Effect of homocysteine interventions on the risk of cardiocerebrovascular events: a meta-analysis of randomised controlled trials

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CRD summary
The authors concluded that folic acid supplementation was ineffective in the secondary prevention of cardiovascular disease among individuals with a history of vascular disease. The review had some methodological problems, notably the limited search and unknown quality of the included trials, which limits the reliability of the authors’ conclusions.

Authors’ objectives
To evaluate the effects of homocysteine lowering interventions on the risk of cardiocerebrovascular events and all-cause mortality in randomised controlled trials (RCTs) among participants with pre-existing cardiocerebrovascular or renal disease.

Searching
MEDLINE was searched from January 1966 to December 2008. Search terms were reported. Reference lists of retrieved articles were searched. Internet searches were also conducted.

Study selection
Randomised controlled trials (RCTs) of folic acid (with or without vitamin B supplementation) versus placebo or usual care in participants with cardiocerebrovascular or renal disease were eligible for inclusion. Trials had to report the number of cardiovascular events, coronary heart disease, stroke, or all-cause mortality.

The included trials compared folic acid (0.5mg to 40mg dose) alone or in combination with vitamin B6 (10mg to 100mg dose) and vitamin B12 (0.06mg to 2mg dose). The included participants were diagnosed with coronary heart disease, end-stage renal disease and stroke. The duration of intervention ranged from 6 to 87 months. The mean age of participants ranged from 52 to 69 years (where reported). Most trials had a majority of male patients (where reported); one trial recruited women only.

Two authors independently performed study selection and disagreements were resolved by discussion with a third reviewer.

Assessment of study quality
Two authors independently assessed quality using the Cochrane Reviewers’ Handbook 4.2 criteria. Each individual criterion was graded from A to C, with the trial given an overall grade according to the lowest grade received; criteria assessed included randomisation, blinding and reporting of low to follow-up. Grade A trials were deemed low risk of bias, grade B as moderate risk of bias, and C as high risk of bias.

Data extraction
Two authors independently extracted data on the number of cardiovascular events, coronary heart disease, stroke, and all-cause mortality. These were used to calculate relative risks (RRs) and 95% confidence intervals (CIs).

Methods of synthesis
The pooled relative risks, together with 95% confidence intervals, were calculated using a fixed-effects meta-analysis. Statistical heterogeneity was assessed using the $X^2$ and $I^2$ statistics. Publication bias was assessed using funnel plot and trim-and-fill analyses.

Sensitivity analyses were conducted for trial quality, grain fortification, homocysteine levels, and end-stage renal disease.
Results of the review
Seventeen RCTs were included in the review (n=39,107 participants). These included two trials of folic acid versus placebo, four trials of folic acid versus normal therapy, and eleven trials of folic acid plus B vitamins versus placebo. The sample size of included trials ranged from 81 to 12,064 participants. There was no evidence of publication bias.

There was no significant difference between folic acid supplementation compared with control treatment in terms of cardiovascular events (RR 1.01, 95% CI 0.97, 1.05), coronary heart disease (RR 1.01, 95% CI 0.94 to 1.07), stroke (RR 0.94, 95% CI 0.85 to 1.04), or all-cause mortality (RR 1.00, 95% CI 0.95 to 1.05). Exclusion of the three grade C quality trials did not alter the results. The results were also robust to the exclusion of seven trials with grain fortification, five trials which reduced homocysteine levels to less than 20%, and five trials in end-stage renal disease. The level of statistical heterogeneity in the analyses was low ($\Gamma^2$=0% to $\Gamma^2$=25%).

Authors' conclusions
Folic acid supplementation was ineffective in the secondary prevention of cardiovascular disease among individuals with a history of vascular disease.

CRD commentary
Inclusion criteria for the review were broadly defined and only one relevant database was searched. It was not clear if articles other than those in English were included, which may have introduced language bias into the analysis. There was no evidence of publication bias. Two authors independently undertook study selection, data extraction and quality assessment, which minimised the possibility of error and bias.

The results of the quality assessment were not presented, which made assessing the quality of the included trials difficult. A fixed-effects meta-analysis was undertaken and statistical heterogeneity was explored, which was appropriate. A range of sensitivity analyses were also undertaken to check the robustness of the results.

The review had some methodological problems, notably the limited search and unknown quality of the included trials, which limits the reliability of the authors' conclusions.

Implications of the review for practice and research
Practice: The authors stated that folic acid supplementation was not recommended for the secondary prevention of cardiovascular disease.

Research: The authors stated that more evidence from large-scale RCTs is needed to confirm these results.

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