

Citation:

Bazzano LA, Reynolds K, Holder KN, He J. Effect of folic acid supplementation on risk of cardiovascular diseases: A meta-analysis of randomized controlled trials. *JAMA* 2006 Dec 13; 296 (22): 2,720-2,726. Erratum in: *JAMA*. 2007 Mar 7; 297 (9): 952.

PubMed ID: [17164458](#)

Study Design:

Meta-analysis

Class:

M - [Click here](#) for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To evaluate the effects of folic acid supplementation on risk of cardiovascular diseases and all-cause mortality in randomized controlled trials (RCTs) among persons with pre-existing cardiovascular or renal disease.

Inclusion Criteria:

- RCTs in humans
- Number of events for cardiovascular disease (CVD), coronary heart disease (CHD), stroke or all-cause mortality that occurred during the study were reported by intervention and control groups
- Intervention consisted of folic acid supplementation (with or without additional B-vitamin supplementation) with either placebo or usual care
- Minimum duration of six months
- No language restrictions.

Exclusion Criteria:

- Duplicate reports
- Design or baseline results of a relevant trial.

Description of Study Protocol:**Recruitment**

- Studies were retrieved by searching MEDLINE (January 1966 to July 2006) using the Medical Subject Headings *cardiovascular disease*, *coronary disease*, *coronary thrombosis*, *myocardial ischemia*, *coronary stenosis*, *coronary restenosis*, *cerebrovascular accident*, *randomized controlled trial*, *clinical trials*, *homofolic acid* and *folic acid*, as well as the text

words *folic acid* and *folate*

- Bibliographies of all retrieved articles and relevant review articles were also manually searched and experts in the field were contacted regarding trials nearing completion.

Design

Meta-analysis.

Dietary Intake/Dietary Assessment Methodology

Not applicable.

Blinding Used

Not applicable.

Intervention

Not applicable.

Statistical Analysis

- Data on study design, characteristics of participants, changes in homocysteine levels and cardiovascular disease outcomes were independently abstracted by two investigators using a standardized protocol
- Relative risk was used as a measure of the association between folic acid supplementation and risk of CVD, CHD, stroke or all-cause mortality
- Relative risks were calculated for each trial based on the number of events in each group and they were used for pooled analyses because not all trials reported relative risks for all outcomes
- Calculated relative risks and corresponding standard errors were logarithmically transformed to stabilize variance and normalize the distribution
- Both fixed-effects and DerSimonian and Laird random effects models were used to calculate the pooled relative risk for folic acid supplementation compared with control
- Statistical testing for heterogeneity between studies was not significant
- To assess the potential for publication bias, funnel plots were constructed for each outcome in which the relative risks were plotted against their standard errors
- Begg rank correlation test was used to examine the association between effect estimates and their variances and the Egger linear regression test was used to detect publication bias
- Sensitivity analyses were also conducted in which each trial was excluded in turn to evaluate

the influence of that trial on the pooled estimate.

Data Collection Summary:

- *Timing of measurements:* Trials lasted a minimum duration of six months
- *Dependent variables:* Clinical cardiovascular disease events reported as an end-point
- *Independent variables:*
 - Folic acid supplementation with either placebo or usual care
 - Dosage of folic acid in the intervention groups ranged from 0.5mg per day to 15mg per day, for a duration ranging from six months to five years
- *Control variables:* None.

Description of Actual Data Sample:

- *Initial N:* 165 relevant reports were retrieved; 12 RCTs met criteria and were included
- *Attrition (final N):* 12 RCTs, representing 16,958 participants, both men and women
- *Age:* Not mentioned
- *Ethnicity:* Not mentioned
- *Other relevant demographics:* Not mentioned
- *Anthropometrics:* Not mentioned
- *Location:* International studies
 - Two in the United States
 - One in Australia and New Zealand
 - One in Canada
 - Eight in Europe.

Summary of Results:

Pooled Relative Risk of CVD, CHD, Stroke and All-Cause Mortality

Variables	CVD RR (95% CI)	CHD RR (95% CI)	Stroke RR (95% CI)	All-cause Mortality RR (95% CI)
Pre-existing conditions; CVD	0.96 (0.88-1.05)	1.04 (0.90-1.19)	0.89 (0.74-1.07)	0.97 (0.88-1.06)
Pre-existing conditions; ESRD	0.89 (0.74-1.08)	1.06 (0.75-1.51)	0.68 (0.37-1.25)	0.93 (0.78-1.11)
Control group; Placebo	0.96 (0.87-1.06)	1.05 (0.90-1.23)	0.85 (0.66-1.09)	0.97 (0.89-1.07)
Control group; Usual care	0.89 (0.74-1.07)	1.01 (0.78-1.29)	0.81 (0.48-1.34)	0.87 (0.69-1.09)

Other Findings

- Studies including data from 16,958 participants with pre-existing vascular disease were analyzed using a random-effects model
- Dosage of folic acid in the intervention groups ranged from 0.5mg per day to 15mg per day, for a duration ranging from six months to five years
- All trials showed a reduction in homocysteine levels ranging from -1.5 to -26 μ mol/L
- There was no statistically significant relationship between net change in homocysteine level and relative risk for any of the clinical outcomes
- The overall relative risks of outcomes for patients treated with folic acid supplementation compared with controls were 0.95 (95% CI 0.88-1.03) for cardiovascular diseases, 1.04 (95% CI 0.92-1.17) for coronary heart disease, 0.86 (95% CI 0.71-1.04) for stroke and 0.96 (95% CI 0.88-1.04) for all-cause mortality
- The relative risk was consistent among participants with pre-existing cardiovascular or renal disease
- In sensitivity analysis, no significant heterogeneity was present for trials reporting CVD outcomes ($P=0.33$) and exclusion of any single trial from the analysis did not alter the overall findings of no effect of folic acid supplementation on CVD
- There was no evidence of publication bias in funnel plots or by rank correlation or regression testing.

Author Conclusion:

- Folic acid supplementation has not been shown to reduce risk of cardiovascular diseases or all-cause mortality among participants with prior history of vascular disease
- Several ongoing trials with large sample sizes might provide a definitive answer to this important clinical and public health question
- The findings of this analysis suggest that folic acid supplementation is ineffective in the secondary prevention of CVD among persons with a history of vascular diseases
- Therefore, it is important to focus on strategies of proven benefit in the secondary prevention of CVD, including smoking cessation, lipid reduction, treatment of hypertension and diabetes, maintenance of a healthy weight and physical activity.

Reviewer Comments:

Authors note the lack of data from multiple large trials that have yet to report results.

Research Design and Implementation Criteria Checklist: Review Articles

Relevance Questions

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|----|---|-----|
| 1. | Will the answer if true, have a direct bearing on the health of patients? | Yes |
| 2. | Is the outcome or topic something that patients/clients/population groups would care about? | Yes |

- | | | |
|----|---|-----|
| 3. | Is the problem addressed in the review one that is relevant to nutrition or dietetics practice? | Yes |
| 4. | Will the information, if true, require a change in practice? | Yes |

Validity Questions

- | | | |
|-----|--|-----|
| 1. | Was the question for the review clearly focused and appropriate? | Yes |
| 2. | Was the search strategy used to locate relevant studies comprehensive? Were the databases searched and the search terms used described? | Yes |
| 3. | Were explicit methods used to select studies to include in the review? Were inclusion/exclusion criteria specified and appropriate? Were selection methods unbiased? | Yes |
| 4. | Was there an appraisal of the quality and validity of studies included in the review? Were appraisal methods specified, appropriate, and reproducible? | Yes |
| 5. | Were specific treatments/interventions/exposures described? Were treatments similar enough to be combined? | Yes |
| 6. | Was the outcome of interest clearly indicated? Were other potential harms and benefits considered? | Yes |
| 7. | Were processes for data abstraction, synthesis, and analysis described? Were they applied consistently across studies and groups? Was there appropriate use of qualitative and/or quantitative synthesis? Was variation in findings among studies analyzed? Were heterogeneity issues considered? If data from studies were aggregated for meta-analysis, was the procedure described? | Yes |
| 8. | Are the results clearly presented in narrative and/or quantitative terms? If summary statistics are used, are levels of significance and/or confidence intervals included? | Yes |
| 9. | Are conclusions supported by results with biases and limitations taken into consideration? Are limitations of the review identified and discussed? | Yes |
| 10. | Was bias due to the review's funding or sponsorship unlikely? | Yes |