Alpha-linolenic acid and risk of cardiovascular disease: a systematic review and meta-analysis

CRD summary
The authors concluded that both dietary and biomarker studies suggested that alpha-linolenic acid exposure was associated with a moderately lower risk of cardiovascular disease. The studies were observational and varied, with marginal benefit in dietary studies and non-significant findings in biomarker studies, so the authors’ conclusions seem overly strong.

Authors’ objectives
To investigate the relationship between alpha-linolenic acid (a plant-derived omega-3 fatty acid) and the risk of cardiovascular disease.

Searching
Databases, including PubMed, EMBASE, The Cochrane Library, and ClinicalTrials.gov, were searched through to January 2012, for articles published in English. The search strategy was reported. Reference lists of retrieved articles and reviews were manually searched. Experts on cardiovascular disease were contacted to identify further data.

Study selection
Eligible for inclusion were observational studies assessing the association between alpha-linolenic acid (in the diet or as a biomarker in the blood or adipose tissue) and risk of cardiovascular disease. Eligible studies had to be of adults (aged over 18 years), who were not institutionalised, and had to report an adjusted risk estimate for at least one cardiovascular outcome, such as fatal or nonfatal coronary heart disease, ischaemic heart disease, or myocardial infarction. The authors searched for randomised placebo-controlled trials, but found none.

Most of the included studies were conducted in the USA or Europe. The age of patients, at the start, ranged from 20 to 84 years (where reported). The methods used to assess dietary intake of alpha-linolenic acid differed, and included various fatty acid tests, food-frequency questionnaires, and dietary records. All studies made some adjustments for potential confounding variables.

Two reviewers independently screened studies for inclusion; discrepancies were resolved by consensus or by referral to a third reviewer.

Assessment of study quality
Study quality was assessed using the Newcastle-Ottawa scale. Studies were rated as high or low quality, based on the median overall score from all the studies.

The authors did not explicitly state how many reviewers assessed study quality.

Data extraction
Risk ratios, hazard ratios and odds ratios, and their standard errors, were extracted by two independent reviewers. Hazard ratios and odds ratios were assumed to approximate risk ratios. Risk estimates and standard errors, for each study, were transformed to compare top and bottom thirds of the outcome (top versus bottom tertiles).

Where several risk estimates were reported by one study, the estimate for the most specific coronary outcome (defined in the review), with the largest number of adjustment variables, was extracted.

Methods of synthesis
A DerSimonian and Laird random-effects model was used to pool the risk ratios and their 95% confidence intervals. Statistical heterogeneity was assessed using I². Where this was less than 25%, a fixed-effect model was used.

Stratified analyses and meta-regression were used to explore heterogeneity, including exposure assessment, study
design, age, gender, study quality, study location, and adjustment variables. Sensitivity analysis was performed by removing one study at a time. Where feasible, dose-response analyses were conducted to assess the relationship between dietary intake and disease.

Publication bias was assessed using funnel plots and Begg’s test.

**Results of the review**

Twenty-seven studies (251,049 participants; range 108 to 76,763) were included in the review; 19 were prospective cohort studies and eight were retrospective case-control studies. Where reported, mean follow-up ranged from five to 30.7 years.

**Total cardiovascular disease:** Patients in the top third (tertile) of alpha-linolenic acid exposure, had a marginally statistically significant, lower risk of total cardiovascular disease (RR 0.86, 95% CI 0.77 to 0.97; 33 comparisons; $I^2=71.3\%$). Sensitivity analysis did not alter the findings. Analyses by outcome assessment showed similar results for dietary intake studies (RR 0.90, 95% CI 0.81 to 0.99; 15 comparisons; $I^2=49\%$), and consistent findings for biomarker studies, these were not statistically significant (RR 0.80, 95% CI 0.63 to 1.03; 18 comparisons; $I^2=79.8\%$). Meta-regression did not identify any statistically significant sources of heterogeneity.

**Cardiovascular subtypes:** There was a marginally statistically significant association between dietary alpha-linolenic acid and the risk of fatal coronary heart disease, showing a reduced risk with dietary intake (RR 0.80, 95% CI 0.65 to 0.98; six prospective cohort studies; $I^2=20.7\%$). No other statistically significant associations were found. There were no statistically significant associations between alpha-linolenic acid biomarkers and cardiovascular subtypes.

Other findings were reported. There was no evidence of publication bias.

**Authors’ conclusions**

Both dietary and biomarker studies suggested that alpha-linolenic acid exposure was associated with a moderately lower risk of cardiovascular disease; alpha-linolenic acid consumption might be beneficial, but further research was needed.

**CRD commentary**

The review question was clearly stated and the eligibility criteria were potentially replicable. Various sources were searched for potentially relevant data, but the search was restricted to studies published in English. Selection of studies and data extraction were performed by two people independently, but it was unclear whether this was the case for quality assessment. Study quality was assessed, but the results were not reported.

Many studies were included in the review; some with very long follow-up. The authors acknowledged the variation between studies, which could limit the validity of the overall pooled results. They explored some potential sources of heterogeneity, but the analyses generally were of few studies. All the included studies were observational and used adjusted analyses, but the potential for confounding and bias due to unidentified factors remains. The comparison of top and bottom thirds of exposure ignores people in the middle group, which can overestimate the association between exposure and disease. The outcomes were self-reported, and the benefits of dietary exposure were only marginally significant.

Given the potential limitations of the observational studies, and the marginal benefit in dietary studies and non-significant findings in biomarker studies, the authors’ conclusions seem overly strong.

**Implications of the review for practice and research**

**Practice:** The authors stated that the evidence supported the potential cardiovascular benefits of alpha-linolenic acid, but the best measure of alpha-linolenic acid exposure remained uncertain.

**Research:** The authors stated that further experimental and clinical studies were needed to explore the potential pathways of the effects of alpha-linolenic acid on the cardiovascular outcomes, and whether these effects were independent or could be modified by the intake of other fatty acids.

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