Benefits and risks of fish consumption for the human health

Benefícios e riscos do consumo de peixes para a saúde humana

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ABSTRACT

The article aimed at identifying and discussing scientific evidences on the benefits and risks of fish consumption the human health. There was a systematic survey for articles published from 2003 and May 2011, at the MedLine, Scopus, SciELO, Lilacs and Google Scholar databases. The key words used were: *fish, food intake, omega-3 fatty acids, fatty fish, benefits, risk, and consumption.* The search produced 12,632 articles, 25 eligible cohort studies on possible benefits, 61 on risks and 10 studies that assessed the "risk/benefit" relation. Of the 25 works, 14 suggested a preventive effect of fish consumption related to cardiovascular diseases, depression, cataract and some types of cancer. Evidences of a relation between exposure to mercury and an increase in the risk of neurological disorders, but not of cardiovascular diseases, were also found. Given the importance of fish consumption, its possible risks and the lack of Brazilian studies on the topic, it is important to conduct more longitudinal studies that assess both the benefits and risks of fish consumption for the human health. We also emphasize the need for policies to reduce exposure of fish and seafood to mercury and other contaminants.

Indexing terms: Fishs. Food consumption. Health. Risk.

RESUMO

O artigo objetivou identificar e discutir evidências científicas sobre benefícios e riscos do consumo de peixes para a saúde humana. Realizou-se uma busca de artigos publicados entre 2003 e maio de 2011, nas bases de

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dados MedLine, Scopus, SciELO, Lilacs e Google acadêmico. Utilizaram-se as palavras chaves: fish, food intake, omega-3 fatty acids, fatty fish, benefits, risk, consumption. *Encontraram-se 12.632 artigos, sendo elegíveis 25 estudos de coorte que investigaram possíveis benefícios, 61 sobre riscos e 10 estudos que avaliam a relação "risco/benefício". Dentre os 25 trabalhos, 14 sugeriram efeito protetor do consumo de peixes, relacionado a doenças cardiovasculares, depressão, catarata e alguns tipos de câncer. Foram encontradas evidências de relação entre exposição ao mercúrio e aumento do risco de distúrbios neurológicos, mas não do risco de doenças cardiovasculares. Tendo em vista a importância do consumo de peixes e seus possíveis riscos, bem como a escassez de pesquisas nacionais sobre o tema, observa-se a relevância de se realizarem mais estudos longitudinais que aliem a avaliação dos benefícios e riscos do seu consumo para a saúde humana. Ressalta-se também a necessidade de políticas para redução da exposição de peixes e frutos do mar ao mercúrio e outros contaminantes.*

Termos de indexação: *Peixes. Consumo de alimentos. Saúde. Risco.*

INTRODUCTION

Fishes are rich in essential fatty acids, as well as in iron, vitamin B_{12} and calcium. Fish consumption is recommended by The American Cancer Society and the American Heart Association (AHA) at least two times a week[1,2].

Brazil has great potential for fish farming due to its extensive maritime coast and continental waters, together with the possibility of consumption of great variety of species[2]. Not with standing that, fish consumption in Brazil dropped considerably in recent years[3,4].

Some studies have demonstrated the health benefits of fish consumption thanks to the correlation between omega-3 fatty acids and a decrease in the incidence of coronary heart diseases[5-10], depression[11,12], stroke[13], blood pressure[5,14], glycemic index[14], triglycerides[5], cancer[15,16] and others. On the other hand, researches could also quantify levels of fish contamination in 17 fish and check possible risks linked to its consumption, such as contamination by heavy metals, organochlorine pollutants and dioxins[17-20].

With the incentive to fish consumption and a current discussion on its benefits and risks[21,22], seconded by a lack of scientific studies with clear conclusions about contamination, it is imperative that literature about risks and benefits of fish consumption is reviewed, especially in Brazil. Moreover, in the searches performed, no critical reviews on the subject were found. Therefore, this article aimed at identifying and discussing scientific evidences on the benefits and risks of fish consumption for the human health.

METHODS

The study was designed to answer a guiding question: what are the scientific evidences on benefits and risks of fish consumption for the human health? The methodology adopted followed the basic procedures recommended for studies of literature on systematic reviews[23-25]. In other words, systematic methods were used to critically identify, select and discuss articles published on the theme investigated and related objectives, materials and methods, as well as results observed, with drawing of conclusions on the corresponding state-of-the-art or available scientific knowledge[23-25].

A systematic search to capture scientific articles published was accomplished in the period between January 2003 and May 2011, in the MedLine (National Library of Medicine), Scopus, SciELO (Scientific Electronic Library Online), Lilacs (Caribbean Latin American Literature and in Sciences of the Health) electronic databases and in Google Scholars. The key words used were: fish in combination with food intake (dietary consumption), omega-3 fatty acids, fatty fish, benefits, risk, consumption.

The criteria to include articles, defined prior to the systematic survey on literature were: a) articles discussing the association between fish

consumption and health benefits; b) articles discussing the association between omega-3 fatty acids consumption and health benefits; c) articles discussing the relation between fish consumption and risks to the health; d) articles discussing the relation between consumption of contaminated fish and risks to the health; e) articles on human beings; and f) articles published in the Portuguese, English and Spanish languages. The criteria to exclude articles were: a) articles discussing the association between fish oil consumption and health benefits; b) studies on fish oil and omega-3 fatty acids supplements; c) articles whose discussion and/or objectives did not include fish consumption assessments; d) articles of literature reviews; e) studies on validation of questionnaires; f) studies on software development; g) articles with the same data sources (same study population); h) articles with children or pregnant women; i) articles with incomplete texts even after request to authors through electronic and institutional addresses available in the publications.

Considering all the electronic databases investigated, 12,632 articles were found. After reading of headings and abstracts, studies with no relation with the subject of this review and/or of similar nature were discarded. Initially, 385 articles related to possible benefits and risks of fish consumption were selected for a preliminary analysis. Among which, 152 articles met the right criteria for inclusion.

Of the 152 articles selected for analysis, 81 were related to the possible benefits of fish consumption for the human health; 61 discussed consumption of contaminated fish and its possible risks for the human health; and 10 assessed, simultaneously, the relation "risk/benefit" of fish consumption for the human health. Therefore, the investigation presented the results ahead with the following analysis criteria for the initial grouping of the 152 studies selected: articles related to "benefits", articles related to "risks" and articles related both "risks" and "benefits" of fish consumption for the human health.

After comparative analysis of the 152 studies selected, 25 of them referring to cohort studies about the benefits of fish consumption were selected and the remaining ones discarded for bearing investigations of another methodological nature. For the critical analysis of these 25 articles, it was established a descriptive script in accordance with proposals by Moher *et al*.[23] and von Elm *et al*.[25], where each article selected should be analyzed in relation to its objectives, materials and methods, results and conclusions, displaying a synthesis of the available scientific knowledge investigated on the theme. These 25 articles were characterized according to the following criteria for analysis: year of publication; place of research; size and sample characteristics; analyzed variables; type of statistical analysis of data; and results, including stratification or cut-off point for amount and frequency of fish consumption (Attached).

Just one cohort article on possible risks of fish consumption for the human health was selected. So, as most researches that included risks were observational studies of cross-sectional nature and it was not possible to infer a causal relationship, studies on possible risks or risks/benefits of fish consumption for the human health were analyzed separately.

Attention must be called to absence of conflict of interests in the study design.

RESULTS AND DISCUSSION

General characteristics of studies

The 25 articles on benefits and risks associated to fish consumption investigated and based on cohort studies that attended the inclusion criteria were published in the period from 1/1/2003 to 31/5/201. Of these, 2 were published in 2003[9,15], 5 in 2004[6,8,12,26,27], 3 in 2005[13,28,29], 5 in 2006[7,30-33], 2 in 2007[2,11,34] in 2008[4,10,16] in 2010[35-38] and 2 in 2011[39,40]. Most of them was performed in the Unites States of America (USA)[6,9,10,13,15,26,29,32,35,37] (40%), then

comes Sweden[16,38,39] (12%), Finland[12,27], Holland[8,30], Norway[31,34], Japan[7,40] and Denmark[28,36] (8% each), and Spain[11] and England[33] (4% each one) (Attached).

Regarding size and the characteristics of the investigated samples, there were variations from 229[6] to 310 671[31] individuals, where, in 12 studies, they consisted of men and women[7,8,10-13,20,28,30,36,40], in 10 only women[6,16,26,29,31,34,35,37-39] and in three, only men[15,27,34]. Ages ranged between 25 and 83 years old, where 15 studies included adults and older people[8,10,11,15,16,26-34,39,40], 3 only adults[7,12] and 3 only older people[6,9,13] (Attached).

Of the pathologies investigated, 13 studies assessed the association between fish consumption and cardiovascular diseases (ischemic heart disease, unspecified cardiovascular diseases, atherosclerosis progression, atrial fibrillation, arrhythmia, stroke, heart attack and venous thromboembolism)[6,7,9,10,13,26,28,30,33,35-37,39]; 6 had analyzes on distinct types of cancer (not specified, prostate, breast, colon and renal cell)[15,16,26,31,32,34]; 5 had some psychological and/or neurological disorders (depression, mental disorders, cognitive function, psychotic symptoms, suicide risk)[8,11,12,27,38,40], and one, cataract[29] (Attached).

Regarding statistics, 9 articles[6,7,9,11,13,16,26,29,32] used more than one type of analysis. Thus, it was observed that 14 studies[9,13,16,26,27,30-36,39,40] used survival analysis methods, with the Cox proportional risk model as the main model; one of them also used the Kaplan-Meier survival probability[13]. Nine studies used the regression analysis[8,11,12,15,26,37-40] and 7 used correlation coefficients (Pearson or Spearman) [6,7,10,28,29,32,40]. The odds ratio test[9,13] and the covariance analysis[6,26] were applied in two studies each. Also, the t test and the chi-squared test[6], the linear trend[11] and the Person-time[16] were applied in a study each (Attached).

In the analysis of dietary methods, it was observed that 21 studies used semi-quantitative food frequency questionnaires [6-11,13,15,16,26-34,36,37,40]. In 7 studies, the questionnaire was sent by mail to the participants[8,11,12,15,16,26,34]; in the others, it was delivered in person or applied by the interviewer. The amount of items referring to fish consumption in the questionnaires varied depending on the study from 1 to 19 items analyzed. Not all studies mentioned the number of items included in the questionnaire of dietary frequency or how many of them referred to fish consumption. It was observed there was a validation of dietary methods in 20[6-11,13,15,16,27-32,34-38] of the articles analyzed (Attached).

Regarding studies main results, 14 (56%) displayed a beneficial relation between fish consumption and lower risk of prostate[15] and renal cell cancer[16], of death by ischemic heart disease[9] and by heart failure[35], of myocardial heart attack and non-fatal coronary events[7], of acute coronary syndrome[36], of venous thromboembolism[10], of atherosclerosis progression[6], of stroke[13,39], depression[12], cognitive function damages[8], psychotic symptoms[38] and cataract[29]. However, 11 studies (44%) could not find any associations with cancer in general (not specified)[26], colon[34], prostate[32] and breast[31] cancer; with stroke[26,33]; with atrial fibrillation[26,28,30,37]; with arrhythmia[26,28]; with depression[27]; with risk of suicide[40] and with mental disorders in general[11] (Attached).

An important consideration is that in just two of the studies analyzed[9,13], both conducted in the USA, have considered the preparation methods of fish as a variable in their investigations (Attached). These articles have demonstrated that consumption of grilled or baked fish is associated with lower risk of death by ischemic heart disease or arrhythmia, if consumed more than 3 times a week, and lower risk of stroke, if consumed from 1 to 4 or more than 5 times a week. On the other hand, consumption of fried fish or fish sandwiches revealed an association with higher risk for the same diseases.

These findings follow the Food Guide for the Brazilian Population[2] recommendations, which orients the population to prepare and consume food with little oil, such as baked, stewed, cooked

or grilled dishes, and to prevent the fried ones. This guide was based on recommendations by the Global Strategy on Diet, Physical Activity and Health developed by the World Health Organization[41], which recommends limiting consumption of high-energy food like fats and substituting unsaturated fats for saturated fat while also eliminating trans fatty acids.

Fish consumption and heart diseases

The relation between frequency of fish consumption and benefits for heart diseases could be found in studies on the population of USA, where it was demonstrated that a consumption frequency ≥1 time a week was associated with a reduction in the progression of atherosclerosis in women that have reached menopause and reduction in esthenosis in diabetic women[6]; in the development of the venous thromboembolism in the 45 to 64 year old population, as well as in hospitalization and death rates due to weak heart in adult and aged women[36]. In Sweden, lean fish consumption of ≥3 times a week reduced stroke risk in women[39]. In a study conducted in Denmark[36], the average consumption of ≥7g of fat fish a day was associated with lower risk of coronary syndrome in men, and in Japan[7], fish consumption at 8 times a week was associated with lower risk of myocardial heart attack and non-fatal coronary disease when compared with a once-a-week consumption.

These studies demonstrate that fish consumption at least once a week can be a protective factor for heart diseases and, the higher the consumption frequency, the higher the protective effect is. The explanation for these findings can be: omega-3 fatty acids contribute to reduce the likelihood of blood clotting, and consequently, the risk of heart attacks and stroke[7,10]. Therefore, it is recommended the consumption of fish with high levels of omega-3 fatty acids, such as trout, salmon, tuna, halibut, swordfish and mackerel, to prevent heart diseases, 2 to 3 times a week[42].

On the other hand, studies found no associations between distinct ranges of portions/frequency of fish consumption and any reduction in the risks of atrial fibrillation or arrhythmia (<2 times/week against ≥2 times/week)[28], incidence of atrial fibrillation (~15g/day30 and 37 ~18g/day), of stroke (<1, 1-2 and >2 portions/week)[33] or of death by heart diseases (<0,5 to ≥2, 5 portions/week)[26]. It must be highlighted that two[28,37] of these are among the five studies[7,28,35-37] on cardiovascular benefits with the largest samples investigated. And concerning the other three, two revealed beneficial only for men[36] or only for women[35]. Therefore, it stands out that an ample sampling may, perhaps, lead to a wider variety of life styles and confusion factors, as well as evidence differences inherent to the sexes, with the possibility of a reduced association with the benefits of fish consumption.

It must also be mentioned that the lack of specification on how fish is prepared may take to a misleading conclusion about the benefits of its consumption in heart diseases prevention. When this specification is not investigated, results indicating no benefits may have been caused by the preparation method and not by fish consumption.

Fish consumption and cancer

A study conducted in the USA[15] reported that a fish consumption frequency higher than 3 times a week was associated with a reduction in the risk of prostate cancer in men. Myint *et al*.[33] analyzed the relation between the ingestion of Alpha-Linolenic Acid (ALA) and prostate cancer incidence, and came to the conclusion that consumption from 1.09g to 1.75g/day of ALA, found in foods of plant and animal origin, including fish, was not associated with a risk reduction of prostate cancer development (p=0.76). It is clear that although the relation between fish consumption and prostate cancer were studied in both researches, the variables studied were different from one another, since

Augustsson *et al*.[15] checked a possible reduction in prostate cancer in connection with fatty acid found in seafood, whereas Myint *et al*.[33] have only observed this reduction in relation to ingestion of ALA.

According to a study developed by Paul Terry and published in the American Society Cancer site[42], men who consumed fish less than two times a week had a higher risk of developing prostate cancer than those who consumed it more frequently (2 or more times a week).

A study conducted with 61 433 women who had no previous diagnosis of cancer, with ages between 40 and 76, found an association between consumption of fatty fish, in the frequency ≥1 a month, and a reduction of 74% in the risk of renal cell cancer[16].

Other studies found no association between a possible beneficial relation of fish consumption and a reduction in the risk of cancer development. Folsom & Demissie[26] researched, in the USA, the relation between fish consumption and cancer incidence with risk of death by cancer in 41 836 postmenopausal women, with ages between 55 and 69, initially free of Cancer and Cardiovascular Diseases (CVD). The researchers found no association between ingestion of <0.5 to ≥2.5 portions/week of this food and cancer incidence (p=0.49) or risk of death (p=0.15).

Koralek *et al*.[32] checked the association between ALA total consumption and risk of prostate cancer. Contrary to the study conducted by Myint *et al*.[33], the researchers found no association between ALA total consumption (1.09g to 1.75g/day) obtained from several dietary sources, such as fish, and risk of prostate cancer (p=0.76). It is clear that, in the study of Koralek *et al*.[32], fish was not the only source of ALA. In Norway, Engeset *et al*.[31] found no association between consumption of 5.54g to 96.77g/day of fish and risk of breast cancer development. In this same country, Engeset *et al*.[34] analyzed fish consumption in 63,914 women, with ages between 40 and 71, and found no association between consumption of 46.2g to 167.2g/day with the relative risk of colon cancer (p=0.14). Thus, it was observed that the relation between cancer prevention and fish consumption is not well established, considering that few results were found to prove such beneficial effect, even when specific nutrients, that separately seem to interfere with the appearance and development of cancer, were studied.

Fish Consumption, neuropsychological disorders and cataract

About neuropsychological disorders associated to fish consumption, a study conducted with the adult population of Finland found that a low frequency consumption (up to 1 time/month) compared with the regular consumption (≥1 time/week) was associated with depression in women, but not in the men[12]. In another study developed in that country, with 50 to 69-year-old men, was also found no association between fish consumption (average ~40 g/day) and depression[27].

A study conducted with the adult population of Spain found no association between fish consumption (36.4 to 161.9 g/day) and the risk to develop mental disorders[11]. Another study developed in Japan with 40 to 69-year-old men and women also found no evidence of reduction in suicide risk related to fish consumption (32.5 to 152.84 g/day)[40]. Therefore, the researches abovementioned about risks of mental disorder development, depression or suicide only suggests a preventive effect in fish consumption in the incidence of depression in women.

Kalmijn *et al*.[8] assessed the cognitive function and dietary consumption, including fish consumption. The researchers found that, in 45 to 70 year-old people, the increase omega-3 of sea origin (EPA - Eicosapentaenoic Acid Consumption and DHA - Docosahexaenoic Acid) consumption was associated with reduction in the risk of cognitive function loss (19%). Hedelin *et al*.[38] also found that the risk of psychotic symptoms was 53% lower in women who consumed fish

3-4 times/week when compared to the ones who hardly consumed it.

Lu *et al*.[29] observed an association between fish consumption in the frequency of ≥3 times a week and a lower risk (relative risk =0.89) of developing cataract in women above 45 years of age, compared to the ones who ate fish ≤1 time a week (relative risk=1), p=0.01. It seems to be clear that fish consumption may prevent cataract, psychological disorders like depression and psychotic symptoms, and loss of the cognitive function, especially in women. However, few works approaching the issue were found suggesting a need of development of more studies to produce effective conclusions on the preventive effect of fish for such disease.

Fish consumption and fish contaminants

The cohort studies analyzed did not investigate aspects related to fish contaminants, which could be responsible for the lack of association with benefits observed in part of the studies and its possible effects on consumers' health. Therefore, it stands out that fish consumption may be beneficial to the health due to the presence of fatty acids while, at the same time, it may interfere with risk factors of some pathology, due to the presence of chemical contaminants.

In this sense, researches were conducted to quantify contaminants in fish and compare the values reported with limits recommended, as well as to find out risks involved in the consumption. Among the contaminants more largely studied, the leading ones were the heavy metals, mainly mercury, the Polychlorinated Biphenyls (PCB) and the Polybrominated Diphenyl Ethers (PBDE).

Kim & Lee[43], in a study developed with 1,790 Korean 20 to 49 year-old men and women, found a relation between fish consumption and blood levels of mercury. Benefice *et al*.[44] reported that the increase in blood mercury levels among Amerindians living in the Bolivian Amazon, also related with fish consumption, was associated with a higher susceptibility in developing neurological disorders. .Most of the other studies that explain the risks of fish consumption are limited to identification and quantification of contaminants in varied species.

Because contaminants may bring risks to the human health, studies were conducted in order to quantify contaminants and omega-3 contents, and to compare ratios between these substances[45,46]. Foran *et al*.[46] developed a risk-benefit ratio, relating cancer risk and other diseases with the cumulative exposure to organic contaminants and to the omega-3 contents present in fish. In this study, for some fish, the risk of contaminants was apparently compensated by the omega-3 fatty acid benefits to the health. Other researches revealed that salmon is the species with the highest omega-3 ratio in relation to contaminantes[17,45,47]. Wennberg *et al*.[48] found no association between omega-3 and mercury, and the risk of stroke.

However, few population-based studies were found, including cohort studies, which could meet the criteria for inclusion and which quantified fish consumption, relating the effects of omega-3 and the contaminants to the health of the population studied.

It is worth mentioning the study developed by Mozaffarian *et al*.[49], who analyzed data of 6,854 participants of the Health Professionals Follow-up Study (HPFS) and Nurses' Health Study (NHS). It was observed that mercury concentrations were positively associated with fish consumption and high ingestion of EPA and DHA, low ingestion of saturated fats, monounsaturated fats, trans fats and cholesterol, and high ingestion of protein and polyunsaturated fats. Individuals exposed to a higher mercury concentration did not present an increased risk of cardiovascular events. Moreover, fatal associations with non-fatal myocardial heart attack, heart diseases or stroke were not observed.

Thus, evidences between exposure to mercury and an increase in the risk of heart diseases were not observed, although Benefice

et al.[44] suggest that there may be a relation with higher susceptibility of developing other diseases, such as neurological disorders.

CONCLUSION

In the review performed, it was observed that more frequent studies on fish consumption related it to potential benefits to the health of consumers. Heart diseases were the most frequently studied issue and also the ones that presented the most significant associations between health prevention and fish consumption.

Studies on risks suggested a relation between consumption of contaminated fish and cancer predisposition, heart diseases and neurotoxicity, but only cross-sectional studies suggesting them could be found instead of cohort studies that might help prove such associations.

Researches about the benefits of fish consumption were applied to similar populations as regards age, but with differences with relation to sample sizes, methods, statistical analyses and especially to results, which remain contrasting.

Besides, there were disagreements concerning the amount and frequency recommended for fish consumption in order to enjoy the benefits. However, despite the disagreements, there are national and international recommendations advising an ingestion of at least 2 times a week. Moreover, most of the studies about fish consumption is developed in the north hemisphere, and may not reflect the Brazilian reality since the fish species consumed are different as are the ways of preparation.

In view of fish consumption recommendations, especially concerning omega-3 intake, and of current discussions on fish contaminants together with the scarcity of national researches on the subject, it becomes clear the importance of a development of longitudinal studies that may integrate assessments on the benefits and on the risks of fish consumption with the human health. It is also fundamental the creation of policies to reduce fish and seafood exposure to mercury and other sources of contamination.

CONTRIBUTION

AC FERNANDES, CO MEDEIROS, GL BERNARDO and MV EBONE took part in the project design, data collection, analysis and interpretation, and in the article composition. PF DI PIETRO and MAA ASSIS took part in the accurate critical review of the intellectual content and in the final review of the version. FAG VASCONCELOS took part in the project design, article composition, accurate critical revision of the intellectual content and in the final version.

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STUDIES ON THE POTENTIAL BENEFITS OF FISH CONSUMPTION FOR THE HUMAN HEALTH, PUBLISHED BETWEEN 2003 AND 2011, AND IDENTIFIED BY AUTHOR, COUNTRY, YEAR, STUDY TYPE, SAMPLE CHARACTERISTIC AND STUDY VARIABLES, STATISTICAL ANALYSIS AND THE MAIN RESULTS. FLORIANÓPOLIS (SC), BRAZIL, 2011

Author, year country	Size (n) and sample characteristic	Study Variables	Statistical Analysis	Dietary methods	Results
Mozaffarian *et al*. (2003)[9] USA	3,910 Men and women >65 years	Fish Consumption and way of preparation Risk of IHD and arrhythmia	Cox proportional Hazard Model; probability ratio test	1 semi-quantitative food frequency questionnaire, on usual consumption, validated*	Consumption of grilled or baked fish ≥3x/week ↓ death risk for IHD or arrhythmia. Fried fish or fish sandwich ↑ risk of these diseases
Augustsson *et al*. (2003)[15] USA	47,882 Men 40-to 75-year-old	Fish consumption Risk of prostate CA Vasectomy historical background	Logistic regression	3 posted FFQ (*t*=0, *t*=4, *t*=8) of 1 year, semiquantitative, validated*	Fish consumption >3x/week ↓ risk of prostate CA. Ingestion of 0.5g of fatty acids/day from seafood ↓ 24% risk of metastatic CA
Erkkilä *et al*. (2004)[6] USA	229 Postmenopausal women 64/65 years old (average)	Fish consumption Progression of coronary disease	*t* Test chi-squared test; covariance analysis; Spearman correlation coefficient	1 semiquantitative FFQ of 1 year, with 126 item (3 of fish) validated	Consumption of ≥2 portions of fish or ≥1 portion/week of tuna/dark meat fish ↓ stenosis in the diabetic ones. Consumption ≥1 portion of fish/week ↓ progression of atherosclerosis in women with CAD
Kalmijn *et al*. (2004)[8] Holland	1,613 Men and women 45-to 70-year-old	Fish consumption Assessment of the cognitive function	Logistic regression analysis	1 semiquantitative FFQ of 1 year, with 178 items (3 of fish) validated	The increase of 4g/day in fat fish consumption was associated with ↓ risk of damages in the cognitive function
Timonen *et al*. (2004)[12] Finland	5 689 Men and women	Fish consumption Risk of depression and suicide ideas Sex	Logistic regression analysis	1 FFQ posted of 6 months (1 of fish) without validation register	Lower frequency in fish consumption (rarely) was associated with depression in women, but not in men
Folsom & Demissie (2004)[26] USA	4 836 Postmenopausal women, free of cancer and CVD 55-to 69-year-old	Fish consumption Risks of death by CVD or stroke Cancer incidence	Covariance analysis; poisson regression model of relative risk	1 posted semiquantitative FFQ on usual consumption with 127 item (4 of fish), without a validation register	There was no association between fish consumption (<0.5 ≥2.5 portions/week) and incidence of CA or risks of death by CVD or CA
Hakkarainen *et al.* (2004)[27] Finland	29,133 Men 50-to 69-year- old	Omega-3 and fish consumption Depression	Cox proportional Hazard Model	1 semiquantitative FFQ of 1 year validated*	There was no association between fish consumption and depression (average of 39.35g/day and 39.62g/day respectively among patients with and without depression)
Mozaffarian *et al*. (2005)[13] USA	4,775 Men and women 65-to 98-year-old	Fish consumption Way of preparation Plasma levels of omega-3 stroke incidence	Cox proportional Hazard Model; Kaplan-Meyer survival method; probability ratio test	1 semiquantitative FFQ of 1 year (3 items of fish) validated	Consumption of tuna or other grilled/baked fish ↓ risk of ischemic stroke (1-4x/week and ≥5x/week). Consumption >1x/week of fried fish/fish sandwiches ↑ risk of ischemic stroke

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CONTINUATION

Author, year country	Size (n) and sample characteristic	Study Variables	Statistical Analysis	Dietary methods	Results
Frost & Vestergaard (2005)[28] Denmark	47,949 men and women 50-to 64year-old	Omega-3 fish consumption Risk of atrial fibrillation and/or arrhythmia	Spearman correlation coefficient	1 self-managed semiquantitative FFQ on usual consumption (2 items of fish) validated	Omega-3 fish consumption (average 0.16 to 1.29 g/day) and fish (<2 x/week to ≥2x/ week) was not associated with ↓ risk of atrial fibrillation or arrhythmia
Lu *et al.* (2005)[29] USA	71,083 women >45 years-old	Dietary consumption Cataract incidence	Pearson and Spearman correlation coefficient	5 semiquantitative FFQ (*t*=0, *t*=2, *t*=6, *t*=10, *t*=14) of 1 year (3 items of fish) validated	Fish consumption ≥3x/ week ↓ risk (RR=0.89) of developing cataract compared to those who consumed fish ≤1x/week (RR=1)
Iso *et al.* (2006)[7] Japan	41,578 men and women, free of CVD or cancer 40-to 59-year-old	Omega-3 and fish consumption Coronary disease	Pearson correlation coefficient; Spearman correlation coefficient; (95% confidence interval)	2 semiquantitative FFQ (*t*=0, *t*=5) of 1 month and 1 year (4 and 19 fish items) validated	High fish consumption (8x/ week or 180 g/day) ↓ risk of myocardial heart attack and not-fatal coronary disease, compared with a meager consumption (1x/ week or 23g/day)
Wolk *et al.* (2006)[16] Sweden	61 433 women free of cancer 40-to 76-year-old	Consumption of fat and lean fish Renal cell carcinoma	Person-time, Cox proportional Hazard Model ($p<0.05$)	2 semiquantitative FFQ posted (*t*=0 and *t*=10 years) of 1 year (*t*=0 - 67 items; *t*=10 - 96 items) validated	Fat fish consumption ≥1x/ month ↓ risk of renal cell cancer
Brouwer *et al.* (2006)[30] Holland	5 184 men and women, free of atrial fibrillation ≥55 years of age	Fish consumption Incidence of atrial fibrillation	Cox proportional Hazard Model (95% CI)	1 semiquantitative FFQ of 1 year validated, applied by trained nutritionists.*	There was no association between fish consumption (average 15.7g/day) and atrial fibrillation incidence
Engeset *et al.* (2006)[31] Norway	310,671 women 25-to 70-year-old	Fish consumption Risk of breast cancer	Cox proportional Hazard Model (95% CI)	Different types of historical dietary questionnaires and semiquantitative FFQ of 1 year (7 fish items) validated	There was no association between fish consumption (of 5.54g to 96.77g/day) and risk of breast cancer development
Koralek *et al.* (2006)[32] USA	29,592 men 55-to 74year-old	Fish and fatty alpha linoleic consumption Risk of prostate cancer	Coeficiente de correlação de Pearson; Pearson correlation coefficient; Cox proportional Hazard Model	5 semiquantitative FFQ (*t*=0, *t*=1, *t*=2, *t*=3, *t*=4) of 1 year, with 137 items (6 fish items) without validation register	There was no association between ALA total consumption (1.09g to 1.75g/day) and of ALA in fish, and risk of prostate cancer
Myint *et al.* (2006)[33] England	24.312 men and women, with historical background of stroke 40-79-year-old	Fish consumption stroke incidence Arterial pressure Blood tests (lipid profile)	Cox proportional Hazard Model	1 semiquantitative FFQ of 1 year, with 131 items (3 fish items) validation not mentioned	There was no association between fish, crustaceans or fish roe consumption and risk of stroke incidence

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CONCLUSION

Author, year country	Size (n) and sample characteristic	Study Variables	Statistical Analysis	Dietary methods	Results
Sanchez Villegas *et al.* (2007)[11] Spain	7 903 men and women	Omega-3 and fish consumption Mental disorders	Non-conditional logistic regression analysis, linear tendency cross-sectional tests (p<0.05)	2 semiquantitative FFQ posted (t=0 and t=2 years) of 1 year (136 items) validated	There was no association between fish consumption (36.43g to 161.90g/day) or of omega-3 (0.39g to 1.89g/day) and risk of mental disorders
Engeset *et al.,* (2007)[34] Norway	63 914 women 40-to 71-year-old	Fish consumption Colon cancer	Cox Proportional Hazard Model	1 semiquantitative FFQ posted of 1 year (14 fish items) validated	There was no association between fish consumption (46.2g to 167.2g/day) and a relative risk of colon cancer
Steffen (2008)[10] USA	14 962 men and women 45-to 64-year-old	Dietary consumption Venous thromboembolism incidence	Spearman correlation coefficient (p<0.001)	2 semiquantitative FFQ (t=6) of 1 month and 1 year (66 items) validated	Fish consumption ≥1x/week ↓ risk of venous thromboembolism development
Levitan *et al*. (2010)[35] USA	36 234 women 48-to 83-year-old	Omega-3 and fish consumption Weak heart	Cox Proportional Hazard Model (95% CI)	1 self-administered FFQ of 1 year (96 item) validated	Moderate fish consumption (1-2 portions/week) and omega-3 was associated with a lower number in hospitalizations for weak heart or death.
Bjerregaard *et al.* (2010)[36] Denmark	57 053 men and women 50-to 64-year-old	Fat and lean fish consumption Acute coronary syndrome (ACS)	Cox Proportional Hazard Model (95% CI)	1 self-administered semiquantitative FFQ (t=0) of 1 year (14 fish items) validated	Moderate consumption of fat fish (≥7g/day) was associated with a lower risk of ACS in men
Berry *et al*. (2010)[37] USA	44 720 Postmenopausal women 50-to 79-year-old	Fish consumption Atrial fibrillation incidence	Multivariable logistic regression analysis (p<0.05)	1 self-administered semiquantitative FFQ (t=0) of 3 months (3 fish items) validated	There was no association between fish consumption (average 1.5 portions of 85g/week) and atrial fibrillation incidence
Hedelin *et al*. (2010)[38] Sweden	33,623 women 30-to 49-year-old	Fish, omega-3 and vitamin D consumption Psychotic symptoms	Multinomial logistic regression (95% IC)	1 self-administered FFQ of 6 months (8 groups of food and drinks) validated	Risk of psychotic symptoms was 53% lower with the consumption of fish 3-4 times/week compared to no consumption at all.
Larsson *et al*. (2011)[39] Sweden	34,670 women 49-to 83-year-old	Fish consumption stroke risk Anthropometric data	Cox Proportional Hazard Model (95% CI) Multivariate regression model	1 self-administered FFQ of 1 year (76 item)	Fish consumption (≥3 times/ week), especially lean fish, may reduce risk of stroke in women
Poudel Tandukar, *et al*. (2011)[40] Japan	101,507 men and women 40-to 69-year-old	Fish, EPA and DHA consumption Risk of suicide	Cox Proportional Hazard Model (95% IC), Spearman correlation coefficient, residuals from regressions, multivariate model (p<0.05)	1 semiquantitative self-administered FFQ (19 fish items). No validation mentioned	High fish consumption (152.84g/day) was not associated with lower risk of suicide

* Items assessed in the food frequency questionnaires were not cited in the article.

Note: FFQ: Frequency Food Questionnaire; CA: Cancer; CVD: Cardiovascular Disease; CAD: Coronary Arterial Disease; CI: Confidence Interval; ALA: Alpha-Linolenic Acid; RR: Relative Risk; IHD: Ischemia Heart Disease; ACS: Acuté Corohary Syndrome; EPA: Eicosapentaenoic Acid Consumption; DHA: Docosahexaenoic Acid.