N-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials
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Authors' objectives
To assess the effects of dietary or supplemental n-3 polyunsaturated fatty acids on coronary heart disease (CHD).

Searching
MEDLINE, EMBASE, Pascal Biomed, Index Medicus, the Cochrane Library and the reference lists of relevant articles were searched. The search dates covered 1966 to 1999 and the terms used were reported. Trials published in any language were sought.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) that reported at least 6 months follow-up data were eligible for inclusion. The average follow-up in the included studies was 20 months (range: 6 to 46).

Specific interventions included in the review
Studies that compared n-3 polyunsaturated fatty acids as a dietary or supplement intervention with a control diet or placebo were eligible for inclusion. The supplement interventions in the included studies were eicosapentaenoic acid, docosahexanoic acid, and gamma-linoleic acid with eicosapentaenoic acid. Eicosapentaenoic acid and docosahexanoic acid were given in doses of 0.3 to 6.0 g/day and 0.6 to 3.7 g/day, respectively. The dietary interventions were fish, and advice on fish consumption together with alpha-linoleic acid. The mean duration of the intervention was the same as the duration of follow-up (range 6 to 46 months).

Participants included in the review
Studies in people with CHD, either a previous myocardial infarction (MI) or CHD established by angiography, were eligible for inclusion. Studies in people who had undergone coronary bypass or heart transplantation were excluded. One trial in people with peripheral arterial disease or CHD was included. In the included studies, the mean total cholesterol level at enrolment was 4.8 to 6.5 mmol/L and the mean age ranged from 49 to 66 years.

Outcomes assessed in the review
Studies that reported fatal or nonfatal myocardial MI and overall mortality were eligible for inclusion. Sudden death was also reported in the review.

How were decisions on the relevance of primary studies made?
Two pairs of reviewers independently and blinded assessed the studies for inclusion and resolved any disagreements by consensus. Agreement was measured using kappa.

Assessment of study quality
Study quality was assessed by the adequacy of randomisation, allocation concealment, blinding, and descriptions of withdrawals and drop-outs. Two pairs of reviewers independently and blinded assessed study quality and resolved any disagreements by consensus. Agreement was measured using kappa.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The numbers of patients who experienced nonfatal MI, fatal MI or sudden death in each treatment and control group were extracted, [A: Data were extracted independently in duplicate and disagreements resolved by]
Methods of synthesis
How were the studies combined?
A meta-analysis was used to estimate the pooled risk ratio (RR, also known as the relative risk) with 95% confidence intervals (CIs). Intention-to-treat analysis was not mentioned. If statistical heterogeneity was detected a random-effects model was used, otherwise a fixed-effect model was used. Publication bias was assessed using a funnel plot.

How were differences between studies investigated?
Statistical heterogeneity in the meta-analyses was assessed using the Breslow-Day test (P<0.10). Dietary intake versus supplements, duration of follow-up and blinding were explored as potential sources of differences between the studies.

Results of the review
Eleven RCTs (n=15,806) were included.

No difference in nonfatal MI was shown between n-3 polyunsaturated fatty acid enriched diets and control diets or placebo (RR 0.8, 95% CI: 0.5, 1.2), based on 9 RCTs between which there was statistically significant heterogeneity. A pooled analysis of 8 RCTs showed a significant reduction in fatal MI (RR 0.7, 95% CI: 0.6, 0.8) with no statistically significant heterogeneity.

Data on sudden death available from 5 trials showed a benefit (RR 0.7, 95% CI: 0.6, 0.9) with no statistically significant heterogeneity. Overall mortality was also significantly reduced (RR 0.8, 95% CI: 0.7, 0.9), based on 9 RCTs with no statistically significant heterogeneity.

The summary end points were similar for dietary (2 RCTs) and supplement (9 RCTs) interventions.

All but one trial scored 3 or more for quality out of a possible 5. In sensitivity analyses blinding of patients, providers or outcome assessment did not explain differences in treatment effect between studies. There appeared to be evidence of publication bias and, hence, possible overestimation of the treatment effects.

Authors' conclusions
The findings suggested a reduction in overall mortality, mortality due to MI, and sudden death in people with CHD as a result of dietary and nondietary n-3 polyunsaturated fatty acid intake.

CRD commentary
The inclusion criteria concerning study design and the outcomes of interest were clearly defined, while those for the participants were less so, and the review appeared to adopt a broad definition for the intervention. The search for studies was designed to minimise language bias, but suggested limited efforts to identify unpublished studies. Steps were taken to minimise reviewer bias and errors in the study selection, data extraction, and quality assessment processes. Standard statistical methods were used to pool the data and potential sources of heterogeneity were explored, but the number of participants for whom data were available was not shown. The extent of loss to follow-up was not reported and could not be assessed from the aggregate quality scores. The review appears to have been basically well-conducted, but independent endorsement of the conclusions is somewhat hindered by the reporting.

Implications of the review for practice and research
Practice: The authors stated that, in the secondary prevention of CHD, n-3 polyunsaturated fatty acids may lead to a reduction in fatal MI and overall mortality.

Research: The authors stated that adequately powered trials are needed to determine any additional benefit of n-3 polyunsaturated fatty acid supplements to treatment with statins, antiplatelets, beta-blockers or angiotensin-converting enzyme inhibitors for the secondary prevention of CHD.
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