Antioxidant vitamins intake and the risk of coronary heart disease: meta-analysis of cohort studies
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CRD summary
This review examined the evidence for the use of antioxidant vitamins in coronary heart disease, concluding that an increase in dietary intake of antioxidant rich foods may have beneficial effects. Although there were strengths to this review, certain limitations (including a limited search and lack of validity assessment) mean that the authors' conclusions should be interpreted with caution.

Authors' objectives
To examine the evidence for the use of antioxidant vitamins in coronary heart disease (CHD).

Searching
MEDLINE was searched for articles published up to May 2007. Search terms were reported. Relevant references and review articles were searched manually.

Study selection
Long-term prospective cohort studies assessing the relationship between the intake of antioxidant vitamins (for example, vitamins C, E, and Beta-carotene) through diet or supplement, and first incident CHD (for example, nonfatal myocardial infarction (MI) or CHD death) were eligible for inclusion. Eligible studies were required to report relative risk (RR) and 95% confidence intervals (CI) of risk of CHD.

The majority of included studies were conducted in the USA. Most patients were middle aged at baseline (range 25 to approximately 105 years). Time of baseline survey ranged from 1958 to 1996. The majority of studies reported on vitamin C. Population sources varied and methods of sampling were either random or complete. Median intake of antioxidants varied considerably between studies. Follow-up ranged from four to 24 years (median follow-up for antioxidant type ranging between approximately 8.5 and 15 years). All but one study adjusted for various combinations of relevant factors such as age, smoking and alcohol consumption.

The authors stated neither how many reviewers selected studies for relevance nor how discrepancies were resolved.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
For each study, the log ratio of the risk of CHD in patients in the top third versus those in the bottom third of baseline measurement of the relevant factor was calculated. For association in dose-response, weighted linear regression was used to model the log relative risk of CHD as a linear function of vitamins intake.

The authors stated neither how many reviewers extracted the data nor how discrepancies were resolved.

Methods of synthesis
A random-effects model was used to pool RRs with their 95% CIs. Results reported as hazard ratio and mortality ratio were assumed to be similar to relative risk. $X^2$ and $I^2$ tests and random-effects regression models with restricted maximum likelihood estimation were used to test and investigate heterogeneity according to pre-defined characteristics. Sensitivity analyses were undertaken for vitamin C and E to examine the influence of study size, sex, duration of follow-up, location, vitamin intake and intake method. Publication bias was assessed using the Egger's test and funnel plots.

Results of the review
Fifteen cohort studies were included in the review (n=381,903; 7,415 incidents of CHD, ranging between 101 and 1,356 events). The extent of population overlap between studies was not clear.

Comparison of participants in the upper third versus the lower third at baseline showed small to moderately statistically significantly greater risk of CHD in the lower third for patients receiving vitamin C with RR 0.84 (95% CI: 0.73, 0.95; 14 study arms) and vitamin E with RR of 0.76 (95% CI: 0.63, 0.89; nine study arms). No statistically significant relationship was found between Beta-carotene and CHD, 0.78 (95% CI: 0.53, 1.04; three study arms).

There was evidence of statistical heterogeneity among studies for intake of vitamin C ($I^2=63$, $p=0.0005$), vitamin E ($I^2=42$, $p=0.08$) and Beta-carotene ($I^2=64$, $p=0.06$). Sensitivity analyses did not significantly alter the results for vitamin C and E. A dose relationship was reported for vitamin E, with an increase of 30IU per day potentially lowering the risk of CHD by four per cent. No statistically significant dose-response relationship was found for vitamin C or Beta-carotene.

There was no evidence of publication bias for any antioxidant using funnel plot analysis.

**Authors’ conclusions**
An increase in dietary intake of antioxidant rich foods may have beneficial effects for CHD.

**CRD commentary**
The review question was clear and was supported by appropriate inclusion criteria. Limiting the literature search to one electronic database plus references may have resulted in the omission of other relevant studies. No attempts to minimise language bias were reported. Validity was not assessed, which may affect the reliability of the subsequent conclusions. The process for study selection and data extraction were not reported, thus the potential for reviewer error and bias cannot be ruled out. Although appropriate methods were used to combine the results and investigate statistical heterogeneity, there appeared to be clinical and methodological differences between studies. Although the large sample sizes, long follow-up periods and prospective designs of the included studies helped moderate the potential for selection bias, the authors acknowledged certain limitations with the report (such as failure to account for other potential confounding factors and the potential for other bias). Forest plots were presented. RRs and CIs for individual studies were not reported, and this information may have been useful considering the width of some of the CIs presented graphically. Although there were certain strengths to this review, given the limitations the authors’ conclusions should be interpreted with caution.

**Implications of the review for practice and research**
Practice: The authors did not state any implications for practice.

Research: The authors stated that it may be necessary for future research into the relationship between antioxidant vitamins and CHD to consider statistical adjustment for lifestyle and socio-economic factors.

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