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The efficacy of fish oil in preventing coronary heart disease: A systematic review and meta-analysis

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Abstract: To evaluate the efficacy of fish oil for protection against coronary heart disease (CHD), we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) evaluating the use of fish oil for protection against CHD. We retrieved relevant articles published from January 1966 to January 2020 by searching the PubMed, EMBASE, Cochrane CENTRAL, and Web of Science databases. RCTs of fish oil in preventing CHD were selected. The study quality was evaluated using the Cochrane Risk of Bias tool with RevMan 5.3 software. The first selection involved 350 citations. After screening and evaluation of suitability, 19 RCTs adjusted for clustering were included in the meta-analysis. All selected manuscripts considered that fish oil was effective in preventing CHD, secondary outcome measures included angina, sepsis and death. Compared with the control group, fish oil may confer significant protection against CHD (odds ratio = 0.84; 95% confidence interval: 0.72–0.98). There was no significant difference in the incidence of secondary outcomes between the observation group and the control group ($P > 0.05$). The above results show that fish oil plays an important role in reducing CHD and cardiovascular events. However, because of the suboptimal quality of the studies included into the meta-analysis, these results do not justify adding fish oils systematically to the heavy pharmaceutical assortment already recommended in CHD patients.

Keywords: Fish oil; Prevention; CHD; Meta-analysis

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1. Introduction

Coronary heart disease (CHD) is one of the leading causes of death and disease burden in the world. While age-adjusted mortality rates appear to be falling globally, they remain high in low- and middle-income regions and countries, where there is a particularly high prevalence of risk factors [1]. In developing countries such as China, the rising momentum of CHD burden has not been effectively curbed [2]. Control of risk factors such as hypertension, diabetes, hyperlipidemia, obesity and smoking can reduce incidence and mortality rates of CHD [3]. The use of antiplatelet drugs, statins, renin angiotensin aldosterone system blockers and β receptor blockers can also improve the prognosis of patients with CHD [4]. Although efforts such as these have yielded some improvement in ameliorating CHD burden, a number of potential therapies that could be of further benefit remain to be fully explored. Recent years have seen growing interest in the notion that fish oil and ω-3 polyunsaturated fatty acids (PUFA) may be beneficial in the prevention and treatment of CHD, with A considerable number of studies have been carried out on the roles of fish oil and ω-3 PUFA in the clinical application of primary prevention and secondary prevention of CHD, including large-scale randomized controlled trials, multi center and single center cohort studies and observational studies. In this study, we conducted a comprehensive meta-analysis of the efficacy of fish oil for the prevention of CHD in order to establish its scientific basis, for the purposes of informing policies related to the use of fish oil.

2. Materials and Methods

2.1. Application protocol and website recording data

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A protocol including the investigation methods and the inclusion criteria for the current study was submitted in advance and documented on the Center for Review and Dissemination (CRD) York website PROSPERO, an international prospective register of systematic reviews. The parameters and the analytic structure of the present work can be viewed using the CRD identification code: CRD42020183719.

This systematic investigation was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) protocols [5].

2.2. Search strategy

Articles published in English from January 1994 to January 2020 that explored the relationship between fish oil and protection against CHD were retrieved from PubMed, EMBASE, Cochrane CENTRAL, and Web of Science databases. The following search terms were used: "CHD", "coronary heart disease", "cardiovascular diseases", "prevention" and "fish oil". Logical operators (OR, NOT, AND) were used to combine keywords and subject words (Table 1).

2.3. Inclusion criteria

Articles that met the following criteria were selected: study design was randomized controlled trial (RCT), and the study was peer reviewed; the study population was human; the exposure of interest was using fish oil; the outcome of interest was the proportion of fish oil use in the experimental and control groups; the main outcome measure was CHD. Secondary outcome measures included angina, sepsis and death. Studies took place in healthcare settings worldwide.

2.4. Exclusion criteria

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The following exclusion criteria were applied: Trials in which patients were being treated with blood pressure disease, virus infected patients, osteoporosis, immunologic disorders, uncontrolled diabetes mellitus, or other surgical risk related systemic conditions; not enough information regarding the selected topic; trials that were not RCTs; no access to the title and abstract number in the English language.

2.5. Data extraction

Data extraction was conducted in two stages. First, literature was screened by two researchers according to inclusion criteria. The screened literature was then searched and evaluated by two other researchers according to inclusion and exclusion criteria. To avoid errors, a pre-designed form was used to select the study characteristics, baseline patient characteristics and outcomes and definitions included in the literature. Any inconsistencies in recommendations were resolved through consultation. The main data extracted were as follows: the number of people who were assigned to using fish oil and those who were not assigned to using fish oil.

2.6. Literature quality assessment

The quality of the methodology in the included studies was evaluated by using the Cochrane Risk of Bias tool [6]. The quality of RCTs was evaluated using RevMan 5.3 software. The risk of bias was evaluated from six perspectives: choice bias, performance bias, measurement bias, attrition bias, reporting bias, other biases (Table 2). According to the criteria for low, unclear and high risk, the quality of the methodology of the included studies was divided into three levels: mild bias, where four or more of the above six items are low risk; moderate bias, where two or three of the above six items are low risk; and severe bias, where none or only one of the above six items is low risk.

2.7. Statistical methods

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RevMan 5.3 software provided by the Cochrane Collaboration was used to conduct this meta-analysis of the proportions of fish oil use between the experimental and control groups. Q and I^2 tests were used to evaluate the heterogeneity of the included studies (Q tests is the traditional method in the heterogeneity test of meta-analysis; I^2 tests can measure the degree of difference among multiple research effects, and can describe the percentage of inter-research variation as a proportion of the total variation). When $I^2 \leq 50\%$ and $P > 0.1$, a fixed effect model was used to merge the data; when $I^2 > 50\%$ or $P < 0.1$, a random effect model was used to merge the data. The odds ratio (OR) and 95% confidence interval (CI) were used to express the enumeration data. $P < 0.05$ was considered to indicate statistical significance.

2.8. Document retrieval flow chart (Figure 1)

3. Results

3.1. Literature search results

After searching 350 papers from four databases, 19 articles were included in the final screening (Figure 1). Of the 350 papers identified through database queries, we screened out 120, then searched the full texts of the remaining 230 articles, excluding 209 that did not meet our inclusion criteria, leaving 19 RCTs (Table 3). All of these RCTs analyzed the effectiveness of fish oil for protection against CHD. Moreover, they all analyzed the effect of fish oil on death, sepsis and angina. There was no real evidence to suggest publication bias (Figure 2A, 2B, 2C, 2D)

3.2. Randomized controlled trials

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Assessment of the risk bias of 19 RCTs using RevMan 5.3 software showed moderate overall bias (Figure 3A, 3B).

3.3. Fish oil use versus no fish oil use for protection against CHD

19 RCTs compared CHD risk in people using fish oil to that of controls using no fish oil. Using no fish oil conferred significantly greater protection against CHD (OR = 0.84; 95% CI: 0.72–0.98; $P < 0.05$) (Figure 4A). Because of heterogeneity, the data were divided for subgroup analysis according to the following: single-blind and double-blind; and Europe, North America and Asia. Subgroup analysis showed that heterogeneity of single-blind data was $I^2 = 67\%$ ($P = 0.0005$) and the heterogeneity for double-blind was $I^2 = 6\%$ ($P = 0.38$). This indicated that the heterogeneity of the double-blind data was much less than that of the single-blind data. Subgroup analysis by region showed that data heterogeneity for Europe was $I^2 = 32\%$ ($P = 0.14$), for North America $I^2 = 79\%$ ($P = 0.0007$), and for Asia $I^2 = 26\%$ ($P = 0.25$), indicating that the North American data was far more heterogeneous than those of Europe and Asia.. Therefore, the possibility that the heterogeneity of the data in the included studies was related to the type of blinding and continent could not be excluded (Figure 4B, 4C).

3.4. The effect of fish oil on angina, sepsis and death

Secondary outcome measures included angina, sepsis and death. Meta-analysis showed that there was no significant difference in the incidence of secondary outcomes between the observation group and the control group ($P > 0.05$) (Figure 5A, 5B, 5C).

4. Discussion

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The clinical application of fish oil has attracted much research attention in recent years. In the present meta-analysis we sought to evaluate the evidence base on the efficacy of the use of fish oil in CHD. Fish oil is rich in ω-3 PUFA, the effects of which on cardiovascular metabolism are still under extensive study. Preliminary studies have shown that ω-3 PUFA can reduce blood pressure, improve arterial elasticity, improve endothelial function, increase arrhythmia threshold, reduce platelet aggregation and improve autonomic nervous tension [26].

The results of the present meta-analysis of 19 RCTs show that the use of fish oil has a significant protective effect against CHD incidence when compared to no fish oil intervention [7-25]. Some of the first suggestions of the putative relationship between dietary fish intake and CHD appear in the literature between 1985 and 1995 [27-30]. In 1996, Stone et al. reviewed a number of prospective epidemiological studies, concluding that, compared with no fish oil consumption, eating fish oil can reduce mortality rate of patients with CHD [31]. A subsequent retrospective analysis of physician-initiated health studies in 2002 found that basal plasma long chain ω-3 PUFA was significantly negatively correlated with sudden death [32]. This study was divided into four groups according to plasma ω-3 PUFA levels. Compared with the lowest level group (group 1), the relative risk of sudden death in group 3 was 0.28, and that in group 4 was 0.19 (81% less). These findings are somewhat consistent with those of the present meta-analysis. However, we remain cautious in our interpretation due to the suboptimal quality of the studies included. The results we have obtained are too weak to justify adding fish oils systematically to the already heavy burden of pharmaceuticals prescribed to CHD patients. Moreover, no significant differences in death, sepsis and angina were found to be associated with fish oil use.

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There were limitations to this meta-analysis. First, the number of included studies was small, which may have resulted in distribution bias. Analysis of a greater number of studies would be required to reduce the risk of distribution bias. Second, there may have been measurement bias, publication bias and selection bias in the included articles. Third, heterogeneity among the data in the included studies was identified, which may be related to the research population, region, and CHD subtypes. Although the subgroup analysis of the use of fish oil was conducted for some indicators in this study, it was not conducted for different populations or CHD subtypes. Therefore, more detailed subgroup analysis would be required to provide a more convincing basis for our conclusions. Finally, the source of CHD was not identified in all trials and some subjects may have been sicker than others before trial commencement.

5. Conclusions

Here, we conducted a literature review and meta-analysis of RCTs of the protective effects of fish oil against CHD. Our analysis provides some evidence to support the universal use of fish oil in the high risk CHD patient group. However, the evidence is not sufficiently strong to support the addition of fish oils to the already heavy pharmaceutical assortment given to CHD patients.

Author Contributions: GW and HG participated in the study design and writing of the manuscript; YJ and WS participated in the English grammar correction and writing of the manuscript; XPZ and XLZ supervised the design and execution of the study, performed the final data analyses and contributed to the writing of the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1. Search strings for the four databases

Database	Search string
PubMed	(fish oil [MeSH Terms] OR ω-3 polyunsaturated fatty acids [Title/Abstract] OR Coronary heart disease [Title/Abstract] OR CHD [Title/Abstract] OR Cardiovascular diseases [Title/Abstract] OR prevention [Title/Abstract] OR control [Title/Abstract] OR measure [Title/Abstract] OR evaluate [Title/Abstract] OR effect [Title/Abstract] OR Health [Title/Abstract] OR Public health [Title/Abstract]
EMBASE	('Coronary heart disease':ab, ti OR 'CHD':ab, ti) AND ('Fish oil':ab, ti OR 'ω-3 polyunsaturated fatty acids':ab, ti) AND ('Health':ab, ti OR 'Public health':ab, ti OR 'Cardiovascular diseases':ab, ti) AND ('prevention':ab, ti OR 'control':ab, ti OR 'measure':ab, ti OR 'evaluate':ab, ti OR 'effect':ab, ti OR 'prevent':ab, ti OR 'control':ab, ti OR 'intervention':ab, ti OR 'outcome':ab, ti)
Web of Science	TS=(Fish oil OR Fish OR 'oil' OR 'ω-3 polyunsaturated fatty acids' OR Coronary heart disease OR CHD OR 'Cardiovascular diseases' OR 'prevention' OR 'control' OR 'prevention and control' OR PPE OR 'measur' OR 'evaluat' OR 'effect' OR 'Public' OR 'Public Healths')
Cochrane CENTRAL	Coronary heart disease OR CHD in Title, Abstract, Keywords, AND 'fish oil' OR 'fish' OR 'ω-3 polyunsaturated fatty acids' in Title, Abstract, Keywords, AND practice OR control OR measure OR evaluate OR effect OR prevent OR prevention and control OR intervention OR outcome in Title, Abstract, Keywords, Publication Year from 1966 to 2020 in Trials

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Table 2 Cochrane Risk of Bias assessment form

Evaluation items	Evaluation content	
Choice bias	Random sequence generation	The method of generating random assignment sequence is described in detail, which is convenient for evaluation of the comparability between groups.
	Assignment hidden	The method of hiding random distribution sequence is described in detail, which is convenient for judging whether the distribution of intervention measures can be predicted.
Performance bias	Blind method for researchers and subjects	The method of blinding used to prevent researchers and subjects from knowing the intervention measures is described in detail. This provides information that can be used to judge whether the blinding method is effective.
Measurement bias	Blind evaluation of research results	The method of blinding used to prevent the evaluators of the research results from knowing the intervention measures is described in detail. This provides information that can be used to judge whether the blinding method is effective.
Attrition bias	Integrity of result data	The data for each major outcome indicator, including those of subjects who were lost or withdrew from the study, are reported completely. Including subjects who were lost or withdrew, the total number of people in each group (compared with the total number of randomly enrolled people), and the reasons for the loss of interview/withdrawal are clearly reported, so as to facilitate assessment of the relevant treatment by the system evaluator.
Reporting bias	Selective reporting of	The information described can be used by system evaluators to judge the possibility of selective reporting of research results and

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	research results	relevant information.
Other biases	Other sources of bias	In addition to the above biases, the information provided can be used to assess the existence of other bias factors. If a question or factor is mentioned in the plan, corresponding answers are required.

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Table 3. Summary of RCTs assessing the effectiveness of fish oil for protection against CHD (n = 19).

First author, year [reference number]	Journal	Study design	Continent	Blinding	Experimental group (n)				Control group (n)			
					a	b	c	d	a	b	c	d
Borchgrevink, 1966 [7]	*Lancet*	RCTs	Europe	Single-blind	10	1	1	0	14	2	0	0
Dayton, 1968 [8]	*Lancet*	RCTs	North America	Double-blind	53	1	0	0	71	3	0	0
MRC, 1968 [9]	*Lancet*	RCTs	Europe	Single-blind	45	2	0	0	51	2	0	0
Leren, 1970 [10]	*Circulation*	RCTs	North America	Single-blind	61	1	0	0	81	3	1	1
Turpeinen, 1979 [11]	*Int J Epidemiol*	RCTs	Europe	Single-blind	25	1	1	1	47	1	1	1
Miettinen, 1983 [12]	*Int J Epidemiol*	RCTs	Europe	Single-blind	27	2	1	1	46	3	3	2
Frantz, 1989 [13]	*Arteriosclerosis*	RCTs	North	Double-blind	121	3	0	2	131	4	1	1

			America									
Burr, 1989 [14]	*Lancet*	RCTs	Europe	Single-blind	132	1	1	1	144	2	0	0
Reis, 1989 [15]	*Lancet*	RCTs	North America	Single-blind	71	1	2	0	15	1	1	1
B-urr, 1989 [16]	*Lancet*	RCTs	Europe	Single-blind	127	1	0	0	180	1	0	1
Nye, 1990 [17]	*Aust N Z J Med*	RCTs	Oceania	Single-blind	5	0	1	1	11	0	1	1
Watts, 1992 [18]	*Lancet*	RCTs	Europe	Single-blind	2	0	0	1	5	0	0	2
Kaul, 1992 [19]	*Int J Cardiol*	RCTs	Asia	Single-blind	26	1	1	2	16	1	1	3
Bellamy, 1992 [20]	*Eur Heart J*	RCTs	Europe	Double-blind	31	0	0	1	33	1	0	1
Franzen, 1993 [21]	*Cathet Cardiovasc Diagn*	RCTs	Europe	Double-blind	22	1	1	1	16	1	0	0
Sacks, 1995 [22]	*Am Coll Cardiol*	RCTs	North America	Double-blind	5	0	0	2	7	0	1	1
Singh, 1997 [23]	*Cardiovasc Drugs Ther*	RCTs	Asia	Double-blind	38	1	1	0	80	1	1	0
Von Schaky, 1999 [24]	*Ann Intern Med*	RCTs	Europe	Double-blind	2	0	0	1	10	0	0	0

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GISSI prevenzione trial, 1999 [25]	*The Cochrane Collaboration*	RCTs	Europe	Single-blind	459	2	2	0	509	3	2	2

Note: a: CHD; b: Death; c: Sepsis; d: Angina

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Figures

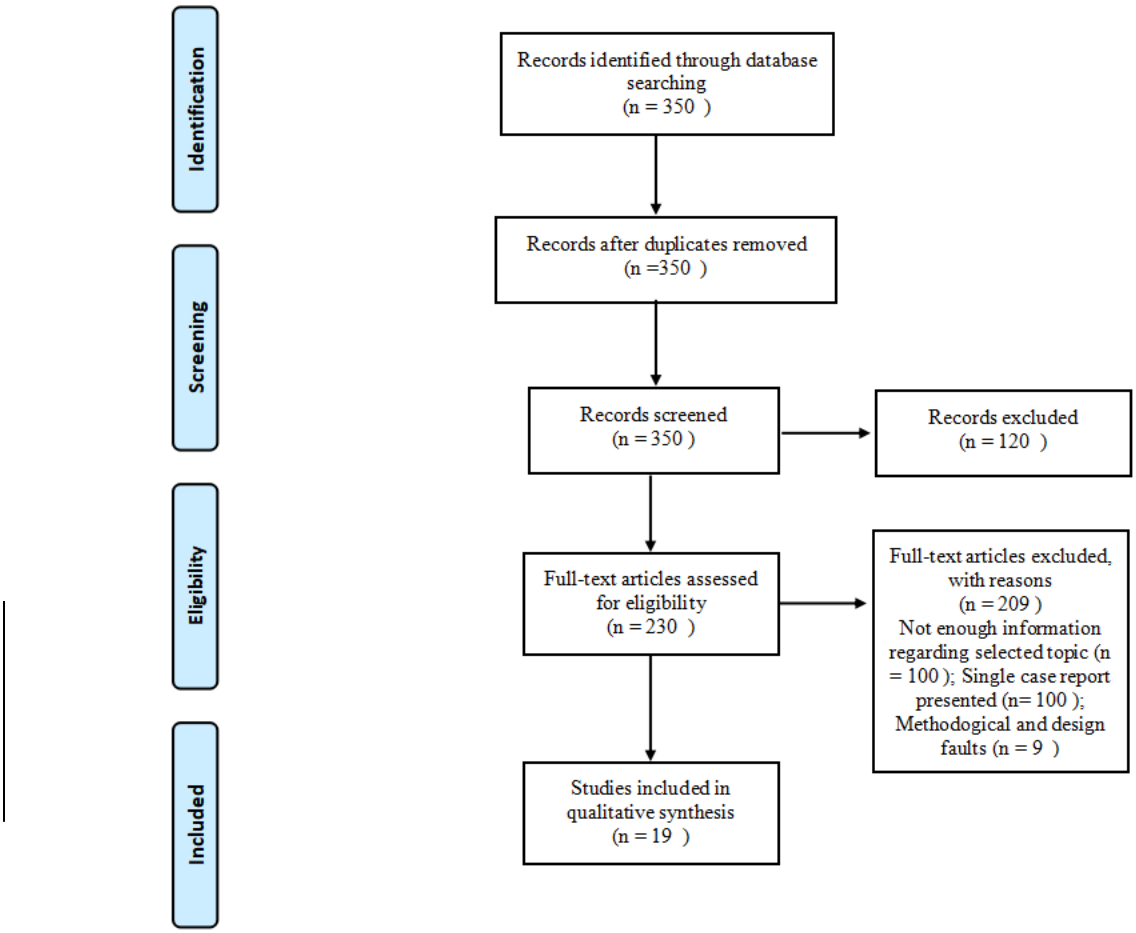

Figure 1. Summary of the literature search and inclusion process.

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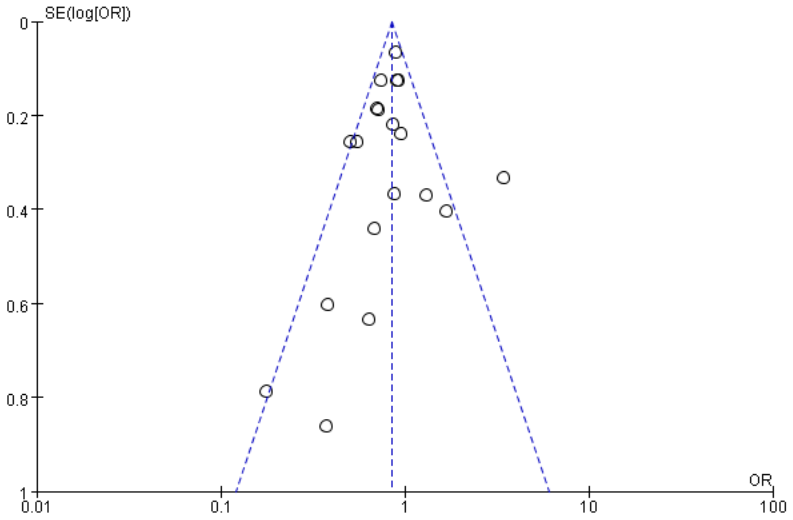

Figure 2A. RCTs effect of fish oil compared to no fish oil

Legend: Funnel plot assessing publication bias in RCTs investigating the effectiveness of fish oil for protection against CHD; Harbord's estimated bias coefficient: -0.44; P = 0.491.

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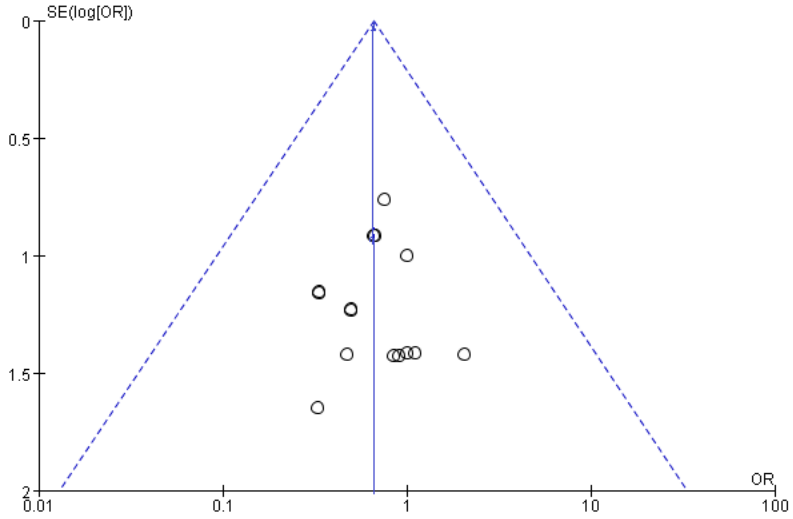

Figure 2B. RCTs effect of fish oil compared to no fish oil

Legend: Funnel plot assessing publication bias in RCTs investigating the effect of fish oil on death; Harbord's estimated bias coefficient: 0.40; P = 0.635.

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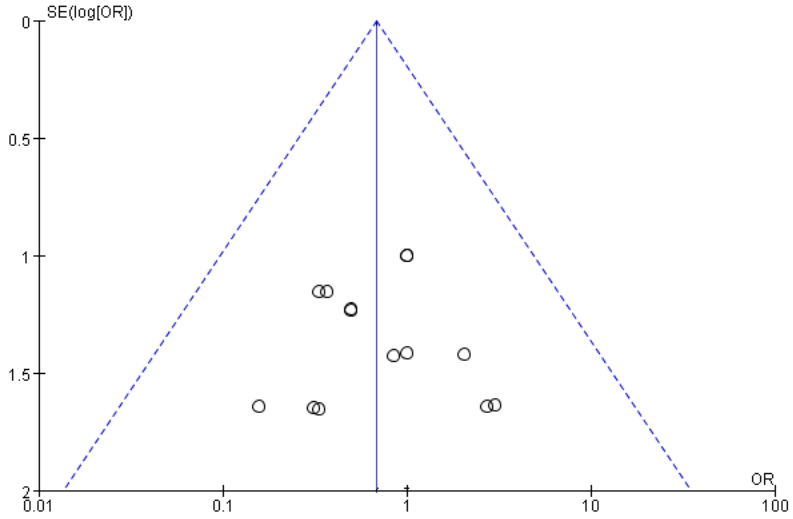

Figure 2C. RCTs effect of fish oil compared to no fish oil

Legend: Funnel plot assessing publication bias in RCTs investigating the effect of fish oil on sepsis; Harbord's estimated bias coefficient: -0.58; $P = 0.599$.

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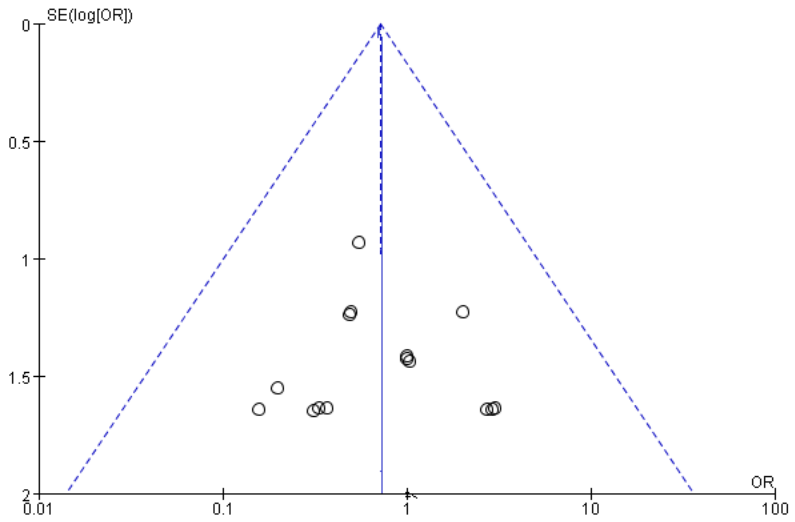

Figure 2D. RCTs effect of fish oil compared to no fish oil

Legend: Funnel plot assessing publication bias in RCTs investigating the effect of fish oil on angina; Harbord's estimated bias coefficient: 0.41; P = 0.636.

Funnel plots were generated to evaluate publication bias in RCT. The unadjusted effect estimates in some studies correspond to their standard errors. The real line and dotted line represent the aggregate effect estimates of different standard errors and their 95% CI, respectively. To determine publication bias, the Harbord test of small-study effects was used to assess funnel plot asymmetry.

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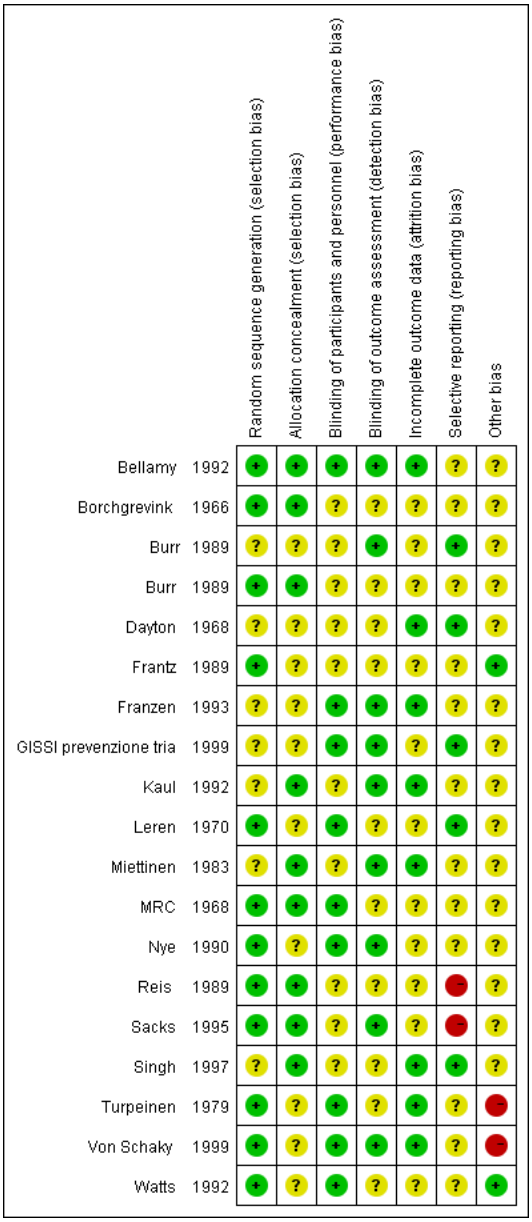

Figure 3A. RCTs received a high (red), low (green) or uncertain (yellow) risk of bias score for each of the domains.

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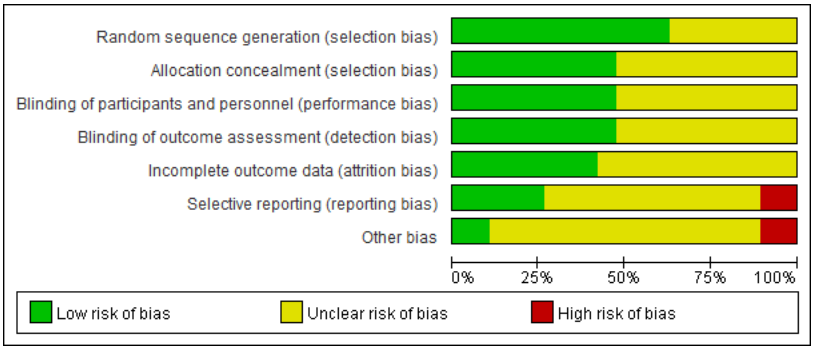

Figure 3B. Percentage of RCTs with high, low or uncertain risk of bias in each domain.

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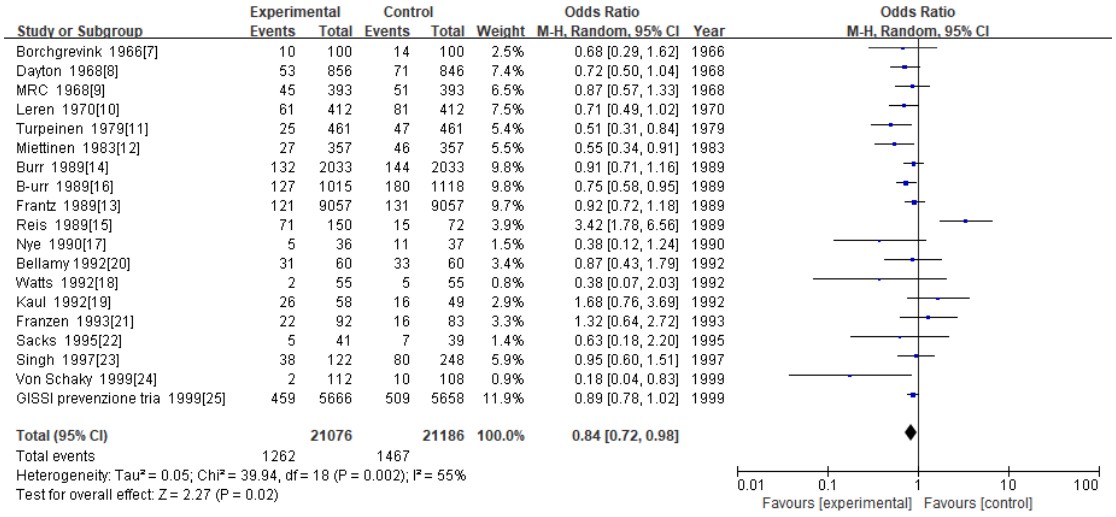

Figure 4A. Meta-analysis of the effect of using fish oil for protection against CHD.

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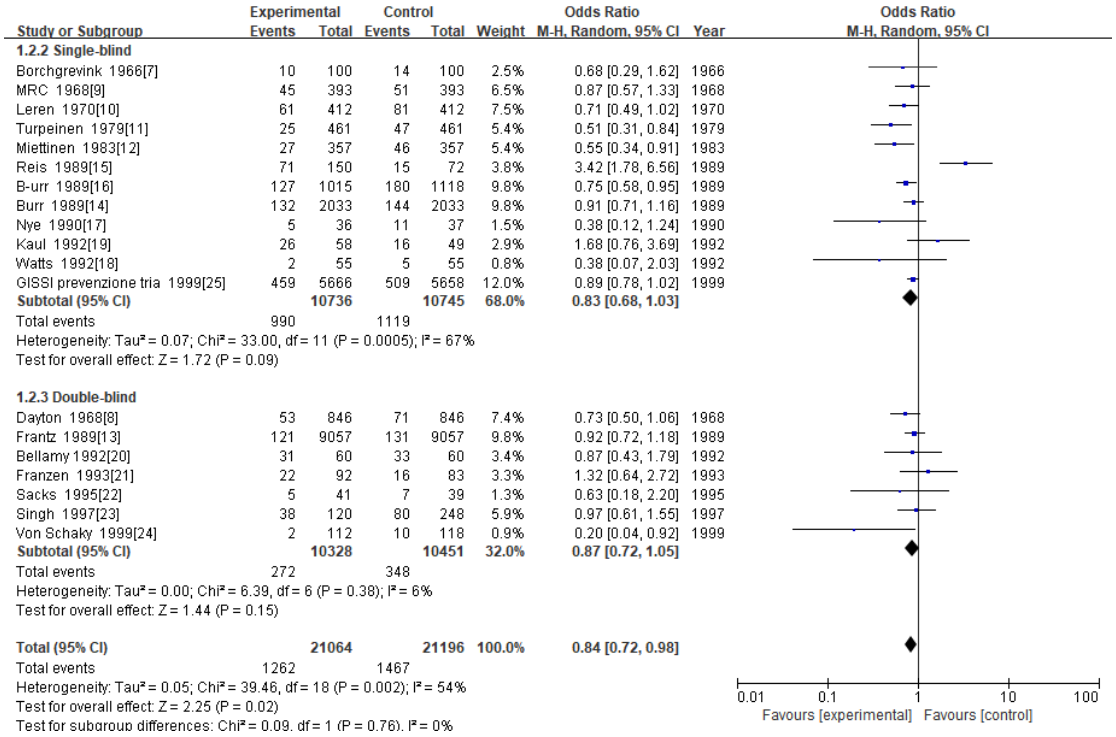

Figure 4B. Subgroup analysis of the effect of using fish oil for protection against CHD.

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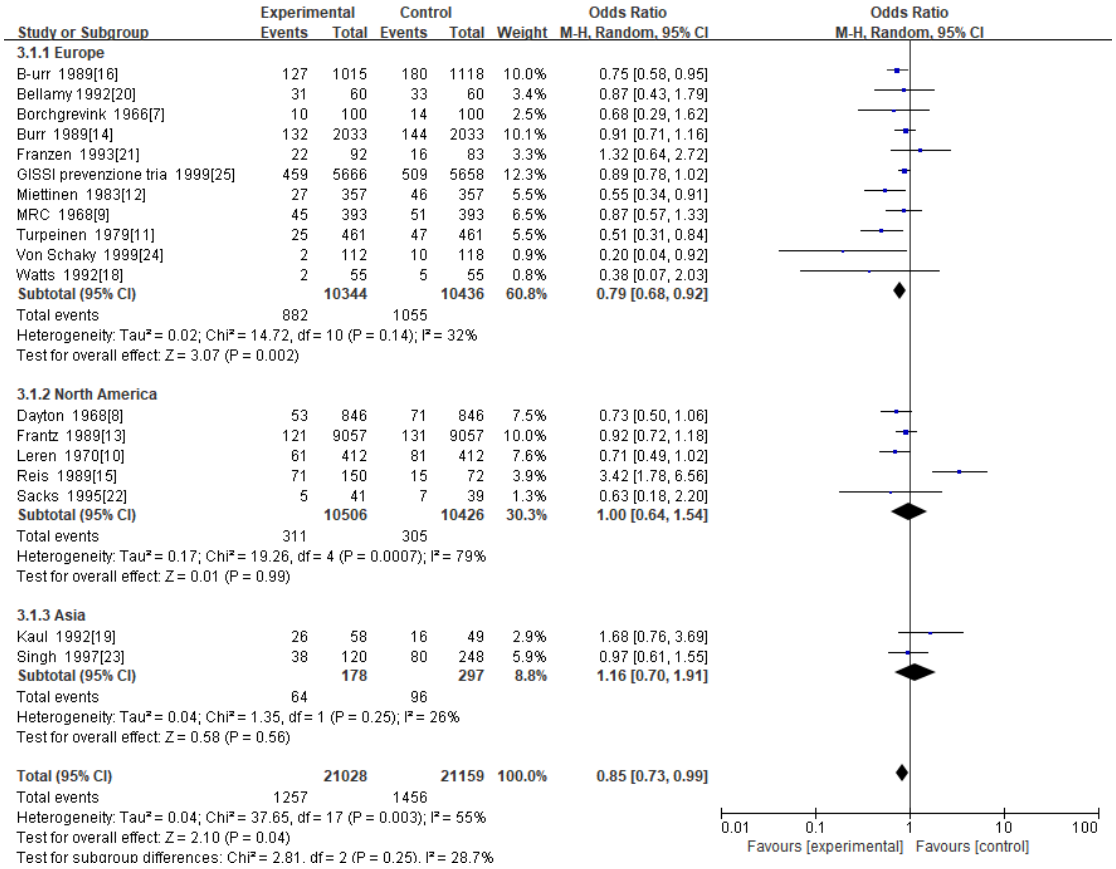

Figure 4C. Subgroup analysis of the effect of using fish oil for protection against CHD.

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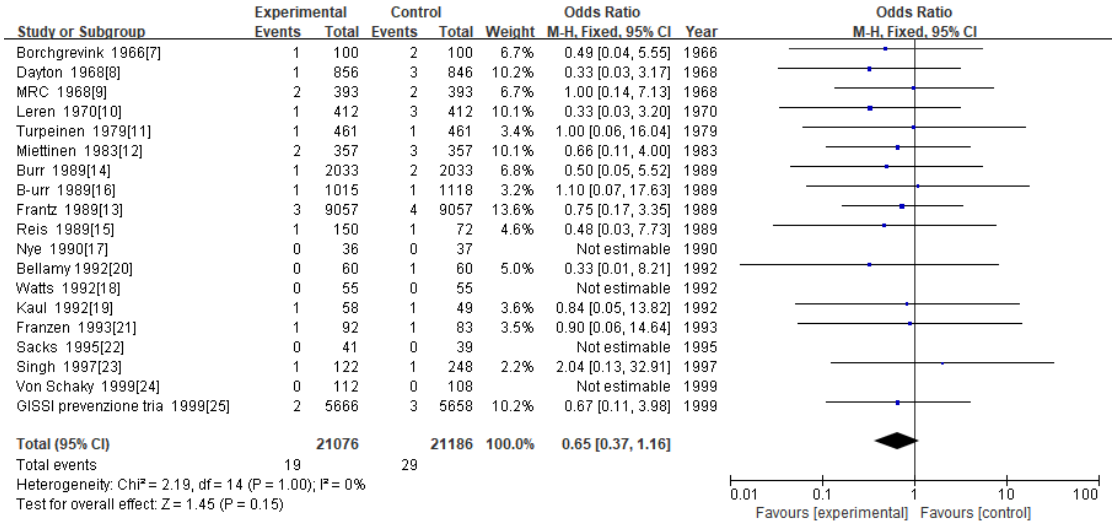

Figure 5A. Meta-analysis of the effect of fish oil on death.

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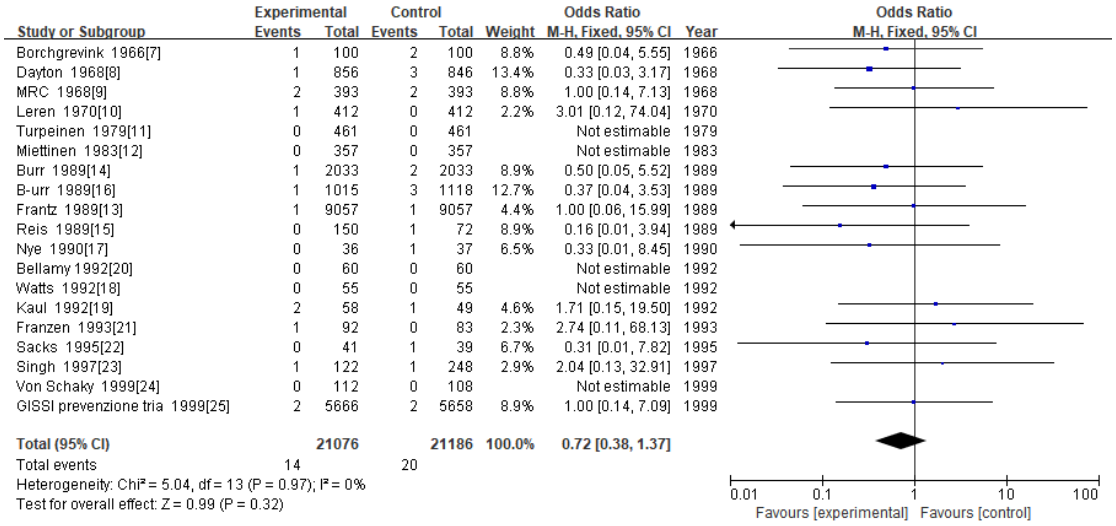

Figure 5B. Meta-analysis of the effect of fish oil on sepsis.

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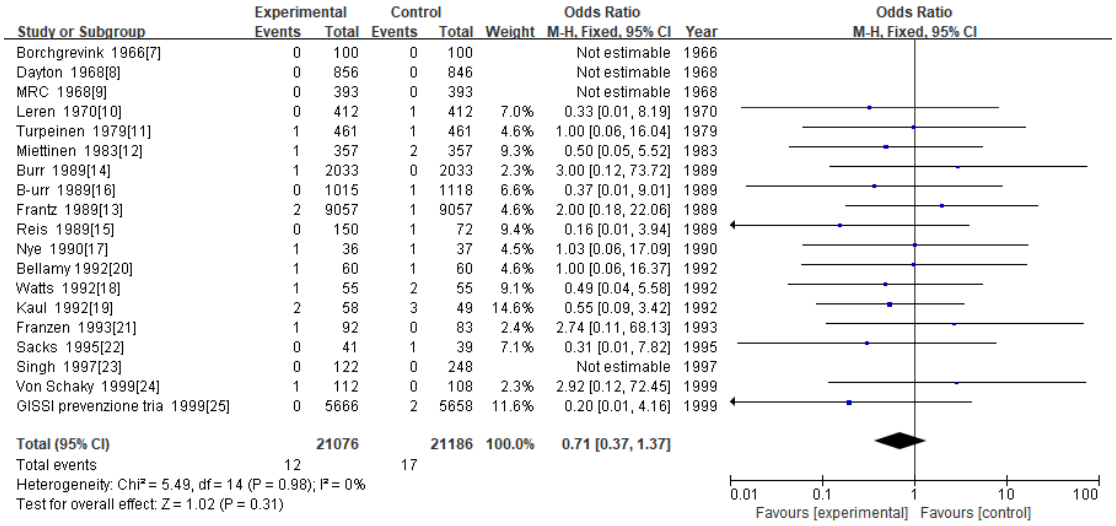

Figure 5C. Meta-analysis of the effect of fish oil on angina.