

What effect does folic acid supplementation (with or without additional B vitamin supplementation) have on risk of stroke among persons with or without pre-existing vascular disease?

Conclusion

Evidence that folic acid supplementation might prevent stroke is limited due to inconsistency, with the most recent meta-analysis documenting no benefit.

Grade: Limited

Overall strength of the available supporting evidence: Strong; Moderate; Limited; Expert Opinion Only; Grade not assignable For additional information regarding how to interpret grades, [click here](#).

Evidence Summary Overview

One randomized control trial (RCT) (Saposnick et al, 2009) and one meta-analysis (Wang et al, 2007) demonstrated a reduce risk of stroke with folic acid supplementation. The second meta-analysis (Bazzano et al, 2006) did not demonstrate a reduction in stroke. With the exception of two studies, the two meta-analyses included the same trials in their respective analyses. The reasons for the different findings between Wang et al (2007) and Bazzano et al (2006) may be small methodological differences and that there is a stronger effect with primary prevention vs. secondary prevention with stroke (Wang et al, 2007).

Evidence summary paragraphs:

Meta-Analysis

Bazzano et al, 2006 (positive quality). This meta-analysis evaluated the effects of folic acid supplementation on risk of cardiovascular diseases (CVD) and all-cause mortality using a random-effects model. The 12 RCTs represented 16,958 men and women. The overall relative risk (RR) confidence intervals (CI) of outcomes for patients treated with folic acid supplementation compared with controls were 0.95 (0.88, 1.03) for CVD, 1.04 (0.92, 1.17) for coronary heart disease (CHD), 0.86 (0.71, 1.04) for stroke, and 0.96 (0.88, 1.04) for all-cause mortality. The relative risk was consistent among participants with pre-existing cardiovascular or renal disease. 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. Studies included US, Canadian and European subjects.

Miller et al, 2010 (positive quality). This study aimed to explore the interaction between folic acid (FA) and baseline homocysteine levels on CVD through a meta-analysis of randomized controlled trials. The authors searched MEDLINE for trials of FA supplementation to prevent CVD events (January 1966 to July 2009). Articles included in the sample met the following criteria: 1) RCT

study design; 2) Intervention included FA supplementation; 3) Intervention and control groups reported number of events for CVD, stroke and other health issues; and 4) Intervention lasted six months or more. Trials with children, pregnant women and patients with end-stage renal disease were excluded. Fourteen trials published from 2002 to 2009 were selected, and they included 38,941 randomized participants (trials ranged from 240 to 12,064 participants; mean age ranged between 52.2 to 68.9 years). Nine trials recruited patients after acute CVD events, four trials had patients with pre-existing CVD or those at high risk of CVD and one trial targeted patients at low risk of CVD. Overall, the findings suggest FA supplementation does not affect CVD or stroke (RR=1.02, 95% CI: 0.93 to 1.13, P=0.66; RR=0.95, 95% CI: 0.84 to 1.08, P=0.43). The authors concluded that FA supplementation should not be recommended as a way to prevent or treat stroke or CVD.

Wang et al, 2007 (positive quality). This meta-analysis collected data from eight randomized trials of folic acid that had stroke reported as one of the endpoints. Relative risk (RR) was used as a measure of the effect of folic acid supplementation on the risk of stroke with a random effect model. Folic acid supplementation significantly reduced the risk of stroke by 18% (RR=0.82, 95% CI: 0.68, 1.00; P=0.045). In the stratified analyses, a greater beneficial effect was seen in those trials with a treatment duration of more than 36 months (RR=0.71; 96% CI: 0.57, 0.87; P=0.001). When stratifying the trials by fortification status, the RR for trials in regions with fortified grain was 0.89 (95% CI: 0.55, 1.42; P=0.62); and for trials in regions without fortification was 0.75 (0.62, 0.91; P=0.003). When the trials were stratified by history of stroke, the RR for the trials in which there was a history of stroke was 1.04 (95% CI: 0.84, 1.29; P=0.71); the RR for trials with such history was 0.75 (95% CI: 0.62, 0.94; P=0.002). These findings indicate that folic acid supplementation can effectively reduce risk of stroke in primary prevention. Studies are from the US, Canada, China, Australia, New Zealand and various European countries.

Randomized Clinical Trial

Saposnik et al, 2009 (positive quality). This RCT studied men and women 55 years of age or older who had a history of stroke, transient ischemic attack (TIA), vascular disease (coronary, cerebrovascular or peripheral vascular) or diabetes, as well as additional risk factors for atherosclerosis, irrespective of their homocysteine levels. Participants are from countries with mandatory folate fortification of food (Canada and the United States) and countries without mandatory folate fortification (Brazil, western Europe and Slovakia). Stroke occurred in 258 (4.7%) individuals during a mean of five years of follow-up. The geometric mean homocysteine concentration decreased by 2.2µmol per L in the vitamin therapy group and increased by 0.80µmol per L in the placebo group. The incidence rate of stroke was 0.88 per 100 person-years in the vitamin therapy group and 1.15 per 100 person-years in the placebo group (HR, 0.75; 95% CI: 0.59, 0.97). Vitamin therapy also reduced the risk of non-fatal stroke (HR, 0.72; 95% CI: 0.54, 0.95), but did not have an impact on neurological deficit at 24 hours (P=0.45) or functional dependence at discharge or at seven days (OR, 0.95, 95% CI: 0.57, 1.56). The authors concluded that lowering homocysteine with folic acid and vitamins B₆ and B₁₂ did reduce the risk of overall occurrence of stroke but not its severity.

[View table in new window](#)

Author, Year, Study Design, Class, Rating	Population/Sample description	Measurements of Intervention	Significant Outcomes
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<p>Miller ER, Juraschek S et al, 2010</p> <p>Study Design: Meta-analysis or Systematic Review</p> <p>Class: M</p> <p>Rating: </p>	<p>Fourteen trials published from 2002 to 2009 were selected, and they included 38,941 randomized participants (trials ranged from 240 to 12,064 participants; mean age ranged between 52.2 and 68.9 years).</p> <p>Nine trials recruited patients after acute CVD events, four trials had patients with pre-existing CVD or those at high risk of CVD and one trial targeted patients at low risk of CVD.</p>	<p>Pool estimates and 95% CIs of net Δ in homocysteine and log-transformed risk ratio for each clinical outcome were calculated using inverse-variance weighted random-effects models.</p>	<p>Supplementation had no effect on CVD or stroke (RR=1.02, 95% CI: 0.93 to 1.13, P=0.66; RR=0.95, 95% CI: 0.84 to 1.08, P=0.43). The risk ratio was not altered dramatically by exclusion of each trial serially.</p> <p>There was moderate heterogeneity across trials ($I^2=38\%$). There was no evidence of publication-related bias (P=0.63).</p> <p>There were NS differences between countries with and without food fortification in baseline homocysteine, net homocysteine \downarrow or primary clinical effects.</p> <p>Supplementation had no effect on pooled risk ratios, and there was no evidence of heterogeneity or publication bias, for the following specific outcomes:</p> <ul style="list-style-type: none"> • CVD (P=0.42; $I^2=0\%$) • CHD (P=0.42; $I^2=31\%$) • Stroke (P=0.43; $I^2=25\%$) • All-cause mortality (P=0.78; $I^2=0\%$).
<p>Bazzano I, Reynolds K et al, 2006</p> <p>Study Design: Meta-analysis</p>	<p>12 RCTs, representing 16,958 participants, both men and women.</p> <p>The studies were conducted in:</p>	<p>Clinical CVD events were reported as an end point.</p> <p>Folic acid supplementation was with</p>	<p>Relative risks (RR) for folic acid supplemental patients vs. control were 0.86, 95% CI: 0.71, 1.04 for stroke.</p>

<p>meta-analysis</p> <p>Class: M</p> <p>Rating: </p>	<ul style="list-style-type: none"> • US (two) • Australia and New Zealand (one) • Canada (one) • European countries (eight). 	<p>either placebo or usual care.</p> <p>Dosage of folic acid supplementation in the intervention groups ranged from 0.5mg per day to 15mg per day, for a duration ranging from six months to five years.</p>	<p>The RR was consistent among participants with pre-existing CVD or renal disease.</p>
<p>Wang X, Qin X et al, 2007</p> <p>Study Design: Meta-analysis</p> <p>Class: M</p> <p>Rating: </p>	<p>Eight RCTs, consisting of 16,841 individuals with pre-existing condition.</p> <p>The studies were conducted in:</p> <ul style="list-style-type: none"> • US and Canada (three) • Australia and New Zealand (one) • China (one) • European countries (three). 	<p>Stroke is reported as one of the endpoints.</p> <p>Relative risk (RR) was used as a measure of the effect of folic acid supplementation on the risk of stroke with a random effect model.</p> <p>The dosage of folic acid in the intervention groups ranged from 0.5mg per day to 15mg per day.</p>	<p>Folic acid supplementation significantly ↓ the risk of stroke by 18% (RR=0.82, 95% CI: 0.68, 1.00; P=0.045).</p> <p>In the stratified analyses, a greater beneficial effect was seen in those trials with a treatment duration of more than 36 months (RR=0.71; CI: 0.57 to 0.87; P=0.001).</p> <p>When stratified the trials by fortification status, the RR for trials in regions with fortified grain was 0.89 (95% CI: 0.55, 1.42; P=0.62); and for trials in regions without fortification was 0.75 (0.62, 0.91; P=0.003).</p> <p>When stratified the trials by history of stroke, the RR for the trials in which there was a history of stroke was 1.04 (0.84, 1.29; P=0.71); the RR for trials with such history was 0.75 (0.62, 0.94; P=0.002).</p>

<p>Saposnik G, Ray JG et al, 2009</p> <p>Study Design: Randomized clinical trial</p> <p>Class: A</p> <p>Rating: </p>	<p>5,522 men and women, 55 years of age or older, were recruited from 145 participating centers within 13 countries, including:</p> <ul style="list-style-type: none"> • Canada (N=3568), the US (N=414); countries with mandatory folic acid fortification policy • Brazil (N=265), Western Europe (N=426), and Slovakia (N=849); countries without mandatory folic acid fortification policy. 	<p>Measurements: Stroke events and homocysteine.</p> <p>Intervention: Daily combination of 2.5mg folic acid, 50mg vitamin B₆, and 1mg vitamin B₁₂, or matching placebo, for five years.</p>	<p>Stroke occurred in 258 (4.7%) individuals during a mean of five years of follow-up.</p> <p>The geometric mean homocysteine concentration ↓ by 2.2μmol per L in the vitamin therapy group, and ↑ by 0.80μmol per L in the placebo group.</p> <p>The incidence rate of stroke was 0.88 per 100 person-years in the vitamin therapy group and 1.15 per 100 person-years in the placebo group (HR, 0.75; 95% CI: 0.59,0.97).</p> <p>Vitamin therapy also ↓ the risk of nonfatal stroke (HR, 0.72 95% CI: 0.54-0.95), but did not impact on neurological deficit at 24 hours (P=0.45) or functional dependence at discharge or at seven days (OR, 0.95, 95% CI: 0.57-1.56).</p>
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Research Design and Implementation Rating Summary

For a summary of the Research Design and Implementation Rating results, [click here](#).

Worksheets

 [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.](#)

 [Miller ER 3rd, Juraschek S, Pastor-Barriuso R, Bazzano LA, Appel LJ, Guallar E. Meta-analysis of folic acid supplementation trials on risk of cardiovascular disease and risk interaction with baseline homocysteine levels. *Am J Cardiol* 2010. Abstracted prior to publication.](#)

 [Saposnik G, Ray JG, Sheridan P, McQueen M, Lonn E; Heart Outcomes Prevention Evaluation 2 Investigators. Homocysteine-lowering therapy and stroke risk, severity, and](#)

[disability: Additional findings from the HOPE 2 trial. *Stroke*. 2009; 40 \(4\): 1,365-1,372.](#)

 [Wang X, Qin X, Demirtas H, Li J, Mao G, Huo Y, Sun N, Liu L, Xu X. Efficacy of folic acid supplementation in stroke prevention: A meta-analysis. *Lancet*. 2007; 369 \(9,576\): 1,876-1,882.](#)