Meta-analysis of folic acid supplementation trials on risk of cardiovascular disease and risk interaction with baseline homocysteine levels

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CRD summary
This review concluded that folic acid supplementation had no effect on cardiovascular disease, mortality and stroke. Stratified analysis showed higher risk of cardiovascular disease with folic acid with high baseline homocysteine level and lower risk with lower homocysteine. The authors’ conclusions on the overall outcomes appeared reasonable, but those for stratified analyses should be treated with caution.

Authors’ objectives
To assess the effects of folic acid supplementation on cardiovascular disease risk.

Searching
MEDLINE (July 2006 to June 2009) was searched to update the search of a previous review with a search from 1966 to 2006 (see Other Publications of Related Interest). No language restrictions were applied. Search terms were reported. Searches were made for unpublished or ongoing trials and those presented at scientific meetings.

Study selection
Randomised controlled trials (RCTs) that lasted at least six months and reported the effects of folic acid supplementation on cardiovascular disease, coronary heart disease, stroke, deep vein thrombosis, pulmonary embolism or all-cause mortality were eligible for inclusion. The primary outcome of interest was defined as that within each trial. Trials of children, pregnant women and people with end-stage renal disease were excluded.

In the included studies, mean age ranged from 59 to 69 years. One study was on women and in others most participants were men. Participants had acute cardiovascular disease events, pre-existing cardiovascular disease or were at high risk of cardiovascular disease. One study was on people with no evidence of cardiovascular disease or diabetes. Baseline homocysteine levels ranged from 9.6μmol/L to 13.5μmol/L. Folic acid doses ranged from 0.5mg to 5mg per day. Some participants also had vitamin B12 and/or B6. Participants in one study participants were separately randomised to high or low dose simvastatin. Comparators were placebo or usual care. Most studies were carried out in North America and Western Europe. Some studies were conducted in countries with mandatory folic acid fortification programmes. Average follow-up ranged from six months to 7.3 years.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
Studies were assessed for blinding.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
Data were extracted on an intention-to-treat principle to calculate net mean changes in homocysteine levels and risk ratios (RR) and 95% confidence intervals (CI) for cardiovascular disease, coronary heart disease, stroke and all-cause mortality. Where different dosages of folic acid were compared to control in the same study, groups that used folic acid were treated as one group. In trials that did not report on coronary heart disease events, data for myocardial infarction were extracted. Where trials did not report numbers of participants and events stratified by baseline homocysteine levels stratum-specific relative risks and 95% CI were extracted.

Three authors independently extracted data. Disagreements were resolved by consensus.
Methods of synthesis
Pooled net changes in homocysteine and risk ratios and 95% CI for clinical outcomes were calculated using a random-effects model. Heterogeneity was assessed using $I^2$. Sensitivity analyses removed each trial individually. Subgroup analyses were performed according to country-specific folic acid food fortification policy (yes versus no). Inverse-variance weighted random-effects meta-regression was used to analyse data stratified by baseline homocysteine levels. Sensitivity analyses were undertaken grouped according to baseline homocysteine level (above or below the average 12μmol/L).

Publication bias was investigated using Egger's test.

Results of the review
Fourteen RCTs (38,941 participants) were included. Study size ranged from 240 to 12,064 participants. Twelve trials were double-blind placebo-controlled and two were open control, compared to usual care. Tests found no evidence of publication bias.

Compared to control, folic acid decreased homocysteine levels in all trials. The pooled net reduction was 2.9μmol/L (95% CI 2.4 to 3.4, $I^2$=91%).

Compared to control, folic acid had no effect on the primary clinical outcomes ($I^2$=38%), risk of cardiovascular disease ($I^2$=0%), coronary heart disease ($I^2$=31%), stroke ($I^2$=25%) and all-cause mortality ($I^2$=0%). Tests showed no evidence of publication bias. Sensitivity analyses that removed one trial at a time did not significantly alter the results.

Subgroup analyses according to country status of folic acid fortification showed no significant difference in baseline homocysteine, net homocysteine decrease and the primary clinical outcome.

In sensitivity analyses grouped according to baseline homocysteine levels that compared folic acid to control there was a significant difference ($p=0.030$) in risk ratios for the primary outcome between those above and below the mean (12μmol/L). Those with a higher baseline homocysteine had a higher risk of cardiovascular disease (RR 1.06, 95% CI 1.00 to 1.13) compared with those with a lower than average homocysteine level (RR 0.94, 95% CI 0.86 to 1.03). When results were analysed stratified by baseline homocysteine levels, comparing folic acid to control, on average the pooled risk ratio for primary clinical outcomes increased risk by 3.9% (95% CI -3.0 to 11.3) for each 5μmol/L increase in baseline homocysteine ($I^2$=8%).

Authors' conclusions
Data showed that folic acid supplementation had no effect on overall cardiovascular disease, mortality and stroke. Analysis stratified by baseline homocysteine levels showed a higher risk of cardiovascular disease events with folic acid in people with a higher baseline homocysteine level and lower risk with those with lower homocysteine levels.

CRD commentary
The aims of the review were clearly stated in terms of inclusion criteria. The search covered only one database, but was supplemented by checks of other sources. No language restrictions were applied and unpublished studies were sought, which were likely to have reduced any effects of language and publication biases. Tests found no evidence of publication bias. Methods of data extraction aimed at reduced reviewer error and bias; it was impossible to comment on methods for study selection or quality assessment as these were not described. The authors appeared to assess study quality only on the basis of double blinding, so it was difficult to comment on the overall validity of included studies even though all were RCTs and most were double blind.

Methods of synthesis were generally appropriate. There was heterogeneity between studies for some outcomes, particularly for changes in homocysteine levels. The authors investigated sources of heterogeneity for the clinical outcomes. For results stratified by baseline homocysteine levels it was unclear how many studies failed to report numbers of participants or events (necessitating extraction of data as risk ratios) or the effect that this may have had on stratified outcomes. Study quality was not assessed formally, but data generally came from large double-blind RCTs.

Given the details of the included data, the authors' conclusions on overall outcomes seemed to reflect the evidence.
However, results stratified by homocysteine levels need to be treated with some caution.

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

**Practice:** The authors stated that folic acid supplementation should not be recommended for preventing cardiovascular disease or stroke.

**Research:** The authors stated that further RCTs to assess the effects of folic acid on cardiovascular risk factors were underway and a collaborative meta-analysis was planned. The authors suggested that these should include testing for an interaction between baseline homocysteine levels.

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