

The efficacy of fish oil in preventing coronary heart disease

A systematic review and meta-analysis

Gaohong Wu, MM^a, Qingyang Ji, MB^a, Huiwen Huang, MM^{a,*}, Xueping Zhu, MD, PhD^b

Abstract

Background: Coronary heart disease (CHD) is one of the most common causes of death and disease burden in the world. Current fish oil aiming to prevent and treat CHD have shown a large variety of effects with low levels of evidence.

Objective: To evaluate the efficacy of fish oil for protection against CHD, we conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) evaluating the use of fish oil for protection against CHD.

Methods: 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 360 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.

Results: 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 > .05).

Conclusion: 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.

Registration details: CRD42020183719.

Abbreviations: CHD = coronary heart disease, CI = confidence interval, OR = odds ratio, RCTs = randomized controlled trials.

Keywords: coronary heart disease, fish oil, meta-analysis, prevention

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GW, QJ, and HH contributed equally to this work.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

Coronary heart disease (CHD) is one of the leading causes of death and disease burden in the world, the burden of disease is enormous both in the United States of America and around the world. In 2006, 18 million of the estimated 81 million adults in the America had CHD, and more than 400,000 Americans died of CHD. CHD is the cause of one in every 6 deaths in the America.^[1] 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.^[2] In developing countries such as China, the rising momentum of CHD burden has not been effectively curbed.^[3] Control of risk factors such as hypertension, diabetes, hyperlipidemia, obesity and smoking can reduce incidence and mortality rates of CHD.^[4] The use of antiplatelet drugs, statins, renin angiotensin aldosterone system blockers and β receptor blockers can also improve the prognosis of patients with CHD.^[5] 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

Table 1

Search strings for	r the 4 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

CHD = coronary heart disease.

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.^[6] 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

Table 2

This work is a systematic review of published clinical studies. If necessary, meta-analysis will be possible. The data used in this systematic review will be all from published literature. Therefore, there is no need to provide ethical approval.

2.1. Application protocol and website recording data

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 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 center for review and dissemination identification code: CRD42020183719.

This systematic investigation was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols.^[7]

2.2. Search strategy

Articles published in English from January 1966 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," "cardiovas-cular diseases," "prevention," and "fish oil". Study design was randomized controlled trial (RCT), and the study was peer reviewed; the study population was human. Logical operators (OR, NOT, AND) were used to combine keywords and subject words. (Table 1).

Cochrane risk of bi	as 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 research results	The information described can be used by system evaluators to judge the possibility of selective reporting of research results and 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.

2.3. Inclusion criteria

Articles that met the following criteria were selected: 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

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 2 stages. First, literature was screened by 2 researchers according to inclusion criteria. The

screened literature was then searched and evaluated by 2 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.^[8] The quality of RCTs was evaluated using RevMan 5.3 software. The risk of bias was evaluated from 6 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 3 levels: mild bias, where 4 or more of the above 6 items are low risk; moderate bias, where 2 or 3 of the above 6 items are low risk; and severe bias, where none or only one of the above 6 items is low risk.



Table 3

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Summary	of RCTs	assessing	the effect	tiveness of	fish oil	for prote	ction ag	ainst C	HD (n = 19)

						Exper	imenta	l group	(n)	Con	trol gi	oup ((n)
First author, year [reference numb Borchgrevink, 1966 ^[9] Dayton, 1968 ^[10] MRC, 1968 ^[11] Leren, 1970 ^[12] Turpeinen, 1979 ^[13] Miettinen, 1983 ^[14] Frantz, 1989 ^[15] Burr, 1989 ^[16] Reis, 1989 ^[17] B-urr, 1989 ^[18] Nye, 1990 ^[19] Watts, 1992 ^[20] Kaul, 1992 ^[21] Belamy, 1992 ^[22]	Journal	Study design	Continent	Blinding	Overall sample size	а	b	C	d	а	b	C	d
Borchgrevink, 1966 [9]	Lancet	RCTs	Europe	Single-blind	200	10	1	1	0	14	2	0	0
Dayton, 1968 ^[10]	Lancet	RCTs	North America	Double-blind	1702	53	1	0	0	71	3	0	0
MRC, 1968 ^[11]	Lancet	RCTs	Europe	Single-blind	786	45	2	0	0	51	2	0	0
Leren, 1970 ^[12]	Circulation	RCTs	North America	Single-blind	824	61	1	0	0	81	3	1	1
Turpeinen, 1979 ^[13]	Int J Epidemiol	RCTs	Europe	Single-blind	922	25	1	1	1	47	1	1	1
Miettinen, 1983 ^[14]	Int J Epidemiol	RCTs	Europe	Single-blind	714	27	2	1	1	46	3	3	2
Frantz, 1989 ^[15]	Arteriosclerosis	RCTs	North America	Double-blind	18114	121	3	0	2	131	4	1	1
Burr, 1989 ^[16]	Lancet	RCTs	Europe	Single-blind	4066	132	1	1	1	144	2	0	0
Reis, 1989 ^[17]	Lancet	RCTs	North America	Single-blind	222	71	1	2	0	15	1	1	1
B-urr, 1989 ^[18]	Lancet	RCTs	Europe	Single-blind	2133	127	1	0	0	180	1	0	1
Nye, 1990 ^[19]	Aust N Z J Med	RCTs	Oceania	Single-blind	73	5	0	1	1	11	0	1	1
Watts, 1992 ^[20]	Lancet	RCTs	Europe	Single-blind	110	2	0	0	1	5	0	0	2
Kaul, 1992 ^[21]	Int J Cardiol	RCTs	Asia	Single-blind	107	26	1	1	2	16	1	1	3
Bellamy, 1992 [22]	Eur Heart J	RCTs	Europe	Double-blind	120	31	0	0	1	33	1	0	1
Franzen, 1993 [23]	Cathet Cardiovasc Diagn	RCTs	Europe	Double-blind	175	22	1	1	1	16	1	0	0
Sacks, 1995 [24]	Am Coll Cardiol	RCTs	North America	Double-blind	80	5	0	0	2	7	0	1	1
Singh, 1997 ^[25]	Cardiovasc Drugs Ther	RCTs	Asia	Double-blind	370	38	1	1	0	80	1	1	0
Von Schaky, 1999 [26]	Ann Intern Med	RCTs	Europe	Double-blind	220	2	0	0	1	10	0	0	0
GISSI prevenzione trial, 1999 [27]	The Cochrane Collaboration	RCTs	Europe	Single-blind	11524	459	2	2	0	509	3	2	2

CHD = coronary heart disease, RCTs = randomized controlled trials.

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



Figure 2. (A). RCTs effect of fish oil compared to no fish oil. 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 = .491. (B). RCTs effect of fish oil compared to no fish oil. Funnel plot assessing publication bias in RCTs investigating the effect of fish oil on death; Harbord's estimated bias coefficient: 0.40; P = .635. C. RCTs effect of fish oil compared to no fish oil. Funnel plot assessing publication bias in RCTs investigating the effect of fish oil on death; Harbord's estimated bias coefficient: 0.40; P = .635. C. RCTs effect of fish oil compared to no fish oil. Funnel plot assessing publication bias in RCTs investigating the effect of fish oil on sepsis; Harbord's estimated bias coefficient: -0.58; P = .599. D. RCTs effect of fish oil compared to no fish oil. Funnel plot assessing publication bias in RCTs investigating the effect of fish oil on angina; Harbord's estimated bias coefficient: 0.41; P = .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.





2.7. Statistical methods

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

Study of Cubarous	Experin	nental	Cont	Total	Mainht	Odds Ratio	Vant	Odds Ratio
Study of Subgroup	Events	10121	Events	100	vveight	M-H, Kandom, 95% CI	tear	M-H, Random, 95% CI
Derten 106000	50	056	14	0.46	2.3%	0.00 [0.29, 1.02]	1900	
Daytori 1966[6]	03	202	51	303	1.470 6.50	0.72 [0.50, 1.04]	1908	
MRC 1968[9]	40	393	01	393	0.0%	0.87 [0.57, 1.33]	1908	
Leren 1970[10]	01	412	81	412	1.5%	0.71 [0.49, 1.02]	1970	
Turpeinen 1979[11]	25	401	41	401	5.4%	0.51 [0.31, 0.84]	19/9	
Miettinen 1983[12]	21	357	40	357	5.5%	0.55 [0.34, 0.91]	1983	
Burr 1989[14]	132	2033	144	2033	9.8%	0.91 [0.71, 1.16]	1989	
B-urr 1989[16]	127	1015	180	1118	9.8%	0.75 [0.58, 0.95]	1989	
Frantz 1989[13]	121	9057	131	9057	9.7%	0.92 [0.72, 1.18]	1989	
Reis 1989[15]	/1	150	15	72	3.9%	3.42 [1.78, 6.56]	1989	
Nye 1990[17]	5	36	11	31	1.5%	0.38 [0.12, 1.24]	1990	
Bellamy 1992[20]	31	60	33	60	3.4%	0.87 [0.43, 1.79]	1992	
vvatts 1992[18]	2	55	5	55	0.8%	0.38 [0.07, 2.03]	1992	
Kaul 1992[19]	26	58	16	49	2.9%	1.68 [0.76, 3.69]	1992	
Franzen 1993[21]	22	92	16	83	3.3%	1.32 [0.64, 2.72]	1993	
Sacks 1995[22]	5	41	7	39	1.4%	0.63 [0.18, 2.20]	1995	
Singh 1997[23]	38	122	80	248	5.9%	0.95 [0.60, 1.51]	1997	
Von Schaky 1999[24]	2	112	10	108	0.9%	0.18 [0.04, 0.83]	1999	
GISSI prevenzione tria 1999[25]	459	5666	509	5658	11.9%	0.89 [0.78, 1.02]	1999	•
Total (95% CI)		21076		21186	100.0%	0.84 [0.72, 0.98]		•
Total events	1262		1467					
Heterogeneity: Tau ² = 0.05; Chi ² =	39.94, df	= 18 (P =	= 0.002);	1 ² = 55%				
Test for overall effect: Z = 2.27 (P =	= 0.02)							0.01 0.1 1 10 100
A								Favours [experimental] Favours [control]
	Experin	nental	Cont	Ion		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
1.2.2 Single-blind					5.859.6	100000 1000 1000		
Borcharevink 1966[7]	10	100	14	100	2.5%	0.68 [0.29, 1.62]	1966	
MRC 1968[9]	45	393	51	393	6.5%	0.87 [0.57, 1.33]	1968	
Leren 1970[10]	61	412	81	412	7.5%	0.71 [0.49, 1.02]	1970	
Turpeinen 1979[11]	25	461	47	461	5.4%	0.51 (0.31, 0.84)	1979	
Miettinen 1983[12]	27	357	46	357	5.4%	0.55 (0.34, 0.91)	1983	
Reis 1989[15]	71	150	15	72	3.8%	3 42 11 78 6 561	1989	
B-urr 1989[16]	127	1015	180	1118	9.8%	0 75 10 58 0 951	1989	
Burr 1989[14]	132	2033	144	2033	9.8%	0.91 (0.71 1.16)	1989	
Nve 1990[17]	5	36	11	37	1 5%	0 38 10 12 1 241	1990	
Kaul 1992[19]	26	58	16	49	29%	1 68 10 76 3 691	1992	· · · · · · · · · · · · · · · · · · ·
Watts 1992[18]	2	55	5	55	0.8%	0.38 [0.07 2.03]	1992	
GISSI prevenzione tria 1999/251	450	5666	500	5658	12.0%	0.99 (0.79 1.02)	1000	-
Subtotal (95% CI)	400	10736	000	10745	68.0%	0.83 [0.68, 1.03]	1000	•
Total events	aan		1110			ores forest real		
Heterogeneity: Tau ² = 0.07; Chi ² =	33.00, df	= 11 (P =	= 0.0005)	; I ² = 679	6			
Test for overall effect: Z = 1.72 (P =	= 0.09)							
1.2.3 Double-blind								
Davton 1968[8]	53	846	71	846	7.4%	0.73 (0.50, 1.06)	1968	
Frantz 1989[13]	121	9057	131	9057	9.8%	0.92 10 72 1 181	1989	-
Bellamy 1992[20]	31	60	33	60	3 4 9%	0.87 10 43 1 701	1992	
Franzen 1993[21]	22	92	16	83	3 394	1 32 10 64 2 721	1992	
Sacks 1995[22]	5	41	7	30	1 396	0.63 (0.18, 2.20)	1995	
Singh 1997[23]	30	120		249	5 9%	0.97 [0.61 1.65]	1997	
Von Schaky 1999/241	30	112	10	110	0.9%	0.20 (0.04, 0.02)	1990	
Subtotal (95% CI)	4	10328	10	10451	32.0%	0.87 [0.72, 1.05]	1999	•
Total events	272	10520	240	10-101	52.07	0.01 [0.12, 1.05]		
Hotorogeneity Tours - 0.00: Chiz-	C 20 df-	C /D - 0	2011 12-1	CO/				
Heterogeneity. Tau-= 0.00, Chi-=	= 0.15)	6 (P = 0	.38), F=1	070				
Test for overall effect: Z = 1.44 (P =								
Test for overall effect: Z = 1.44 (P =				Sand Statements				
Test for overall effect: Z = 1.44 (P = Total (95% CI)	(20.22	21064	1	21196	100.0%	0.84 [0.72, 0.98]		•
Test for overall effect: Z = 1.44 (P = Total (95% CI) Total events	1262	21064	1467	21196	100.0%	0.84 [0.72, 0.98]		•
Test for overall effect: Z = 1.44 (P = Total (95% CI) Total events Heterogeneity: Tau ² = 0.05; Chi ² =	1262 39.46, df	21064 = 18 (P =	1467 = 0.002);	21196 I ² = 54%	100.0%	0.84 [0.72, 0.98]		◆ 0.01 0.1 1 10 100

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Figure 4. (A). Meta-analysis of the effect of using fish oil for protection against CHD. (B). Subgroup analysis of the effect of using fish oil for protection against CHD. (C). Subgroup analysis of the effect of using fish oil for protection against CHD.

of inter-research variation as a proportion of the total variation). When $I^2 \leq 50\%$ and P > .1, a fixed effect model was used to merge the data; when $I^2 > 50\%$ or P < .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 < .05 was considered to indicate statistical significance.

2.8. Document retrieval flow chart (Fig. 1)

3. Results

3.1. Literature search results

After searching 360 papers from 4 databases, 19 articles were included in the final screening (Fig. 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 (Fig. 2A, B, C, D)

3.2. Randomized controlled trials

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

3.3. Fish oil use versus no fish oil use for protection against coronary heart disease

Nineteen RCTs compared CHD risk in people using fish oil to that of controls using no fish oil. Using fish oil conferred significantly greater protection against CHD (OR=0.84; 95% CI: 0.72–0.98; P < .05) (Fig. 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 = .0005) and the heterogeneity for double-blind was $I^2 = 66\%$ (P = .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

	Experin	nental	Cont	rol		Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
3.1.1 Europe							
B-urr 1989[16]	127	1015	180	1118	10.0%	0.75 [0.58, 0.95]	
Bellamy 1992[20]	31	60	33	60	3.4%	0.87 [0.43, 1.79]	
Borchgrevink 1966[7]	10	100	14	100	2.5%	0.68 [0.29, 1.62]	
Burr 1989[14]	132	2033	144	2033	10.1%	0.91 [0.71, 1.16]	
Franzen 1993[21]	22	92	16	83	3.3%	1.32 [0.64, 2.72]	
GISSI prevenzione tria 1999[25]	459	5666	509	5658	12.3%	0.89 [0.78, 1.02]	-
Miettinen 1983[12]	27	357	46	357	5.5%	0.55 [0.34, 0.91]	
MRC 1968[9]	45	393	51	393	6.5%	0.87 [0.57, 1.33]	
Turpeinen 1979[11]	25	461	47	461	5.5%	0.51 [0.31, 0.84]	the second se
Von Schaky 1999[24]	2	112	10	118	0.9%	0.20 [0.04, 0.92]	
Watts 1992[18]	2	55	5	55	0.8%	0.38 [0.07, 2.03]	
Subtotal (95% CI)		10344		10436	60.8%	0.79 [0.68, 0.92]	•
Total events	882		1055				2
Heterogeneity: Tau ² = 0.02; Chi ² =	14.72. df	= 10 (P =	0.14); I ²	= 32%			
Test for overall effect: Z = 3.07 (P	= 0.002)						
3.1.2 North America							
Dayton 1968[8]	53	846	71	846	7.5%	0.73 [0.50, 1.06]	
Frantz 1989[13]	121	9057	131	9057	10.0%	0.92 [0.72, 1.18]	
Leren 1970[10]	61	412	81	412	7.6%	0.71 [0.49, 1.02]	
Reis 1989[15]	71	150	15	72	3.9%	3.42 [1.78, 6.56]	
Sacks 1995[22]	5	41	7	39	1.3%	0.63 [0.18, 2.20]	
Subtotal (95% CI)		10506		10426	30.3%	1.00 [0.64, 1.54]	*
Total events	311		305			a first and the second second	
Heterogeneity: Tau ² = 0.17; Chi ² = Test for overall effect: Z = 0.01 (P	= 19.26, df = 0.99)	= 4 (P =	0.0007);	²= 79%			
3.1.3 Asia							
Kaul 1992[19]	26	58	16	49	2.9%	1.68 [0.76, 3.69]	
Singh 1997[23]	38	120	80	248	5.9%	0.97 [0.61, 1.55]	-
Subtotal (95% CI)		178		297	8.8%	1.16 [0.70, 1.91]	+
Total events	64		96				
Heterogeneity: Tau ² = 0.04; Chi ² =	1.35, df=	1(P = 0)	25); I ² = 3	26%			
Test for overall effect: Z = 0.58 (P	= 0.56)		1004103-009				
Total (95% CI)		21028		21159	100.0%	0.85 [0.73, 0.99]	•
Total events	1257		1456				W/ W 24
Heterogeneity: Tau ² = 0.04; Chi ² = Test for overall effect: Z = 2.10 (P	= 37.65, df = 0.04)	= 17 (P =	: 0.003); I	²= 55%			0.01 0.1 1 10 100 Favours [experimental] Favours [control]
Test for subaroup differences: Ch	ni ² = 2.81. (df = 2 (P :	= 0.25), 13	= 28.79	6		· · · · · · · · · · · · · · · · · · ·

that data heterogeneity for Europe was $I^2=32\%$ (P=.14), for North America $I^2=79\%$ (P=.0007), and for Asia $I^2=26\%$ (P=.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 (Fig. 4B, C).

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

Secondary outcome measures included death, sepsis and angina. Nineteen RCTs compared angina risk in people using fish oil to that of controls using no fish oil. There was no significant difference in the incidence of death between the observation group and the control group (OR = 0.65; 95% CI: 0.37–1.16; P > .05) (Fig. 5A). There was no significant difference in the incidence of sepsis between the observation group and the control group (OR = 0.72; 95% CI: 0.38–1.37; P > .05) (Fig. 5B). There was no significant difference in the incidence of sepsis between the observation group and the control group (OR = 0.71; 95% CI: 0.37–1.37; P > .05) (Fig. 5C).

4. Discussion

CHD is caused by coronary atherosclerotic plaque formation leading to vascular stenosis or obstruction caused by the supply area of myocardial ischemia, hypoxia or necrotic lesions. In recent years, diagnosis and treatment of CHD has been in the

	Experin	iental	Cont	rol		Odds Ratio		Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95	% CI	
Borchgrevink 1966[7]	1	100	2	100	6.7%	0.49 [0.04, 5.55]	1966			
Dayton 1968[8]	1	856	3	846	10.2%	0.33 [0.03, 3.17]	1968	· · · · · ·	-	
MRC 1968[9]	2	393	2	393	6.7%	1.00 [0.14, 7.13]	1968			
_eren 1970[10]	1	412	3	412	10.1%	0.33 [0.03, 3.20]	1970		-	
Turpeinen 1979(11)	1	461	1	461	3.4%	1.00 (0.06, 16.04)	1979			
Miettinen 1983[12]	2	357	3	357	10.1%	0.66 (0.11, 4.00)	1983			
Burr 1989[14]	1	2033	2	2033	6.8%	0.50 10.05 5.521	1989			
B-urr 1989[16]	1	1015	1	1118	3.2%	1 10 0 07 17 63	1989			
Frantz 1989[13]	3	9057	4	9057	13.6%	0 75 10 17 3 351	1989			
Reis 1989[15]	1	150	1	72	4 6%	0 48 0 03 7 73	1989			
Nve 1990[17]	0	36		37	4.070	Not estimable	1000			
Pollomy 1002(20)	0	60	1	60	5.0%	0.2210.01.0.211	1002			
Alotto 1002(10)		66		66	5.0%	0.33 [0.01, 0.21]	1992			
Valls 1992[10]	1	50	1	40	2.60	0.04 (0.05, 12,02)	1992			
Caul 1992[19]		00		49	3.0%	0.84 [0.05, 13.82]	1992			
-ranzen 1993[21]	1	92	1	83	3.5%	0.90 [0.06, 14.64]	1993			
Sacks 1995[22]	0	41	0	39		Not estimable	1995			
Bingh 1997[23]	1	122	1	248	2.2%	2.04 [0.13, 32.91]	1997			
/on Schaky 1999[24]	0	112	0	108	1.000	Not estimable	1999			
GISSI prevenzione tria 1999[25]	2	5666	3	5658	10.2%	0.67 [0.11, 3.98]	1999	50	_	
Total (95% CI)		21076		21186	100.0%	0.65 [0.37, 1.16]		-		
Total events	19		29							
								1		1.1.1.1
Heterogeneity: Chi ² = 2.19. df = 14	(P = 1.00)	1 = 10%						0.04 0.4 4	4.0	4.0
Heterogeneity: Chi ² = 2.19, df = 14 Test for overall effect: 7 = 1.45 (P =	(P = 1.00 = 0.15));						0.01 0.1 1	10	10
Heterogeneity: Chi ² = 2.19, df = 14 Test for overall effect: Z = 1.45 (P =	(P = 1.00 = 0.15));						Favours [experimental] Favo	urs [control]	10
Heterogeneity: Chi² = 2.19, df = 14 Test for overall effect: Z = 1.45 (P =	(P = 1.00 = 0.15));						Favours [experimental] Favo	urs [control]	10
Heterogeneity: Chi≆ = 2.19, df = 14 Test for overall effect: Z = 1.45 (P =	(P = 1.00 = 0.15) Experin); * = 0%	Cont	rol		Odds Ratio		Favours [experimental] Favo	urs [control]	10
Heterogeneity: Chi ² = 2.19, df = 14 Test for overall effect: Z = 1.45 (P = Study or Subgroup	(P = 1.00 = 0.15) Experin Events); I* = 0% nental Total	Cont	rol Total	Weight	Odds Ratio M-H, Fixed, 95% Cl	Year	GUUT U.1 T Favours [experimental] Favo Odds Ratio M-H, Fixed, 95	urs [control]	10
Heterogeneity: Chi ² = 2.19, df = 14 Test for overall effect: Z = 1.45 (P = Study or Subgroup Borchgrevink 1966[7]	(P = 1.00 0.15) Experin Events 1	nental <u>Total</u> 100	Cont Events 2	rol Total 100	Weight 8.8%	Odds Ratio M-H, Fixed, 95% Cl 0.49 (0.04, 5.55)	Year 1966	0.01 0.1 Favo Favours [experimental] Favo Odds Ratio	urs [control]	10
Heterogeneity: Chi ² = 2.19, df = 14 Test for overall effect: Z = 1.45 (P = Study or Subgroup Borchgrevink 1966[7] Dayton 1968[8]	(P = 1.00 = 0.15) Experin Events 1 1	nental <u>Total</u> 100 856	Cont Events 2 3	rol Total 100 846	Weight 8.8% 13.4%	Odds Ratio M-H, Fixed, 95% Cl 0.49 [0.04, 5.55] 0.33 [0.03, 3.17]	Year 1966 1968	0.01 0.1 Favours [experimental] Favo Odds Ratio M-H, Fixed, 95	wci	10
Heterogeneity: Chi [≈] = 2.19, df = 14 Test for overall effect: Z = 1.45 (P = Study or Subgroup Borchgrevink 1966[7] Dayton 1968[8] MRC 1968[9]	(P = 1.00 = 0.15) Experin Events 1 1 2	nental Total 100 856 393	Cont Events 2 3 2	rol Total 100 846 393	Weight 8.8% 13.4% 8.8%	Odds Ratio M-H, Fixed, 95% Cl 0.49 [0.04, 5.55] 0.33 [0.03, 3.17] 1.00 [0.14, 7.13]	Year 1966 1968 1968	0.01 0.1 Favours [experimental] Favo Odds Ratio M-H, Fixed, 95	s CI	10
Heterogeneity: Chi≊ = 2.19, df = 14 Test for overall effect: Z = 1.45 (P = Study or Subgroup Borchgrevink 1966[7] Dayton 1968[8] MRC 1968[9] _eren 1970[10]	(P = 1.00 = 0.15) Experin Events 1 1 2 1	nental Total 100 856 393 412	Cont Events 2 3 2 0	rol Total 100 846 393 412	Weight 8.8% 13.4% 8.8% 2.2%	Odds Ratio M-H, Fixed, 95% CI 0.49 [0.04, 5.55] 0.33 [0.03, 3.17] 1.00 [0.14, 7.13] 3.01 [0.12, 74.04]	Year 1966 1968 1968 1970	0.01 0.1 1 Favours [experimental] Favo Odds Ratio M-H, Fixed, 95	wrs [control]	10
Heterogeneity: Chi [≥] = 2.19, df = 14 Test for overall effect: Z = 1.45 (P = Study or Subgroup Borchgrevink 1966[7] Dayton 1968[8] wRC 1968[9] Leren 1970[10] Turpeinen 1979[11]	(P = 1.00 = 0.15) Experim Events 1 1 2 1 0	nental Total 100 856 393 412 461	Cont <u>Events</u> 2 3 2 0 0	rol 100 846 393 412 461	Weight 8.8% 13.4% 8.8% 2.2%	Odds Ratio M-H, Fixed, 95% CI 0.49 [0.04, 5.55] 0.33 [0.03, 3.17] 1.00 [0.14, 7.13] 3.01 [0.12, 74.04] Not estimable	Year 1966 1968 1968 1970 1979	0.01 0.1 Favours [experimental] Favo Codds Ratio M-H, Fixed, 959		
Heterogeneity: Chi [≈] = 2.19, df = 14 Test for overall effect: Z = 1.45 (P = Study or Subgroup Borchgrevink 1966[7] Dayton 1968[8] wRC 1968[9] Leren 1970[11] Murpeinen 1979[11] Miettinen 1983[12]	(P = 1.00 = 0.15) Experim Events 1 1 2 1 0 0	nental Total 100 856 393 412 461 357	Cont <u>Events</u> 2 3 2 0 0 0 0	rol 100 846 393 412 461 357	Weight 8.8% 13.4% 8.8% 2.2%	Odds Ratio M-H, Fixed, 95% CI 0.49 [0.04, 6.55] 0.33 [0.03, 3.17] 1.00 [0.14, 7.13] 3.01 [0.12, 74.04] Not estimable Not estimable	Year 1966 1968 1968 1970 1979 1983	0.01 0.1 Favours [experimental] Favo Odds Ratio M-H, Fixed, 95	wrs [control]	
Heterogeneity: Chi ² = 2.19, df = 14 Test for overall effect: Z = 1.45 (P = Study or Subgroup Borchgrevink 1966[7] Dayton 1968[8] MRC 1968[9] Leren 1970[10] Turpeinen 1979[11] Miettinen 1983[12] Burr 1989[14]	(P = 1.00 = 0.15) Experim Events 1 1 2 1 0 0 1	nental Total 100 856 393 412 461 357 2033	Cont <u>Events</u> 2 3 2 0 0 0 0 2	rol 100 846 393 412 461 357 2033	Weight 8.8% 13.4% 8.8% 2.2% 8.9%	Odds Ratio M-H, Fixed, 95% Cl 0.49 (0.04, 5.55) 0.33 (0.03, 3.17) 1.00 (0.14, 7.13) 3.01 (0.12, 74.04) Not estimable 0.50 (0.05, 5.52)	Year 1966 1968 1968 1970 1979 1983 1989	0.01 0.1 Favours [experimental] Favo Odds Ratio M-H, Fixed, 95	wrs [control]	
Heterogeneity: Chi [≥] = 2.19, df = 14 Test for overall effect: Z = 1.45 (P = Study or Subgroup Borchgrevink 1966[7] Dayton 1968[8] MRC 1968[9] Leren 1970[10] Turpeinen 1979[11] Miettinen 1983[12] Burr 1989[14] B-urr 1989[16]	(P = 1.00 = 0.15) Experim Events 1 1 2 1 0 0 1 1	nental Total 100 856 393 412 461 357 2033 1015	Cont Events 2 3 2 0 0 0 0 0 2 3	rol 100 846 393 412 461 357 2033 1118	Weight 8.8% 13.4% 8.8% 2.2% 8.9% 12.7%	Odds Ratio M-H, Fixed, 95% Cl 0.49 [0.04, 5.55] 0.33 [0.03, 3.17] 1.00 [0.14, 7.13] 3.01 [0.12, 74.04] Not estimable Not estimable 0.50 [0.05, 5.52] 0.37 [0.04, 3.53]	Year 1966 1968 1968 1970 1979 1983 1989 1989	0.01 0.1 1 Favours [experimental] Favo Odds Ratio M-H, Fixed, 95	s Cl	
Heterogeneity: Chi [≥] = 2.19, df = 14 Test for overall effect: Z = 1.45 (P = Study or Subgroup Borchgrevink 1966[7] Dayton 1968[8] MRC 1968[9] Leren 1970[10] Turpeinen 1979[11] Miettinen 1983[12] Burr 1989[14] B-urr 1989[13]	(P = 1.00 = 0.15) Experint 1 1 2 1 0 0 1 1 1 1 1 1	nental Total 100 856 393 412 461 357 2033 1015 9057	Cont <u>Events</u> 2 3 2 0 0 0 0 2 3 1	rol 100 846 393 412 461 357 2033 1118 9057	Weight 8.8% 13.4% 8.8% 2.2% 8.9% 12.7% 4.4%	Odds Ratio M-H, Fixed, 95% Cl 0.49 [0.04, 5.55] 0.33 [0.03, 3.17] 1.00 [0.14, 7.13] 3.01 [0.12, 74.04] Not estimable 0.50 [0.05, 5.52] 0.37 [0.04, 3.53] 1.00 [0.06, 15.99]	Year 1966 1968 1968 1970 1979 1983 1989 1989 1989	0.01 0.1 1 Favours [experimental] Favo Odds Ratio M-H, Fixed, 95	k CI	
Heterogeneity: Chi [≥] = 2.19, df = 14 Test for overall effect: Z = 1.45 (P = Study or Subgroup Borchgrevink 1966[7] Dayton 1968[8] MRC 1968[9] Leren 1970[10] Turpeinen 1979[11] Miettinen 1983[12] Burr 1989[14] B-urr 1989[15] Frantz 1989[15]	(P = 1.00 = 0.15) Experim 1 1 2 1 0 0 1 1 1 0 0 1 1 1 0 0 1 1 0 0 1 1 0 0 1 1 0 0 0 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0	nental Total 100 856 393 412 461 357 2033 1015 9057 150	Cont <u>Events</u> 2 3 2 0 0 0 0 2 3 1 1	rol Total 100 846 393 412 461 357 2033 1118 9057 72	Weight 8.8% 13.4% 8.8% 2.2% 8.9% 12.7% 4.4%	Odds Ratio M-H, Fixed, 95% CI 0.49 [0.04, 5.55] 0.33 [0.03, 3.17] 1.00 [0.14, 7.13] 3.01 [0.12, 74.04] Not estimable 0.50 [0.05, 5.52] 0.37 [0.04, 3.53] 1.00 [0.06, 15.99] 0.16 [0.01, 3.94]	Year 1966 1968 1968 1970 1979 1983 1989 1989 1989 1989	OUT U.1 1 Favours [experimental] Favo Odds Ratio	w ci	
Heterogeneity: Chi [≥] = 2.19, df = 14 Test for overall effect: Z = 1.45 (P = Study or Subgroup Borchgrevink 1966[7] Dayton 1968[8] MRC 1968[9] Leren 1970[10] Turpeinen 1979[11] Miettinen 1983[12] Burr 1989[14] B-urr 1989[16] Frantz 1989[15] Nee 1980[17]	(P = 1.00 = 0.15) Experin <u>Events</u> 1 1 1 2 1 0 0 1 1 1 0 0 0	nental Total 100 856 393 412 461 357 2033 1015 9057 150 36	Cont Events 2 3 2 0 0 0 0 2 3 1 1 1	rol 100 846 393 412 461 357 2033 1118 9057 72 37	Weight 8.8% 13.4% 8.8% 2.2% 8.9% 12.7% 4.4% 8.9% 6.5%	Odds Ratio M-H, Fixed, 95% CI 0.49 [0.04, 6.55] 0.33 [0.03, 3.17] 1.00 [0.14, 7.13] 3.01 [0.12, 74.04] Not estimable 0.50 [0.05, 5.52] 0.37 [0.04, 3.53] 1.00 [0.06, 15.99] 0.16 [0.01, 3.94] 0.33 [0.01, 8.45]	Year 1966 1968 1968 1970 1979 1983 1989 1989 1989 1989	Guine Control	w ci	
Heterogeneity: Chi [≥] = 2.19, df = 14 Test for overall effect: Z = 1.45 (P = Study or Subgroup Borchgrevink 1966[7] Dayton 1968[8] MRC 1968[9] Leren 1970[10] Turpeinen 1979[11] Miettinen 1983[12] Burr 1989[14] B-urr 1989[16] Frantz 1989[15] Reis 1989[17] Bellamy: 1990[17] Bellamy: 1990[17] Bellamy: 1990[17]	(P = 1.00 = 0.15) Experin Events 1 1 2 1 0 0 1 1 1 1 0 0 0 1 1 1 0 0 0 0	nental Total 100 856 393 412 461 357 2033 1015 9057 150 36 60	Cont Events 2 3 2 0 0 0 0 2 3 1 1 1 1	rol Total 100 846 393 412 461 357 2033 1118 9057 72 37 60	Weight 8.8% 13.4% 8.8% 2.2% 8.9% 12.7% 4.4% 8.9% 6.5%	Odds Ratio M-H, Fixed, 95% Cl 0.49 (0.04, 5.55) 0.33 (0.03, 3.17) 1.00 (0.14, 7.13) 3.01 (0.12, 74.04) Not estimable 0.50 (0.05, 5.52) 0.37 (0.04, 3.53) 1.00 (0.06, 15.99) 0.16 (0.01, 3.94) 0.33 (0.01, 8.45) Not estimable	Year 1966 1968 1968 1970 1979 1983 1989 1989 1989 1989 1990	C.01 U.1 1 Favours [experimental] Favo Odds Ratio M-H, Fixed, 95 	wci	
Heterogeneity: Chi [≥] = 2.19, df = 14 Test for overall effect: Z = 1.45 (P = Study or Subgroup Borchgrevink 1966[7] Dayton 1968[8] MRC 1968[9] Leren 1970[10] Turpeinen 1979[11] Miettinen 1983[12] Burr 1989[14] B-urr 1989[16] Frantz 1989[15] Nye 1990[17] Bellamy 1992[20] Arate 1022[19]	(P = 1.00 = 0.15) Experint Pevents 1 1 2 1 0 0 0 1 1 1 1 0 0 0 0 0 0 0 0 0	nental Total 1000 856 393 412 461 357 2033 1015 9057 150 36 60 55	Cont <u>Events</u> 2 3 2 0 0 0 0 2 3 1 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0	rol Total 100 846 393 412 461 357 2033 1118 9057 72 37 60 55	Weight 8.8% 13.4% 8.8% 2.2% 8.9% 12.7% 4.4% 8.9% 6.5%	Odds Ratio M-H, Fixed, 95% Cl 0.49 [0.04, 6.55] 0.33 [0.03, 3.17] 1.00 [0.14, 7.13] 3.01 [0.12, 74.04] Not estimable Not estimable 0.50 [0.05, 5.52] 0.37 [0.04, 3.53] 1.00 [0.06, 15.99] 0.16 [0.01, 3.94] 0.33 [0.01, 8.45] Not estimable Not estimable	Year 1966 1968 1968 1970 1979 1983 1989 1989 1989 1989 1989 1990 1992	C.UT U.T T Favours [experimental] Favo Odds Ratio M-H, Fixed, 95	Image: second	
Heterogeneity: Chi [≥] = 2.19, df = 14 Test for overall effect: Z = 1.45 (P = Study or Subgroup Borchgrevink 1966[7] Dayton 1968[8] MRC 1968[9] Leren 1970[10] Turpeinen 1979[11] Miettinen 1983[12] Burr 1989[14] B-urr 1989[15] Reis 1989[15] Nye 1990[17] Bellamy 1992[20] Watts 1992[18] Kaul 1992[19]	(P = 1.00 = 0.15) Experim Pevents 1 1 2 2 1 0 0 0 1 1 1 0 0 0 0 0 0 0 0 0	nental Total 100 856 393 412 461 357 2033 1015 9057 150 36 60 55 55	Cont <u>Events</u> 2 3 2 0 0 0 0 0 2 3 1 1 1 0 0 1 1 1 0 0 1 1 1 0 0 1 1 1 1 1 1 1 1 1 1 1 1 1	rol <u>Total</u> 100 846 393 412 461 357 2033 1118 9057 72 37 60 55 49	Weight 8.8% 13.4% 8.8% 2.2% 8.9% 12.7% 4.4% 8.9% 6.5%	Odds Ratio M-H, Fixed, 95% Cl 0.49 [0.04, 5.55] 0.33 [0.03, 3.17] 1.00 [0.14, 7.13] 3.01 [0.12, 74.04] Not estimable 0.50 [0.05, 5.52] 0.37 [0.04, 3.53] 1.00 [0.06, 15.99] 0.16 [0.01, 3.94] 0.33 [0.01, 8.45] Not estimable Not estimable 1.74 [0.15, 19, 50]	Year 1966 1968 1970 1979 1983 1989 1989 1989 1989 1989 1989 1990 1992 1992	C.UT U.T Favours [experimental] Favo	k CI	
Heterogeneity: Chi [≥] = 2.19, df = 14 Test for overall effect: Z = 1.45 (P = Study or Subgroup Borchgrevink 1968[7] Dayton 1968[8] wRC 1968[9] _eren 1970[10] Furpeinen 1979[11] Wiettinen 1983[12] Burr 1989[14] B-urr 1989[15] Vye 1990[17] Bellamy 1992[20] Watts 1992[18] Kaul 1992[19] Tearope 1092[21]	(P = 1.00 = 0.15) Experin Pvents 1 1 2 1 0 0 0 1 1 1 1 0 0 0 0 0 0 0 0 2 1	nental Total 100 856 393 412 461 357 2033 1015 9057 150 36 60 55 58 80 202 203 2033 1015 9057 150 2033 1015 9057 150 203 203 203 203 203 203 203 203 203 20	Cont <u>Events</u> 2 3 2 0 0 0 0 2 3 1 1 1 0 0 1 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	rol 100 846 393 412 461 357 2033 1118 9057 72 37 60 55 49 902 902 902 902 902 902 902 902 902 90	Weight 8.8% 13.4% 8.8% 2.2% 8.9% 12.7% 4.4% 8.9% 6.5% 4.6%	Odds Ratio M-H, Fixed, 95% CI 0.49 [0.04, 5.55] 0.33 [0.03, 3.17] 1.00 [0.14, 7.13] 3.01 [0.12, 74.04] Not estimable 0.50 [0.05, 5.52] 0.37 [0.04, 3.53] 1.00 [0.06, 15.99] 0.16 [0.01, 3.94] 0.33 [0.01, 8.45] Not estimable Not estimable 1.71 [0.15, 19.50] 2.74 [0.14, 69.13]	Year 1966 1968 1979 1983 1989 1989 1989 1989 1989 1989 198	OUT U.1 1 Favours [experimental] Favo Odds Ratio M-H, Fixed, 95	w ci	
Heterogeneity: Chi [≥] = 2.19, df = 14 Test for overall effect: Z = 1.45 (P = Study or Subgroup Borchgrevink 1966[7] Dayton 1968[8] wRC 1968[9] Leren 1970[10] Furpeinen 1979[11] Miettinen 1983[12] Burr 1989[14] B-urr 1989[16] Frantz 1989[15] Nye 1990[17] Bellamy 1992[20] Watts 1992[18] Kaul 1992[19] Franzen 1993[21] Dayton 1995[21] Calcologia (Content of the second of the s	(P = 1.00 = 0.15) Experim 1 1 1 2 1 0 0 1 1 1 0 0 0 1 1 1 0 0 0 1 1 1 1 0 0 0 1 1 1 1 0 0 1 1 1 1 1 1 1 1 1 1 1 1 1	nental Total 100 856 393 412 461 357 2033 1015 9057 150 36 60 55 58 92	Cont <u>Events</u> 2 3 2 0 0 0 0 2 3 1 1 1 1 0 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	Total 100 846 393 412 461 357 2033 1118 9057 72 37 60 55 49 83	Weight 8.8% 13.4% 8.8% 2.2% 8.9% 12.7% 4.4% 8.9% 6.5% 4.6% 2.3%	Odds Ratio M-H, Fixed, 95% CI 0.49 [0.04, 6.55] 0.33 [0.03, 3.17] 1.00 [0.14, 7.13] 3.01 [0.12, 74.04] Not estimable 0.50 [0.05, 5.52] 0.37 [0.04, 3.53] 1.00 [0.06, 15.99] 0.16 [0.01, 3.94] 0.33 [0.01, 8.45] Not estimable 1.71 [0.15, 19.50] 2.74 [0.11, 68.13] 0.01 7.70	Year 1966 1968 1968 1970 1979 1983 1989 1989 1989 1989 1989 1990 1992 1992 1992	Odds Ratio	w ci	
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Heterogeneity: Chi [≥] = 2.19, df = 14 Test for overall effect: Z = 1.45 (P = Study or Subgroup Borchgrevink 1968[7] Dayton 1968[8] MRC 1968[9] Leren 1970[10] Turpeinen 1979[11] Miettinen 1983[12] Burr 1989[14] B-urr 1989[14] B-urr 1989[15] Nye 1990[17] Bellamy 1992[20] Watts 1992[19] Franzen 1993[21] Backs 1995[22] Singh 1997[23] Von Schaky 1999[24] GISSI prevenzione tria 1999[25] Total (95% CI) Total events	(P = 1.00 = 0.15) Experim Pevents 1 1 2 2 1 0 0 0 0 1 1 1 0 0 0 0 0 0 0 0	rental Total 100 856 393 412 461 357 2033 1015 9057 150 36 60 55 58 9057 150 36 60 55 58 9122 411 122 112 5666 21076	Cont <u>Events</u> 2 3 2 0 0 0 2 3 1 1 1 0 0 1 1 0 2 2 2 2 2 2 2 2 2 3 1 1 1 1 0 0 2 3 3 1 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0	rol 100 846 393 412 461 357 2033 1118 9057 72 37 60 55 49 83 39 248 108 5658 21186	Weightt 8.8% 13.4% 8.8% 2.2% 8.9% 12.7% 4.4% 8.9% 6.5% 4.6% 2.3% 6.7% 2.9% 8.9% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.49 [0.04, 5.55] 0.33 [0.03, 3.17] 1.00 [0.14, 7.13] 3.01 [0.12, 74.04] Not estimable 0.50 [0.05, 5.52] 0.37 [0.04, 3.53] 1.00 [0.06, 15.99] 0.16 [0.01, 3.94] 0.33 [0.01, 3.45] Not estimable 1.71 [0.15, 19.50] 2.74 [0.11, 68.13] 0.31 [0.01, 7.82] 2.04 [0.13, 32.91] Not estimable 1.00 [0.14, 7.09] 0.72 [0.38, 1.37]	Year 1966 1968 1968 1970 1979 1983 1989 1989 1989 1989 1990 1992 1992 1995 1997 1999 1999	Odds Ratio	urs [control]	
Heterogeneity: Chi [≥] = 2.19, df = 14 Test for overall effect: Z = 1.45 (P = Study or Subgroup Borchgrevink 1966[7] Dayton 1968[8] MRC 1968[9] Leren 1970[10] Turpeinen 1979[11] Miettinen 1983[12] Burr 1989[14] B-urr 1989[14] B-urr 1989[15] Reis 1989[15] Nye 1990[17] Bellamy 1992[20] Watts 1992[18] Kaul 1992[19] Franzen 1993[21] Sacks 1995[22] Singh 1997[23] Von Schaky 1999[24] GISSI prevenzione tria 1999[25] Total events Heterogeneity: Chi [≈] = 5.04. df = 13	(P = 1.00 = 0.15) Experim Events 1 1 2 1 0 0 0 1 1 1 0 0 0 0 2 1 0 0 0 2 1 0 0 0 2 1 1 1 2 1 0 0 0 1 1 1 2 1 0 0 0 0 1 1 1 2 1 0 0 0 0 1 1 1 0 0 0 0 1 1 1 0 0 0 0 0 1 1 1 0 0 0 0 0 0 1 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0	nental Total 1000 856 393 412 461 357 12033 1015 9057 1500 366 600 555 588 922 411 1222 5666 21076	Cont <u>Events</u> 2 3 2 0 0 0 0 2 3 1 1 1 1 0 0 1 1 0 2 3 2 3 2 3 1 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0	rol Total 100 846 393 412 461 357 2033 1118 9057 72 37 60 55 49 83 39 248 108 5658 21186	Weightt 8.8% 13.4% 8.8% 2.2% 8.9% 12.7% 4.4% 8.9% 6.5% 4.6% 2.3% 6.7% 2.9% 8.9% 100.0%	Odds Ratio M-H, Fixed, 95% CI 0.49 [0.04, 6.55] 0.33 [0.03, 3.17] 1.00 [0.14, 7.13] 3.01 [0.12, 74.04] Not estimable 0.50 [0.05, 5.52] 0.37 [0.04, 3.53] 1.00 [0.06, 15.99] 0.16 [0.01, 3.94] 0.33 [0.01, 8.45] Not estimable 1.71 [0.15, 19.50] 2.74 [0.11, 68.13] 0.31 [0.01, 7.82] 2.04 [0.13, 32.91] Not estimable 1.00 [0.14, 7.09] 0.72 [0.38, 1.37]	Year 1966 1968 1970 1979 1983 1989 1989 1989 1990 1992 1992 1993 1995 1997 1999	Odds Ratio	urs [control] k ci -	

Figure 5. (A). Meta-analysis of the effect of fish oil on death. (B). Meta-analysis of the effect of fish oil on sepsis. (C). Meta-analysis of the effect of fish oil on angina.

Experim	ental	Cont	rol		Odds Ratio		Odd	s Ratio	
Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fix	ed, 95% Cl	
0	100	0	100		Not estimable	1966			
0	856	0	846		Not estimable	1968			
0	393	0	393		Not estimable	1968			
0	412	1	412	7.0%	0.33 [0.01, 8.19]	1970	-	1	
1	461	1	461	4.6%	1.00 [0.06, 16.04]	1979	-		
1	357	2	357	9.3%	0.50 [0.05, 5.52]	1983			
1	2033	0	2033	2.3%	3.00 [0.12, 73.72]	1989	-		_
0	1015	1	1118	6.6%	0.37 [0.01, 9.01]	1989	· · · ·		
2	9057	1	9057	4.6%	2.00 [0.18, 22.06]	1989			
0	150	1	72	9.4%	0.16 [0.01, 3.94]	1989	• •		
1	36	1	37	4.5%	1.03 [0.06, 17.09]	1990		+ :	
1	60	1	60	4.6%	1.00 [0.06, 16.37]	1992		ł	
1	55	2	55	9.1%	0.49 [0.04, 5.58]	1992			
2	58	3	49	14.6%	0.55 [0.09, 3.42]	1992		<u> </u>	
1	92	0	83	2.4%	2.74 [0.11, 68.13]	1993	1		_
0	41	1	39	7.1%	0.31 [0.01, 7.82]	1995			
0	122	0	248		Not estimable	1997			
1	112	0	108	2.3%	2.92 [0.12, 72.45]	1999		-	-
0	5666	2	5658	11.6%	0.20 [0.01, 4.16]	1999	• •		
	21076		21186	100.0%	0.71 [0.37, 1.37]		-	-	
12		17							
(P = 0.98)	; I ² = 0%						tor de	<u> </u>	
= 0.31)							0.01 0.1	1 10	100
							Favours [experimental]	Favours [control]	
	Experim Events 0 0 0 1 1 1 1 2 0 1 1 1 2 0 1 1 1 2 0 1 1 1 2 0 0 1 1 1 0 2 0 0 1 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0	Experimental Events Total 0 100 0 856 0 393 0 412 1 461 1 357 1 2033 0 1015 2 9057 0 150 1 60 1 55 2 58 1 92 0 41 0 122 1 112 0 5666 2 9087 2 908 1 92 0 41 0 122 (P= 0.98); P= 0% 0.31)	Experimental Cont Total Events 0 100 0 0 856 0 0 393 0 0 412 1 1 461 1 1 357 2 1 2033 0 0 1015 1 2 9057 1 0 150 1 1 36 1 1 36 1 1 60 1 1 55 2 2 58 3 1 92 0 0 41 1 0 5666 2 2 12 17 (P= 0.98); P= 0% = 17	Experimental Control tevents Total Events Total 0 100 0 100 0 856 0 846 0 393 0 393 0 412 1 412 1 461 1 461 1 357 2 357 1 2033 0 2033 0 1015 1 118 2 9057 1 9057 0 150 1 72 1 36 1 37 1 60 1 60 1 55 2 55 2 58 3 49 1 92 0 83 0 411 1 39 0 5666 2 5658 2 112 0 108 0 5666 2 <	Experimental Control Total Feents Total Weight 0 100 0 100 0 856 0 846 0 393 0 393 0 412 1 412 7.0% 1 461 1 461 4.6% 1 357 2 357 9.3% 1 2033 0 2033 2.3% 0 1015 1 1118 6.6% 2 9057 1 9057 4.6% 1 36 1 37 4.5% 1 60 1 60 4.6% 1 36 1 37 4.5% 1 60 1 60 4.6% 1 92 0 83 2.4% 0 41 39 7.1% 0 5666 2 5658 11.6%	Experimental Control Total Weight M-H, Fixed, 95% CI 0 100 0 100 Not estimable 0 856 0 846 Not estimable 0 393 0 393 Not estimable 0 412 1 412 7.0% 0.33 (0.01, 8.19) 1 461 1 463 1.00 [0.06, 16.04] 1 357 2 357 9.3% 0.50 [0.05, 5.52] 1 2033 0 2033 2.3% 3.00 [0.12, 7.3.72] 0 1015 1 1118 6.6% 0.37 [0.01, 9.01] 2 9057 1 9057 4.6% 0.16 [0.01, 3.94] 1 36 1 72 9.4% 0.16 [0.01, 3.94] 1 36 1 72 9.4% 0.16 [0.01, 3.94] 1 36 1 8.03 4.03 1.03 [0.06, 17.09] 1 55 2 55 9.1%	Experimental Control Fodal Weight M-H, Fixed, 95% CI Year 0 100 0 100 Not estimable 1966 0 856 0 846 Not estimable 1966 0 393 0 Not estimable 1968 0 412 1 412 7.0% 0.33 (0.0, 8.19) 1970 1 461 1 412 7.0% 0.33 (0.0, 0.6, 16.04) 1979 1 357 2 357 9.3% 0.50 (0.05, 5.52) 1983 1 2033 0 2033 2.3% 3.00 (0.12, 7.3,72) 1989 0 1015 1 1118 6.6% 0.37 (0.01, 9.01) 1989 2 9057 1 9057 4.6% 0.16 (0.01, 3.94) 1989 1 36 1 37 4.5% 1.03 (0.06, 17.09) 1990 1 36 1 37 4.6% 0.55 (0.09, 3.42) 1992 </td <td>Experimental Control Odds Ratio Odds Ratio Events Total Events Total Weight M-H, Fixed, 95% CI Year Year M-H, Fixed, 95% CI Year M-H, Fixed, 95% CI Year Year</td> <td>Experimental Control Odds Ratio Odds Ratio Events Total Events Total Weight M.H., Fixed, 95% CI Year M.H., Fixed, 95% CI 0 100 0 100 Not estimable 1966 M.H., Fixed, 95% CI M.H., Fixed, 95% CI 0 393 0 393 Not estimable 1968 M.H., Fixed, 95% CI M.H., Fixed, 95% CI 0 412 1 412 7.0% 0.33 [0.01, 8.19] 1970 M.H., Fixed, 95% CI 1 461 1 468 1.00 [0.06, 16.04] 1979 M.H., Fixed, 95% CI M.H., Fixed, 95% CI 1 367 2 357 9.3% 0.50 [0.05, 5.52] 1983 M.H., Fixed, 95% CI 0 1015 1 1118 6.6% 0.37 [0.01, 9.01] 1989 M.H., Fixed, 95% CI M.H., Fixed, 95% CI 1 360 1 72 9.4% 0.16 [0.01, 3.94] 1989 M.H., Fixed, 95% CI M.H., Fixed, 95% CI 2 9057 1</td>	Experimental Control Odds Ratio Odds Ratio Events Total Events Total Weight M-H, Fixed, 95% CI Year Year M-H, Fixed, 95% CI Year M-H, Fixed, 95% CI Year Year	Experimental Control Odds Ratio Odds Ratio Events Total Events Total Weight M.H., Fixed, 95% CI Year M.H., Fixed, 95% CI 0 100 0 100 Not estimable 1966 M.H., Fixed, 95% CI M.H., Fixed, 95% CI 0 393 0 393 Not estimable 1968 M.H., Fixed, 95% CI M.H., Fixed, 95% CI 0 412 1 412 7.0% 0.33 [0.01, 8.19] 1970 M.H., Fixed, 95% CI 1 461 1 468 1.00 [0.06, 16.04] 1979 M.H., Fixed, 95% CI M.H., Fixed, 95% CI 1 367 2 357 9.3% 0.50 [0.05, 5.52] 1983 M.H., Fixed, 95% CI 0 1015 1 1118 6.6% 0.37 [0.01, 9.01] 1989 M.H., Fixed, 95% CI M.H., Fixed, 95% CI 1 360 1 72 9.4% 0.16 [0.01, 3.94] 1989 M.H., Fixed, 95% CI M.H., Fixed, 95% CI 2 9057 1

Figure 5. (A). Meta-analysis of the effect of fish oil on death. (B). Meta-analysis of the effect of fish oil on sepsis. (C). Meta-analysis of the effect of fish oil on angina.

increasing trend especially for prevention.^[27] 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. ω-3 PUFA are essential - to stay healthy we must obtain some from food. The main types of ω -3 PUFA are alpha-linolenic acid, a fat found in plant foods, eicosapentaenoic acid and docosahexaenoic acid, both found in fish oil. There is a common belief that eating more fish oil reduces our risk of CHD, stroke and death.^[28] 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.^[29] However, Studies have also shown that Supplemental long-chain ω -3 PUFA are probably not useful for preventing or treating CHD.^[28] These inconsistent results may be related to the study design and researchers.

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.^[9-26] Some of the first suggestions of the putative relationship between dietary fish intake and CHD appear in the literature between 1985 and 1995.^[30-33] 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.^[34] 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.^[35] This study was divided into 4 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 metaanalysis. 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.

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 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. In light of the evidence in this meta-analysis it would be appropriate to review official recommendations supporting supplemental fish oil intake.

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References

- Lewis SJ. Lipid-lowering therapy: who can benefit? Vasc Health Risk Manag 2011;7:525–34.
- [2] Mondesir FL, Levitan EB, Malla G, et al. Patient perspectives on factors influencing medication adherence among people with coronary heart disease (CHD) and CHD risk factors. Patient Prefer Adherence 2019;13:2017–27.
- [3] Du X, Patel A, Anderson CS, et al. Epidemiology of cardiovascular disease in china and opportunities for improvement: JACC international. J Am Coll Cardiol 2019;73:3135–47.
- [4] Liu W, Wang T, Sun P, et al. Expression of Hcy and blood lipid levels in serum of CHD patients and analysis of risk factors for CHD. Exp Ther Med 2019;17:1756–60.
- [5] Knopf H, Busch MA, Du Y, et al. Secondary prevention of coronary heart disease in women and men in Germany from 1997–1999 and from 2008– 2011-Trend analysis with two national health population surveys. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2019; 62:861–9.
- [6] Zock PL, Blom WA, Nettleton JA, et al. Progressing insights into the role of dietary fats in the prevention of cardiovascular disease. Curr Cardiol Rep 2016;18:111.
- [7] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006–12.
- [8] Michaelis R, Tang V, Wagner JL, et al. Cochrane systematic review and meta-analysis of the impact of psychological treatments for people with epilepsy on health-related quality of life. Epilepsia 2018;59:315–32.
- [9] Borchgrevink CF, Skaga E, Berg KJ, et al. Absence of prophylactic effect of linolenic acid in patients with coronary heart-disease. Lancet 1966;2:187–9.
- [10] Dayton S, Pearce ML, Goldman H, et al. Controlled trial of a diet high in unsaturated fat for prevention of atherosclerotic complications. Lancet 1968;2:1060–2.
- [11] Medical Research CouncilControlled trial of soya-bean oil in myocardial infarction. Lancet 1968;2:693–9.
- [12] Leren P. The Oslo diet-heart study. Eleven-year report. Circulation 1970;42:935–42.
- [13] Turpeinen O, Karvonen MJ, Pekkarinen M. Dietary prevention of coronary heart disease: the Finnish Mental Hospital Study. Int J Epidemiol 1979;8:99–118.

- [14] Miettinen M, Turpeinen O, Karvonen MJ. Dietary prevention of coronary heart disease in women: the Finnish mental hospital study. Int J Epidemiol 1983;12:17–25.
- [15] Frantz ID, Dawson EA, Ashman PL, et al. Test of effect of lipid lowering by diet on cardiovascular risk. Minnesota Coronary Survey, Arteriosclerosis 1989;9:129–35.
- [16] Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). Lancet 1989;2:757–61.
- [17] Reis GJ, Sipperly ME, McCabe CH, et al. Randomised trial of fish oil for prevention of restenosis after coronary angioplasty. Lancet 1989;2: 177–81.
- [18] Nye ER, Ablett MB, Robertson MC, et al. Effect of eicosapentaenoic acid on restenosis rate, clinical course and blood lipids in patients after percutaneous transluminal coronary angioplasty. Aust N Z J Med 1990;20:549–52.
- [19] Watts GF, Lewis B, Brunt JN, et al. Effects on coronary artery disease of lipid-lowering diet, or diet plus cholestyramine, in the St Thomas' Atherosclerosis Regression Study (STARS). Lancet 1992;339: 563–9.
- [20] Kaul U, Sanghvi S, Bahl VK. Fish oil supplements for prevention of restenosis after coronary angioplasty. Int J Cardiol 1992;35:87–93.
- [21] Bellamy CM, Schofield PM, Faragher EB, et al. Can supplementation of diet with omega-3 polyunsaturated fatty acids reduce coronary angioplasty restenosis rate? Eur Heart J 1992;13:1626–31.
- [22] Franzen D, Schannwell M, Oette K, et al. A prospective, randomized, and double-blind trial on the effect of fish oil on the incidence of restenosis following PTCA. Cathet Cardiovasc Diagn 1993;28:301–10.
- [23] Sacks FM, Stone PH, Gibson CM, et al. Controlled trial of fish oil for regression of human coronary atherosclerosis. HARP Research Group. J Am Coll Cardiol 1995;25:1492–8.
- [24] Singh RB, Niaz MA, Sharma JP, et al. Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: the Indian experiment of infarct survival–4. Cardiovasc Drugs Ther 1997;11:485–91.
- [25] von Schacky C, Angerer P, Kothny W, et al. The effect of dietary omega-3 fatty acids on coronary atherosclerosis. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1999;130:554–62.
- [26] Mulrow C, Oxman A. The Cochrane Library [database on disk and CDROM]. The Cochrane Collaboration 1997. DOI: http://dx.doi.org/ 10.7554/eLife.00857.037
- [27] Zhang H, Chang R. Effects of exercise after percutaneous coronary intervention on cardiac function and cardiovascular adverse events in patients with coronary heart disease: systematic review and metaanalysis. J Sports Sci Med 2019;18:213–22.
- [28] Abdelhamid AS, Brown TJ, Brainard JS, et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev 2018;7:CD003177.
- [29] de Bus I, Witkamp R, Zuilhof H, et al. The role of n-3 PUFA-derived fatty acid derivatives and their oxygenated metabolites in the modulation of inflammation. Prostaglandins Other Lipid Mediat 2019;144:106351.
- [30] Kromhout D, Bosschieter EB, de Lezenne Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. N Engl J Med 1985;312:1205–9.
- [31] Shekelle RB, Missell L, Paul O. Fish consumption and mortality from coronary heart disease. N Engl J Med 1985;313:820–4.
- [32] Gorder DD, Dolecek TA, Coleman GG, et al. Dietary intake in the Multiple Risk Factor Intervention Trial (MRFIT): nutrient and food group changes over 6 years. J Am Diet Assoc 1986;86:744–51.
- [33] Kromhout D, Feskens EJ, Bowles CH. The protective effect of a small amount of fish on coronary heart disease mortality in an elderly population. Int J E pidemiol 1995;24:340–5.
- [34] Stone NJ. Fish consumption, fish oil, lipids, and coronary heart disease. Circulation 1996;94:2337–40.
- [35] Albert CM, Campos H, Stampfer MJ, et al. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. N Engl J Med 2002;346:1113–8.