

Citation:

Bucher HC, Hengstler P, Schindler C, Meier G. N-3 polyunsaturated fatty acids in coronary heart disease: A meta-analysis of randomized controlled trials. *Am J Med.* 2002 Mar; 112(4): 298-304.

PubMed ID: [11893369](#)

Study Design:

Meta-analysis.

Class:

M - [Click here](#) for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To investigate the effects of dietary and non-dietary (supplemental) intake of n-3 polyunsaturated fatty acids (PUFA) on coronary heart disease.

Inclusion Criteria:

- Publication between 1966 and 1999
- Randomized trials comparing dietary/supplemental intake of n-3 PUFA with placebo and control
- Report fatal or non-fatal MI and overall mortality
- Trials with patients who had MI or CHD for six or more months.

Exclusion Criteria:

Studies including patients who underwent coronary bypass surgery or heart transplant surgery.

Description of Study Protocol:

Searched MEDLINE, EMBASE, Pascal BioMed, Cochrane Library and Index Medicus; all languages included.

Search strings included n-3 fatty acids, fish oils, diet, dietary therapy and cardiovascular disease with random or control.

Quality Assessment

Study eligibility and quality determined by blinded assessment of two pairs of investigators. A scoring system was used that took into account randomization of participants, blinding and description of withdrawals and drop-outs, with one point given for each. An additional point was

given if randomization was concealed (central allocation) and double blinding with identical placebo, yielding scores from zero to five.

Interventions

- Studies comparing n-3 PUFA given as supplements or via dietary interventions versus placebo or control diet were included
- Dose of eicosapentaenoic acid (EPA) varied from 0.3g to 6.0g, dose of docosahexanoic acid (DHA) ranged from 0.6g to 3.7g.

Data Collection Summary:

Outcomes of interest were fatal and non-fatal MI and mortality data. Plasma lipids were also analyzed when reported by studies.

Analytical Methods

Publication bias assessed by inspecting funnel plots. Data pooled from each trial using fixed-effects model. Random effects model was used if Breslow-Day test for heterogeneity yielded $P < 0.10$.

Variability (heterogeneity) of study results explored by the magnitude of the treatment effects in relation to intervention type (supplementation vs. diet), duration of intervention and blinding methods used.

Researchers tested the differences in combined estimates of subgroups, and used the z-score for each subgroup by dividing the difference in the log relative risk of the subgroup summary by the standard error of the difference.

Description of Actual Data Sample:

A literature search identified 406 studies and 369 articles reviewed in the Cochrane Library.

177 Trials Were Identified

- 129 not related to CAD
- 26 with follow-up of less than six months or no clinical endpoint data
- Seven duplicates
- Four including heart transplant or bypass surgery patients.

11 Trials Included

- Two dietary intervention trials
- Nine supplementation trials with n-3 PUFA.

Of the studies used:

- 7,951 were in intervention groups
- 7,855 were in control groups
- Only one trial with patients with PAD or CHD
- 33% to 100% had a previous MI
- Mean age was 49 to 66 years
- Mean follow-up: 20 months (range six to 46 months)

- Mean TC: 4.8 to 6.5mmol per dL at enrollment
- Mean LDL-C: 2.8 to 4.5mmol per dL at enrollment
- Mean TG: 1.5 to 2.4mmol per dL at enrollment.

Summary of Results:

Incidence of Non-fatal and Fatal MI in Patients Treated with n-3 PUFA-Enhanced Diets vs. Control (N=10)

	Non-fatal MI	Fatal MI	Sudden Death	Overall Death
RR	0.8	0.7	0.7	0.8
(95% CI)	(0.5, 1.2)	(0.6, 0.8)	(0.6, 0.9)	(0.7, 0.9)
P-value	0.16	<0.01	<0.01	<0.001
Heterogeneity	P=0.01	P>0.20	P>0.20	P>0.20

No *a priori* hypotheses explained the heterogeneity observed. For all endpoints where authors found statistically significant heterogeneity, summary estimates were similar in all subgroups. See sensitivity analysis results below.

Sensitivity Analysis

	Diet	Supplement
	RR (95% CI)	
Non-fatal MI	0.7 (0.1, 3.2)	0.8 (0.55, 1.2)
Fatal MI	0.5 (0.3, 1.1)	0.8 (0.7, 0.9)
Overall Mortality	0.7 (0.6, 0.9)	0.8 (0.7, 0.9)

Author Conclusion:

A diet supplemented with n-3 PUFA may decrease mortality due to myocardial reinfarction, sudden death and overall mortality in patients with CAD.

The mortality in control groups of trials that followed patients for an average of 1.5 years varied from 1% to 22%, suggesting that in low-risk patients with mortality of about 2% per year, 250 patients would need to receive n-3PUFA supplementation for 1.5 years to prevent a single premature death. In patients with higher mortality rates (22%), 24 patients would need to supplement with n-3 PUFA for 1.5 years to prevent one event.

Addressed limitations of this review include:

- Publication bias, although a comprehensive literature search was performed. Smaller trial showed larger effect size than GISSI, so small, unpublished trials may have negligible effects on outcomes, therefore decreasing estimates of treatment effect.
- The amount and type of n-3 PUFA varied considerably (EPA and DHA and fish oil supplements, fatty fish intake, ALA). The sensitivity analysis could not determine differences between groups in the effects of dietary and supplemental intake of n-3 on clinical endpoints, which may have been due to lack of power or not identifying other relevant factors from the data.
- Possible overestimation of treatment effects in some studies due to an open intervention design and unblinded clinical endpoint assessments used.
- In trials with restenosis as primary endpoint, neither diagnostic criteria nor blinded outcome assessment of clinical endpoints were provided, which may have introduced bias.

The anti-lipidemic effect of n-3 PUFA was limited to an average of 20% reduction in TG levels, with little effect on LDL and HDL.

Reviewer Comments:

Low number of dietary trials met inclusion criteria. May limit generalizability regarding effectiveness of n-3 PUFA containing diets and cardiac outcomes until more strong dietary studies are published.

Researchers did not address variance in quantities contained in the n-3 PUFA supplements on clinical outcomes. Unable to determine effective dose with this analysis.

Results generalizable primarily to borderline and hyperlipidemic individuals. Gender breakdown of including studies not stated further limiting generalizability.

Research Design and Implementation Criteria Checklist: Review Articles

Relevance Questions

- | | | |
|----|---|-----|
| 1. | Will the answer if true, have a direct bearing on the health of patients? | Yes |
| 2. | Is the outcome or topic something that patients/clients/population groups would care about? | Yes |
| 3. | Is the problem addressed in the review one that is relevant to nutrition or dietetics practice? | Yes |
| 4. | Will the information, if true, require a change in practice? | Yes |

Validity Questions

- | | | |
|----|---|-----|
| 1. | Was the question for the review clearly focused and appropriate? | Yes |
| 2. | Was the search strategy used to locate relevant studies comprehensive? Were the databases searched and the search terms used described? | Yes |

3.	Were explicit methods used to select studies to include in the review? Were inclusion/exclusion criteria specified and appropriate? Were selection methods unbiased?	Yes
4.	Was there an appraisal of the quality and validity of studies included in the review? Were appraisal methods specified, appropriate, and reproducible?	Yes
5.	Were specific treatments/interventions/exposures described? Were treatments similar enough to be combined?	Yes
6.	Was the outcome of interest clearly indicated? Were other potential harms and benefits considered?	Yes
7.	Were processes for data abstraction, synthesis, and analysis described? Were they applied consistently across studies and groups? Was there appropriate use of qualitative and/or quantitative synthesis? Was variation in findings among studies analyzed? Were heterogeneity issues considered? If data from studies were aggregated for meta-analysis, was the procedure described?	Yes
8.	Are the results clearly presented in narrative and/or quantitative terms? If summary statistics are used, are levels of significance and/or confidence intervals included?	Yes
9.	Are conclusions supported by results with biases and limitations taken into consideration? Are limitations of the review identified and discussed?	Yes
10.	Was bias due to the review's funding or sponsorship unlikely?	Yes

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