, DPA, DHA and α-Toc.), 8 weeks	BD ↓ (systolic: –1.7 mmHg, diastolic: –1.0 mmHg)
Ramel et al. [12]	324 overweight men and women (healthy or hypertensive)	energy restricted diet in combination with: 3x/week 150 g cod or 150 g wild salmon or 1.3 g/d fish oil or sun-flower oil, 8 weeks	BD ↓ in all groups; wild salmon (–2.71 mmHg) and fish oil (–2.48 mmHg), more effective than cod but no difference to control
Theobald et al. [13]	38 men and women	700 mg DHA/d, 3 month	diastolic BP: –3.3 mmHg
Wu et al. [20]	84 men and women with cardiovascular risk	1.5 g/d Fish oil, 8 weeks	n. C.
Meta-Analyses			
Geleijnse et al. [10]	90 studies with 2 114 men and women	averagely 3.7 g/d fish oil	systolic BP ↓, diastolic BP ↓, dose- and age-dependent

Table 1: **Influence of Fish-/n3-FA consumption on blood pressure**
BP Blood pressure; n3-FA omega-3-fatty acids; EPA eicosapentaenoic acid; DHA docosahexaenoic acid; GLA gamma linolic acid; DPA docosapentaenoic acid; α-Toc α-tocopherole; n. C. no change; ↓ significant reduction

flammatory markers (CRP) [38, 40]. About ten years ago, results of an epidemiological study [41] showed an inverse correlation between the consumption of marine n3-FA and the plasma levels of inflammatory biomarkers in healthy women (◆ table 3). In this case, women with the highest intake level of EPA and DHA (0.3–1.6 g/d) had shown significantly lower blood levels of E-selectin, IL-6 and CRP compared to non-consumers. These findings were confirmed in a recent meta-analysis. LI et al. (2014) analyzed 68 intervention studies which investigated the influence of a regular consumption of marine n3-FA (0.3–6.6 g/d of EPA and DHA from fish or fish oil) on inflammatory biomarkers in healthy individuals as well as people with pre-existing health conditions (including dyslipidemia, obesity, diabetes mellitus type 2 [DMT2]). The intervention resulted in significant reduced fasting blood levels of TNFα, CRP and IL-6 in both groups [40]. Furthermore, it was demonstrated that the effect size was significantly influenced by the duration and dosage as well as the age and baseline levels of biomarkers. Thus, the strongest effects were seen when participants were older than the median, had higher IL-6 baseline-levels and took longer part in the study.

A dose-dependence was also observed in relation to the endothelial biomarker P-selectin [42]. The level of this biomarker was only reduced in volunteers who daily consumed 6.6 g of EPA and DHA, but not in those with a consumption of only 2.0 g/d. Obese people (BMI > 30 kg/m²) seem to need certain minimum amounts of n3-FA to exert beneficial effects on the inflammatory biomarker CRP. This is probably due to the fatty acid composition of adipose tissues that contain higher concentrations of inflammatory effective n6-PUFA (AA). According to the study of Browning et al. (2007), obese individuals should therefore

Author [Source]	Participants	Parameters	Results
Epidemiological Studies			
Bullyaa et al. [37]	1 000 men and women	FFQ, blood parameters	fish consumers: LDL ↓, HDL ↑; LDL/HDL ↓; TC/HDL ↓
Intervention Studies			
Adamson et al. [36]	86 men and women with mild hypercholesterolemia	nordic diet (regular fish consumption), 6 weeks	LDL ↓
Browning et al. [24]	30 overweight women	fish oil: 1.2 g/d EPA + 2.9 g/d DHA; 4 or 12 weeks	TG ↓
Cazzola et al. [21]	155 men	0; 1.35; 2.7 or 4.05 g EPA/day, 12 weeks	TG ↓; EPA + DHA in plasma ↑
Ciubotaru et al. [27]	30 healthy women	7 g/d or 14 g/d fish oil, 5 weeks	TG ↓; TG/HDL ↓
Goodfellow et al. [25]	30 men and women with hypercholesterolemia	2 g/d n3-FA	TG ↓
Lankinen et al. [34]	131 men and women with MeS and faulty glucose metabolism	100-150/g fatty fish 3x per week, 12 weeks	HDL ↑
Lara et al. [16]	48 men and women	125 g/d wild salmon, 4 weeks	TG ↓ (15 %); LDL ↓ (7 %); HDL ↑ (5 %)
Mori et al. [11]	47 men and women with chronic kidney disease	4 g/d n3-FA capsules (EPA, DPA, DHA and α-Toc.), 8 weeks	TG ↓ (24 %)
Skulas-Ray et al. [28]	26 men and women with modest hypertriglyceridemia	0.85 or 3.4 g EPA+DHA/d, 8 weeks	high dosage: TG ↓ (27%), low dosage: n. C.
Meta-Analyses			
Hartweg et al. [26]	23 studies with 1 075 men and women	effect of averagely 3.5 g/d n3-FA on lipid fractions	TG ↓; VLDL ↓
Maki et al. [35]	8 studies with 406 men and women	effect of fish consumption on lipid fractions	TC ↓; LDL ↓; HDL ↘; TG ↘

Table 2: **Influence of Fish-/n3-FA consumption on blood lipids**
MeS metabolic syndrome; FFQ Food Frequency Questionnaire; n3-FA omega-3-fatty acids; TG triglycerides; VLDL Very Low Density Lipoprotein; LDL Low Density Lipoprotein; HDL High Density Lipoprotein; EPA eicosapentaenoic acid; DHA docosahexaenoic acid; n. C. no change; ↑ significant increase; ↓ significant reduction; ↘ not-significant reduction

receive at least 4.2 g/d of marine n3-FA to achieve beneficial effects on CRP and IL-6 in the blood [24]. By contrast, an intake of 2.0–2.4 g/d of EPA and DHA wasn´t enough to induce a significant improvement in the endothelial function (ICAM-1, VCAM-1 flow-mediated dilatation [FMD]) of overweight individuals (BMI: 27 ± 3.5 kg/m²) with dyslipidemia [25, 43].

Cazzola et al. (2007) conducted a dose- and age-dependent effect in healthy people after an intervention with 1.35–4.05 g/d EPA for 12 weeks [21]. It was found that the highest dosage in young subjects (18–42 years) led to a significant increase in E-selectin, whereas both age groups (18–42 years and 53–70 years) showed a tendency to reduced ICAM-1 level with increasing EPA intake. In addition, MILES et al. (2001) demonstrated that an intake of 1.2 g/d of EPA and DHA led to increased E-selectin levels in young participants (< 40 years), whereas older people (> 55 years) showed decreased levels of this biomarker [44]. Different causes may contribute to the fact that older men and women with different metabolic conditions react more conducive to fish oil supplementation than younger ones. On one hand, elderly seem to integrate n3-FA from fish

Author [Source]	Participants	Parameters	Results
Epidemiological Studies			
Lopez-Garcia et al. [41]	727 women	FFQ	inverse association: n3-FA and VCAM-1 or ICAM-1
Intervention Studies			
Browning et al. [24]	30 overweight women	fish oil: 1.2 g/d EPA + 2.9 g/d DHA; 4 or 12 weeks	after 12 weeks: CRP ↓ , IL-6 ↓
Cazzola et al. [21]	155 men	0; 1.35; 2.7 or 4.05 g EPA/day, 12 weeks	E-Selectin ↑ ; VCAM-1 ↘ trend of positive association between EPA in phospholipids and VCAM-1
Ciubotaru et al. [27]	30 healthy women	7 g/d or 14 g/d fish oil, 5 weeks	CRP ↓ ; IL-6 ↓
Eschen et al. [42]	60 men and women	6.6 g/d ; 2.0 g/d n3-FA or olive oil, 12 weeks	P-Selectin (6,6 g n3-FS) ↓
Geelen et al. [48]	84 healthy	3.5 g/d fish oil (= 1.5 g/d n-3-FA), 12 weeks	n. C.
Goodfellow et al. [25]	30 men and women with hypercholesterolemia	2 g/d n3-FA, 4 month	FMD ↑
Hjerkinn et al. [43]	563 men with hyperlipidemia	2.4 g/d n3-FA, 3 years	I-CAM-1 ↓
Katan et al. [51]	85 men	0, 3, 6 or 9 g/d fish oil, 1.5 years	maximum intake of EPA reached: serum cholesterol-ester after 8 weeks, gluteal fat tissue after 6–12 month, abdominal fat tissue >12 month
Madsen et al. [49]	60 men and women	0.9 g EPA + 0.8 g DHA or 3 g EPA + 2.9 g DHA per day, 12 weeks	n. C.
Miles et al. [44]	28 men and women	1.2 g/d EPA + DHA, 12 weeks	young participants (< 40 years): E-Selectin ↑ ; older participants (> 55 years): E-selectin ↘ , VCAM-1 ↓
Rees et al. [45]	165 men	1.35; 2.7 or 4.05 g EPA/d, 12 weeks	incorporation of EPA in phospholipids of mononuclear cells associated with reduced PGE2-production
Vega-Lopez et al. [50]	80 men and women	0.6 g/d EPA + 0.3 g/d DHA	n. C.
Wu et al. [20]	84 men and women with cardiovascular risk	1.5 g/d fish oil	EPC ↑ ; EMP ↑
Meta-Analyses			
Li et al. [40]	68 studies with 4 601 men and women	supplementation n3-FA on inflammatory parameters	TNFα ↓ ; CRP ↓ ; IL-6 ↓ neg. linear relationship: duration and effect; overweight inhibits effect

Table 3: **Influence of Fish-/n3-FA consumption on inflammatory biomarkers**
n3-FA omega-3-fatty acids; CRP C-reactive protein; IL-6 interleukin 6; VCAM-1 Vascular cell adhesion protein 1; ICAM-1 Intercellular adhesion molecule 1, FMD flow mediated dilatation; EMP endothelial micro particle; EPC endothelial progenitor cells; PGE2 prostaglandin E2; TNFα tumor necrosis factor α; EPA eicosapentaenoic acid; DHA docosahexaenoic acid; n. C. no change; ↑ significant increase; ↓ significant reduction; ↘ not-significant reduction

oil more quickly into cellular membranes [45]. On the other hand, levels of n3-FA increase in adipose tissues with age, wherefore an additional intervention might help to achieve potentially effective concentrations of n3-FA more quickly, which could finally be a reason why a clearer effect was observed in the elderly compared to the younger volunteers [46].

The effect of fish oil on the postprandial, vascular activity is also depending on the age. Thus healthy, younger participants (< 50 years) exhibited a better NO-mediated postprandial response 4 hours after eating than older individuals (> 50 years). This effect was attributed to a possibly better NO-sensitivity of younger individuals, since all participants showed a similar NO level in the blood after 4h [47].

Moreover, the baseline levels of the measured biomarkers are crucial for the anticipated effect. Thus a signifi-

cant reduction in CRP was observed in women who already had elevated CRP baseline-levels [27], whereas no changes were observed in volunteers with lower CRP baseline-levels [48–50]. Finally the effect of an intervention is also determined by its duration. While shifts in the composition of blood lipids (cholesterol esters) can be detected after 4–8 weeks, basic changes in the composition of cell membranes and adipose tissues are only measurable after an intervention period of at least 6–12 months [51]. Since many intervention studies are carried out on an average of 12 weeks, this can be a possible reason for the often unchanged parameters or partly inconsistent results.

Based on the current knowledge, especially older people and individuals with preexisting metabolic diseases may benefit from a regular consumption of marine n3-FA or high-fat fish in terms of inflammatory processes.

Fish/n3-FS-consumption and type 2 diabetes mellitus

Diabetics have an approximately 4-fold higher risk of cardiovascular diseases compared to healthy people. The development of diabetes mellitus type 2 (DMT2) should therefore be avoided [39]. Epidemiological studies showed an inverse relationship between fish consumption and the DMT2 incidence [52, 53]. This could be due to the n3-FA EPA and DHA contained in fish. As components of cell membranes they are able to improve insulin sensitivity inter alia and as PPAR agonists can furthermore positively affect the gene expression of enzymes that are important for the glucose metabolism [30].

The European Prospective Investigation into Cancer (EPIC) study showed that a regular fish consumption of only 1 serving/week is already associated with a 25 % lower risk of DMT2 compared to a lower intake [52]. However, there is also evidence of contrary effects. A positive correlation between the intake of marine n3-FA and the DMT2 incidence was for instance observed in 36 382 healthy individuals [54]. Various other analytical and intervention studies did also find inconsistent results (◆ table 4). While a regular consumption of fish [16, 53] or fish protein [55] or EPA and DHA [56] in some studies was associated with improved insulin sensitivity [16, 55] or lower fasting blood levels of glucose [53, 56], no changes of blood glucose parameters [11] or even increased glucose levels [57] were found in other studies. Intriguingly, several meta-analyses indicated an influence on study results by their geographical origin [58-61]. Asian studies found an inverse relationship between the consumption of high-fat fish (relative risk [RR] = 0.89; 95 % confidence interval [CI] = 0.82–0.96) [60] or n3-FA (RR = 0.86; 95 % CI = 0.79–0.93 [58]; RR = 0.87; 95 % CI = 0.79–0.96 [61]) and the DMT2 risk, whereas no association was found in European studies (RR = 1.03; 95 % CI = 0.96–1.11) [59] and even positive correlations in American studies (RR=1.16; 95 % CI = 1.04–1.28 [61] and RR = 1.05; 95 % CI = 1.02–1.09 [59]). Possible reasons for these conflicting results may be both genetic predispositions [62] as well as differences in the general nutritional behavior or the preparation of the fish [52, 60]. Thus in contrast to a western diet (lots of red meat, processed foods, refined sugars), a typical Asian diet containing lots of vegetables, fish and fiber is inversely associated with for instance DMT2 [63]. Patel et al. (2009) observed in addition a clear influence of the food preparation method [52]. They found a significant inverse relationship between the consumption of fish and the DMT2-risk (odds ratio [OR] = 0.77; 95 % CI = 0.61–0.96) based on 21 984 subjects from the EPIC study, but this association was not observed after regular consumption of fried fish (OR = 1.04; 95 % CI = 0.88–1.24).

Due to the heterogeneous data, a positive effect of regular fish consumption on the DTM2 risk seems possible, but remains to be proven yet.

Fish/n3-FS-consumption and tumor diseases

Causes of tumor diseases are diverse: old age, individual lifestyles, eating habits or genetic predispositions. Due to various mechanisms of action it is currently still discussed controversially, how a regular consumption of fish and n3-FA can possibly contribute to the risk reduction of various tumor diseases. One potential mechanism is the anti-inflammatory effect of n3-FA, because inflammatory processes can favor the tumor development. Besides the inhibition of inflammatory eicosanoids, n3-FA can furthermore reduce cell proliferation processes [64]. They are therefore in theory able to counteract the genesis and development of tumors through these mechanisms. Nevertheless, other fish ingredients showed beneficial effects, too. The micronutrients vitamin D and selenium, which are contained in fish, have both been associated with tumor-protective effects, inter alia, since these nutrients inhibit inflammatory reactions and promote DNA repair mechanisms [65]. So far, several studies have examined the relationship between the consumption of fish or n3-FA and the formation of tumors (◆ table 5) with partly very different results (overview in [22]). For example, investigations on the relationship between n3-FA and colorectal cancer led to both an increased and a decreased RR [22]. So far, rather mixed results were demonstrated by various meta-analyses: While Shen et al. (2012) demonstrated no risk relationship for the entire study population (7 studies with 489 000

Author [Source]	Participants	Parameters	Results
Epidemiological Studies			
Djoussé et al. [54]	36 328 women	FFQ	marine n3-FA positive associated with DMT2
Huang et al. [56]	266 men and women (healthy and DMT2-patients)	blood parameters: glucose, insulin	plasma-glucose and insulin negative correlated with n3-PUFA in plasma; plasma-glucose positive correlated with n6-PUFA in plasma
Patel et al. [52]	21 984 men and women	FFQ	fish consumption associated with significant reduced DMT2-risk
Sotos et al. [53]	945 men and women	FFQ + blood glucose	fish consumption associated with reduced plasma-glucose and reduced DMT2-prevalence
Intervention Studies			
Lara et al. [16]	48 men and women	125 g/d salmon, 4 weeks	Adiponectin ↘
Mori et al. [11]	47 men and women with chronic kidney disease	4 g/d n3-FA capsules (EPA, DPA, DHA and α-Toc.), 8 weeks	n. C.
Quellet et al. [55]	19 men and women with insulin resistance	cod-protein (58–68 % of daily protein intake), 4 weeks	insulin sensitivity ↑
Woodman et al. [57]	51 diabetics (men and women)	4 g/d EPA or DHA or olive oil, 6 weeks	EPA und DHA: glucose ↑
Meta-Analyses			
Muley et al. [58]	16 studies with 679 763 men and women	association n3-FA and DMT2-risk	US-studies RR:1,09; Asian studies RR: 0,86; DMT2-risk ↓ with consumption of fatty fish
Wallin et al. [59]	16 studies with 527 441 men and women	association fish consumption and DMT2-risk	geographic difference: US-studies positive and Asian studies negative association between fish consumption and DMT2-risk
Zhang et al. [60]	11 studies with 549 955 men and women	association fish consumption and DMT2-risk	inverse association: fatty fish and DMT2-risk (RR: 0.89)
Zheng et al. [61]	24 studies with 789 784 men and women	association n3-FA and DMT2-risk	geographic difference at fish consumption/ marine n3-PUFA: US-studies positive (RR: 1.16) and Asian studies negative (RR: 0.87) associated with DMT2-risk

Table 4: **Influence of Fish-/n3-FA consumption on diabetes mellitus type 2**
n3-FA omega-3-fatty acids; n-6-FA omega-6-FA; FFQ Food Frequency Questionnaire; α-Toc α-tocopherole; DMT2 diabetes mellitus type 2; RR relative risk; EPA eicosapentaenoic acid; DHA docosahexaenoic acid; n. C. no change; ↑ significant increase; ↓ significant reduction; ↘ not-significant reduction

participants) and a reduced risk (RR = 0.87; 95 % CI = 0.75–1.0) of colorectal cancer by an increased n3-FA intake only in men [66], YU et al. (2014) reported a significant inverse relationship between fish consumption and the development of tumors in the colorectal area (RR = 0.93; 95 % CI = 0.87–0.99) [67]. The latter meta-analysis also observed a slightly reduced risk of gastrointestinal tumors (RR = 0.98; 95 % CI = 0.96–1.01) by an increase in fish consumption by 20 g/d [67]. Furthermore, some studies were performed with respect to the tumorgenesis in the mammary tissue (reviewed in [68]). Women who regularly ate fish (> 73 mg/d of EPA and DHA) had a reduced risk of breast tumors by approximately 25 % when compared to non-consumers (Hazard Ratio [HR] = 0.74; 95 % CI = 0.58–0.94) [69]. Results of another meta-analysis of 21 studies showed a n3-FA-related risk reduction by approximately 14 % after comparing the groups of the highest and the lowest fish consumption (RR = 0.86; 95 % CI = 0.78–0.94) [70]. These results are consistent with the findings of the meta-analysis presented in 2004 by Saadatian-Elahi et al., which also proved a protective effect of marine n3-FA on breast cancer risk [71]. However, some studies did not show protective effects [72, 73], which was inter alia attributed to low intake-levels of n3-FA [73] or low levels of n3-FA in adipose tissues [72].

Previous studies on the risk of prostate tumors in connection with fish consumption yielded different results. Some studies showed an inverse trend between the consumption of fish or fish oil (> 2 servings/ week) and the emergence risk of these

Author [Source]	Participants	Parameters	Results
Epidemiological Studies			
Amin et al. [74]	917 men	FFQ/incidence prostate cancer	reduced risk with increasing fish consumption
Chavarro et al. [79]	20 167 men	prostate cancer mortality	fish intake inverse associated with risk of prostate cancer -mortality
Leitzmann et al. [75]	47 866 men	FFQ/incidence prostate cancer	EPA and DHA associated with significant reduced risk of prostate cancer
Pham et al. [78]	5 589 men	prostate cancer mortality	fish intake inverse associated with risk of prostate cancer -mortality
Schmidt et al. [72]	1 570 women	FFQ/biopsy fat tissue	composition of fat tissue not associated with Long-term risk of breast cancer
Terry et al. [76]	6 272 men	FFQ/incidence prostate cancer	fish intake inverse associated with risk of prostate cancer and -mortality
Witt et al. [73]	1 148 women	FFQ/biopsy fat tissue	no association between n3-FA nm fat tissue and breast cancer risk
Intervention Studies			
Patterson et al. [69]	3 081 women with stage 1 breast cancer	FFQ/incidence breast cancer	73 mg/d associated with 25 % risk-reduction of breast cancer
Meta-Analyses			
Alexander et al. [80]	21 studies with 446 243 men	association n3-FA and prostate cancer risk	no association
Chua et al. [81]	8 studies with 317 786 men	association n3-FA and prostate cancer risk	trend of association between zwischen n3-FA and prostate cancer-risk
Saadathian-Elahi et al. [71]	10 studies with 4 365 women	association n3-FA and breast cancer risk	n3-FA-conten in breast tissue exerts protective effect
Shen et al. [66]	7 studies with 489 000 men and women	association n3-FA and colorectal tumors	no association between n3-FA and colorectal tumors for whole study population; sub-analysis men: n3-Fa associated with significant reduced risk for colorectal tumors (RR: 0.87)
Yu et al. [67]	27 studies with 232 5040 men and women	association fish consumption and tumor diseases	fish consumption associated with reduced risk for tumors in: esophagus (RR: 0.91), liver (RR: 0.71), colorectal (RR: 0.93); increase of 20 g fish consumption per day associated with 2 % reduced risk of gastrointestinal tumors
Zheng et al. [70]	21 studies with 883 585 women	association n3-FA and breast cancer risk	n3-FA associated with reduced breast cancer risk (RR: 0.86)

Table 5: **Influence of Fish-/n3-FA consumption on emergence of selected cancers**
n3-FA omega-3-Fatty acids; FFQ Food Frequency Questionnaire; RR relative risk; EPA eicosapentaenoic acid; DHA docosahexaenoic acid

tumors ([74–76], reviewed in [77]), and several studies observed a significant lower prostate cancer mortality after high fish consumption (> 2 servings/week) [76,78,79]. However, the meta-analysis by Alexander et al. (2015) did not find an association between the intake of n3-FA and prostate cancer incidence (RR = 1.00; 95 %-CI = 0.93–1.09) [80]. Whereas the meta-analysis by Chua et al. (2012) in contrast even led to the conclusion that an increased intake of n3-FA is associated with an increased risk (RR = 1.135; 95 % CI = 1.008–1.278) of prostate tumors [81].

Thus, the recent data on the effect of fish or n3-FA on cancer risks are insufficient and allow no generalized statements yet.

Conclusion

A regular consumption of fish and n3-FA can help effecting biomarkers of cardiovascular risk factors favorably (BP, TG, blood glucose, inflammatory markers) and thus possibly help preventing cardiovascular diseases. Even a risk reduction of certain cancers by fish or n3-FA-consumption seems possible. By assessing these results it should be

noted that the majority of studies were not conducted with fish but with fish oil or supplements of EPA and DHA. This complicates the assessment since the effect of the supplements is not directly comparable to the consumption of fish. High doses of EPA/DHA (4–5 g) were administered through supplements, which are hardly reachable by moderate fish consumption. According to the European Food Safety Agency (EFSA) these amounts are tolerable because no negative effects were observed so far by supplementation of up to 5 g/d DHA and EPA for a period of 12 weeks. However, due to the lack of data to date it hasn't been possible to establish a tolerable maximum level for these n3-FA [82]. It must also be considered that fish are furthermore rich in other ingredients (e. g. vitamin D, selenium), which may also exert beneficial health effects. For this reason, further studies examining the health effects of regular fish consumption are strongly advised.

In Germany, fish is only consumed in moderate amounts and not by everyone. Approximately 16 % of the participants in the National Nutrition Survey II (NVS II) responded that they consume no fish at all [83]. The reasons for this food pattern are manifold. Vegans or vegetarians often refrain for ethical reasons to the consumption of fish. Other people in contrary worry about negative health effects due to a load of fish with environmental contaminants, such as mercury or dioxins, which can certainly have a negative impact on human health. For example, the uptake of methyl-mercury was associated with a restricted cognitive ability in infants [84]. The levels of these contaminants vary strongly in fish dependent on their age, fat-content and place in the food chain [85]. According to the Federal Institute for Risk Assessment (BfR), tuna (0.9 mg/kg mercury) and halibut (1.03 mg/kg mercury) may already contain amounts of mercury that correspond to the statutory maximum level in fish of 1.0 mg/kg [86]. It is therefore not recommended to regularly consume these fish species. Hence, the EFSA recommends reducing the consumption of fish rich in methyl-mercury for health reasons [87]. However, people do not have to refrain from fish consumption. Some types of fish contain only small amounts of methylmercury (< 0.5 mg/kg), but are still rich in n3-FA (e. g. Herring), wherefore these can be consumed in moderate amounts. However, the consumer should be careful to eat fish regularly (1–2 x per week) while in moderation, because high consumption of slightly contaminated fish can also lead to exceeding the recommended maximum weekly amount of mercury [86]. Moreover, in times of overfishing and in terms of sustainability it is desirable to mind moderate fish consumption [3]. According to the EFSA, 1–4 weekly servings of fish or fish products can exert health-promoting effects, at which a harmful intake of environmental contaminants should be avoided by the consumer [87]. The BfR states in addition that one does not have to reckon with a questionable inclusion of mercury by eating 1–2 servings of fish or fish-products per week [88]. The serving sizes can be oriented on basis of the DGE guidelines, which recommend a consumption of 80–150 g low-fat and 70 g high-fat fish per week [2].

The references of this article are available online: → *www.ernaehrungs-umschau.de/Service/Literaturverzeichnisse*

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Conflict of Interest
The author declares no conflict of interest according to the guidelines of the International Committee of Medical Journal Editors.

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