Effect of folic acid supplementation on risk of cardiovascular diseases: a meta-analysis of randomized controlled trials

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CRD summary
This review showed that, for people with cardiovascular or renal disease, folic acid supplementation had no effect on the risk of further cardiovascular disease (CVD), coronary heart disease, stroke or all-cause mortality. The authors concluded that folic acid is ineffective in the secondary prevention of CVD. The review was generally well conducted and the conclusions are likely to be reliable.

Authors' objectives
To assess the effects of folic acid supplements in people with pre-existing vascular disease.

Searching
MEDLINE was searched from January 1966 to July 2006; the search terms were given. No language restrictions were applied. The bibliographies of relevant studies and reviews identified were checked. Experts were contacted.

Study selection

Specific interventions included in the review
Studies that assessed folic acid supplementation taken for at least 6 months, with or without additional vitamin B supplements, were eligible for inclusion. Dosages of folic acid in the included studies ranged from 0.5 to 15 mg/day. Some studies were conducted in countries where grain was fortified with folic acid. The comparator groups were either placebo or usual care. The duration of treatment ranged from 6 to 60 months.

Participants included in the review
Studies on people with pre-existing vascular disease were eligible for inclusion. In the included studies, where stated, the mean age of the participants ranged from 56 to 68.9 years and the proportion of men ranged from 32.3 to 80.5%. The participants had coronary heart disease (CHD), end-stage renal failure (ESRF) or stroke and, where reported, between 9% and 45.5% of the participants also had diabetes. The mean cholesterol levels ranged from 177.6 to 279.9 mg/dL and the mean homocysteine levels from 11.2 to 50.3 micromoles/L.

Outcomes assessed in the review
Studies that reported on cardiovascular disease events (CVD), CHD, stroke, or all-cause mortality were eligible for inclusion. Net changes in blood homocysteine levels were also presented.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed studies for inclusion. Any discrepancies were resolved through consensus with a third reviewer.

Assessment of study quality
The studies were assessed for blinding. Two reviewers independently extracted data on blinding. Any discrepancies were resolved with a third reviewer and by further checking the original paper.

Data extraction
Two reviewers independently extracted the data using a standardised data extraction form. Any discrepancies were resolved with a third reviewer and by further checking the original paper.

Net changes in homocysteine levels were calculated by taking the change in each group (pre- and post-intervention) and then calculating the difference in change between treatment and control group (i.e. treatment minus control). Relative risks (RRs) and 95% confidence intervals (CIs) were estimated for each outcome in each trial. All data were standardised, where necessary, by converting units to mg/dL for lipids and to micromoles/L for homocysteine. Where studies assessed more than one treatment group (i.e. different dosages of folic acid), the mean doses and mean levels of homocysteine (before and after treatment) were calculated from the combined intervention groups. Similarly, numbers of events and participants in different treatment groups in the same study were combined.

Methods of synthesis

How were the studies combined?
Pooled RRs and 95% CIs were calculated using both random-effects and fixed-effect methods. The results from the random-effects model were presented. Publication bias was assessed using funnel plots, the Begg rank correlation test and the Egger linear regression test.

How were differences between studies investigated?
The authors said that they tested for heterogeneity between the studies, but did not detail the method used.

Subgroup analyses were conducted on the basis of type of existing disease (CVD or ESRF) and use of a control group (placebo or usual care). Sensitivity analyses, in which each trial was individually excluded from the analysis, were also performed.

Results of the review

Twelve RCTs (16,958 participants) were included.

Eight studies were double-blinded; the other four were open.

Statistical tests showed no significant heterogeneity between the studies and no evidence of publication bias.

All studies showed a net reduction in homocysteine levels with folic acid (from -1.5 to -26 micromoles/L).

There was no significant effect on any clinical outcome between treatment and control groups: the CVD was 0.95 (95% CI: 0.88, 1.03; 10 trials) for CVD, 1.04 (95% CI: 0.92, 1.17; 11 trials) for CHD, 0.86 (95% CI: 0.71, 1.04; 8 trials) for stroke and 0.96 (95% CI: 0.88, 1.04; 10 trials) for all-cause mortality.

In the sensitivity analysis, the removal of one large trial showed a significant protective effect of folic acid on stroke in pooled data from the remaining studies (RR=0.76, 95% CI: 0.63, 0.93). No other sensitivity analysis revealed any alterations in the overall result.

In subgroup analyses, stratified by existing disease (CVD or ESRF) and type of control used (placebo or usual care), there was no significant effect of treatment in any of the analyses.

Authors' conclusions

Folic acid supplementation is ineffective for the secondary prevention of CVD in people with a history of vascular disease.

CRD commentary

The aims of this review and the inclusion criteria were clearly stated. Only one relevant database was searched, but this was supplemented by checking relevant bibliographies and contacting experts. However, it is possible that studies were missed; publication bias was assessed and no evidence was found. The methods of the review (study selection and data
extraction) were appropriate for minimising the introduction of reviewer bias and errors. The quality assessment was limited to an evaluation of blinding and this made it difficult to adequately assess the reliability of the studies. Heterogeneity between the studies was assessed, the studies were appropriately pooled, and relevant subgroup analyses were performed. This was generally a well-conducted review and the authors' conclusions are likely to be reliable.

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

Practice: The authors stated that it is important to focus on interventions that have been proven to be effective in the secondary prevention of CVD. These included smoking cessation, lipid reduction, treatment of hypertension and diabetes, maintenance of a healthy weight and physical activity.

Research: The authors stated there is a need for further clinical trials to evaluate folic acid supplementation in special subgroups. The authors noted that several large studies investigating the use of folic acid are already underway.

**Bibliographic details**


**PubMedID**

17164458

**DOI**

10.1001/jama.296.22.2720

**Original Paper URL**

http://jama.ama-assn.org/

**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

Cardiovascular Diseases /epidemiology; Dietary Supplements; Folic Acid /administration & dosage; Humans; Randomized Controlled Trials as Topic; Risk; Vitamin B Complex /administration & dosage

**AccessionNumber**

12006008441

**Date bibliographic record published**

31/03/2007

**Date abstract record published**

31/03/2007

**Record Status**

This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.