Folic acid improves vascular reactivity in humans: a meta-analysis of randomized controlled trials

de Bree A, van Mierlo LA, Draijer R

CRD summary
The review aimed to quantify the effect of folic acid on endothelial function and concluded that high doses improved function after four weeks of supplementation. The presence of review methodology and reporting issues, coupled with the small sample sizes of included studies, means the authors’ conclusions should be interpreted with caution.

Authors’ objectives
To quantify the effect of folic acid on endothelial function, as measured with the use of flow-mediated dilatation.

Searching
MEDLINE was searched from 1966 to September 2005 for studies published in English; search terms were reported. Conference abstract books and reference lists of obtained articles were searched for additional studies. Investigators were contacted for any unpublished results.

Study selection
Randomised controlled trials (RCTs) of adults (>19 years of age) that measured vascular reactivity using percentage of flow-mediated dilatation after folic acid supplementation without a vascular challenge (such as methionine or fat load) were eligible for inclusion. The primary outcome of interest was net change in flow-mediated dilatation.

Median duration of treatment with folic acid was eight weeks (range four to 52 weeks); median dose was 5000ug/day (range 400ug/day to 10,000ug/day). Median age of participants was 55.8 years (mean age range 29.3 to 69.1 years). In most trials most people were male (median 86%). Patient populations were either healthy, healthy but with elevated plasma homocysteine levels, or with cardiovascular disease (or high cholesterol). Some studies supplied additional vitamin B-6 and vitamin B-12. It appeared that all comparator groups received placebo.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
Study quality was independently assessed by two reviewers (with disagreements resolved by discussion) using nine criteria developed using Delphi consensus: randomisation, baseline similarity, eligibility criteria, blinding (treatment allocation, patients, care givers, outcome assessors, all scored separately), measures of variability presented for flow-mediated dilatation measurement and use of intention-to-treat analysis. Trials received a score out of 9.

Data extraction
Data were extracted and/or calculated for the net change (and standard error) in flow-mediated dilatation. Study authors were contacted for data when necessary.

Two reviewers independently extracted data; disagreements were resolved by discussion.

Methods of synthesis
A meta-analysis, seemingly of pooled weighted mean differences, was performed using a random-effects model. Sensitivity analyses were conducted examining study design, mean age, health status, folic acid dose, duration of treatment, use of additional B vitamins and study quality. The authors appeared to use the $I^2$ statistic to assess heterogeneity. Publication bias was assessed using a funnel plot.

Results of the review
Fourteen RCTs (n=732) were included in the review. Six were crossover trials and eight were parallel group trials.
Median sample size was 34 participants. Study quality scores ranged from 7 to 9 out of 9. The funnel plot showed little evidence of publication bias.

Folic acid supplementation improved flow-mediated dilatation compared with placebo by 1.08% (95% CI 0.57 to 1.59, p=0.0005). Patients at a greater risk of cardiovascular disease tended to have a larger improvement and higher quality studies tended to have a smaller improvement (both not statistically significant). Only trials that used a higher dose (≥5000ug/day) showed a beneficial effect (1.42%, 95% CI 1.25 to 1.58). A post hoc analysis showing a dose-response effect was reported.

Authors’ conclusions
This study indicated that high doses of folic acid improved endothelial function after four weeks of supplementation, which could potentially reduce the risk of cardiovascular disease.

CRD commentary
The review addressed a clear question and was supported by appropriate inclusion criteria. Attempts to identify relevant studies were undertaken by searching only one electronic database for studies published in English, so despite the use of other search methods it was possible that relevant studies were missed. Suitable methods were employed to reduce the risks of reviewer error and bias throughout the review process. Study quality was assessed using nine criteria, but half the included studies had 50 or fewer participants; knowledge of whether or not a sample size calculation had been used may have been beneficial in assessing the reliability of the evidence. Synthesis of the data was undertaken using meta-analytic techniques, but details on the effect size used were not reported. Although the authors acknowledged the presence of clinical and methodological heterogeneity, the methods used to assess heterogeneity were poorly reported and heterogeneity was assessed only for the main analysis and not for the sensitivity analyses. In light of the possibility of missed studies, the generally small sample sizes and the minimal assessment and reporting of statistical heterogeneity, 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 a need for large studies in healthy older populations or populations with (reversible) vascular dysfunction. They also stated that it would be worthwhile to investigate acute effects of several doses of folic acid or dietary folate, or both, on flow-mediated dilatation values in subjects with suboptimal folate status.

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