

# Effect of Folic Acid Supplementation on Risk of Cardiovascular Diseases

## A Meta-analysis of Randomized Controlled Trials

Lydia A. Bazzano, MD, PhD

Kristi Reynolds, PhD

Kevin N. Holder, MD

Jiang He, MD, PhD

**C**ARDIOVASCULAR DISEASE (CVD) is the leading cause of death in the United States and worldwide, accounting for 30.9% of global mortality and 10.3% of the global burden of disease.<sup>1</sup> Of all deaths in the United States, 37.3% (910 120, or 1 in every 2.7) are due to CVD.<sup>2</sup> According to the latest estimates, approximately 71.3 million persons in the United States have 1 or more forms of CVD, and the estimated annual direct and indirect cost of caring for these individuals is \$403.1 billion.<sup>2</sup> Hence, CVD is the most important clinical and public health challenge in the United States and worldwide.

As early as 1969, homocysteine was hypothesized to affect atherosclerotic processes.<sup>3</sup> Since that time, substantial evidence has accumulated linking homocysteine in plasma and serum to the risk of CVD.<sup>4-7</sup> Folate and cyanocobalamin (vitamin B<sub>12</sub>) are important regulators of the metabolism of homocysteine in the body, and studies have shown an inverse relationship between levels of these factors and levels of homocysteine in the blood.<sup>8-10</sup> Ob-

**Context** Epidemiologic studies have suggested that folate intake decreases risk of cardiovascular diseases. However, the results of randomized controlled trials on dietary supplementation with folic acid to date have been inconsistent.

**Objective** To evaluate the effects of folic acid supplementation on risk of cardiovascular diseases and all-cause mortality in randomized controlled trials among persons with preexisting cardiovascular or renal disease.

**Data Sources** Studies were retrieved by searching MEDLINE (January 1966-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*, and the text words *folic acid* and *folate*. Bibliographies of all retrieved articles were also searched, and experts in the field were contacted.

**Study Selection** From 165 relevant retrieved reports, 12 randomized controlled trials compared folic acid supplementation with either placebo or usual care for a minimum duration of 6 months and with clinical cardiovascular disease events reported as an end point.

**Data Extraction** Data on study design, characteristics of participants, changes in homocysteine levels, and cardiovascular disease outcomes were independently abstracted by 2 investigators using a standardized protocol.

**Data Synthesis** Studies including data from 16 958 participants with preexisting vascular disease were analyzed using a random-effects model. The overall relative risks (95% confidence intervals) of outcomes for patients treated with folic acid supplementation compared with controls were 0.95 (0.88-1.03) for cardiovascular diseases, 1.04 (0.92-1.17) for coronary heart disease, 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 preexisting cardiovascular or renal disease.

**Conclusions** 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.

JAMA. 2006;296:2720-2726

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servational epidemiologic studies have indicated that folate intake is inversely related to the risk of CVD, and randomized controlled trials have documented that dietary supplementation with folic acid reduces blood levels of homocysteine.<sup>11-14</sup> Recently, several ran-

**Author Affiliations:** Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine (Drs Bazzano, Reynolds, and He); and Department of Medicine, Tulane University School of Medicine (Drs Bazzano, Holder, and He), New Orleans, La. **Corresponding Author:** Lydia A. Bazzano, MD, PhD, Department of Epidemiology and Medicine, Tulane University School of Public Health and Tropical Medicine, 1440 Canal St, SL-18, New Orleans, LA 70112-2715 (lbazzano@tulane.edu).

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domized controlled trials have been published evaluating the effects of supplemental folic acid and B vitamins on the risk of CVD; all were conducted among patients with preexisting vascular disease.<sup>15-26</sup> In addition, several large trials are still under way.<sup>27-33</sup> In general, these trials have insufficient statistical power on their own and have provided inconsistent findings. We thus performed a meta-analysis of randomized clinical trials to qualify the relationship between folic acid supplementation and risk of CVD and all-cause mortality among persons with preexisting vascular disease.

## METHODS

### Study Selection

We conducted a literature search of the MEDLINE database (from January 1966 through 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*, and the text words *folic acid* and *folate*. The search was restricted to human studies. There were no language restrictions. We also performed a manual search of references cited by the published original studies and relevant review articles<sup>34-36</sup> and contacted experts in the area who may know of trials nearing completion.

The contents of 165 abstracts or full-text manuscripts identified through the literature search were reviewed independently by 2 investigators (L.A.B., K.N.H.) in duplicate to determine whether they met eligibility criteria for inclusion. Where discrepancies between investigators occurred for inclusion or exclusion, a third investigator (K.R.) was involved to conduct additional evaluation of the study, and discrepancies were resolved in conference. Studies were eligible for inclusion if (1) the study design was a randomized controlled trial; (2) the number of events for CVD, coronary heart dis-

ease (CHD), stroke, and/or all-cause mortality that occurred during the study were reported by intervention and control groups; (3) the intervention consisted of folic acid supplementation (with or without additional B vitamin supplementation); and (4) the intervention duration was at least 6 months. FIGURE 1 depicts the flow of studies in this analysis. Among 16 studies that met the inclusion criteria, 4 were excluded.<sup>27,37-39</sup> Two represented duplicate reports, and 2 reported only design or baseline results of a relevant trial. We included a total of 12 trials representing data from 16 958 participants in the present analysis.<sup>15-26</sup> All of these trials were conducted among patients with preexisting cardiovascular or renal disease.

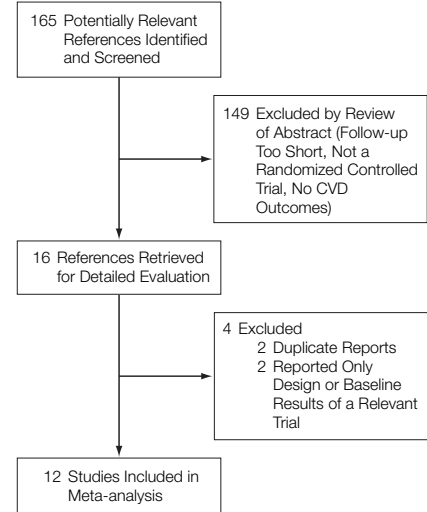
### Data Abstraction

All data were independently abstracted in duplicate by 2 investigators (L.A.B., K.N.H.) using a standardized data-collection form. Discrepancies were resolved by discussion with a third investigator (K.R.) and by referencing the original report. We did not contact authors to request additional information. Study characteristics recorded were as follows: first author's name; year of publication; source of publication; country of origin; inclusion criteria; exclusion criteria; outcomes; number enrolled; mean age in each group; percentage male; preexisting conditions among the study participants (CVD or end-stage renal disease [ESRD]); percentage with diabetes; mean levels of lipids and homocysteine prior to and after treatment or control periods; study design (factorial, parallel, crossover, other); type of blinding; number of intervention groups; intervention regimen; type of control (placebo, usual care, untreated); fortification of grains in the country of origin; duration of intervention; and number of CVD, CHD, stroke, and/or all-cause mortality events that occurred in each group.

### Statistical Analysis

Relative risk (RR) was used as a measure of the association between folic

**Figure 1.** Flow of Study Selection Process



CVD indicates cardiovascular disease.

acid supplementation and risk of CVD, CHD, stroke, or all-cause mortality. We calculated RRs for each trial based on the number of events in each group and used them for pooling analyses because not all trials reported RR for all outcomes. Calculated RRs and corresponding standard errors were logarithmically transformed to stabilize variance and normalize the distribution.

Some of the studies included in our meta-analysis differed in the units used for reporting levels of lipids (mg/dL vs mmol/L) and homocysteine (mg/L vs  $\mu\text{mol/L}$ ). Therefore, we converted these different units to mg/dL (for lipids) and  $\mu\text{mol/L}$  (for homocysteine), using the conversion factors 1 mg/dL = 0.0259 mmol/L for cholesterol, 1 mg/dL = 0.0113 mmol/L for triglycerides, and 1 mg/L = 7.397  $\mu\text{mol/L}$  for homocysteine.

For studies in which more than 1 folic acid intervention regimen existed, we report the mean dosage of folic acid supplementation and the mean level of homocysteine both prior to and after the intervention period for the folic acid intervention groups combined. In these studies, we also combined the number of events and participants across folic acid intervention groups to

**Table 1.** Baseline Characteristics of Participants in 12 Randomized Controlled Trials of Folic Acid Supplementation

Source	Participants, No.	Age, Mean (SD), y	Men, %	Preexisting Condition	Diabetes Mellitus, %	Total Cholesterol, Mean (SD), mg/dL	Homocysteine, Mean (SD), μmol/L
Baker et al, <sup>26</sup> 2002	1882	NR	NR	CHD	NR	NR	11.2 (6.9)
Schnyder et al, <sup>25</sup> 2002	553	62.6 (10.8)	80.5	CHD	27.5	213.0 (44.5)	11.3 (4.6)
Righetti et al, <sup>24</sup> 2003	81	64 (14)	55.7	ESRD	12.9	198.7 (90.0)	50.3 (6.0)
Lange et al, <sup>22</sup> 2004	636	61.4 (10.3)	77.0	CHD	14.7	197.6 (47.2)	12.6 (4.9)
Liem et al, <sup>23</sup> 2004	283	59.0	69.5	CHD	NR	279.9	NR
Toole et al, <sup>21</sup> 2004	3680	66.3	62.5	Stroke	29.1	201.9 (46.7)	13.4
Wrone et al, <sup>20</sup> 2004	510	60.2 (15.1)	50.0	ESRD	45.5	183.8 (44.0)	32.9 (20)
Liem et al, <sup>19</sup> 2005	593	65.2 (9.8)	78.0	CHD	9.0	177.6 (29.0)	12.1 (4.3)
Bonaa et al, <sup>16</sup> 2006	2815	63.0 (11.7)	73.7	CHD	9.8	222.7 (47.6)	13.1 (5.2)
Lonn et al, <sup>17</sup> 2006	5522	68.9 (6.9)	71.8	CHD	40.0	185.8 (32.6)	11.8
Righetti et al, <sup>15</sup> 2006	88	64.3 (11.7)	56.0	ESRD	16.2	196.0 (78.8)	35.0 (13.1)
Zoungas et al, <sup>18</sup> 2006	315	56 (13.5)	32.3	ESRD	23.2	200.8 (46.3)	27 (13.0)

Abbreviations: CHD, coronary heart disease; ESRD, end-stage renal disease; NR, not reported. SI conversion factor: To convert total cholesterol values to mmol/L, multiply by 0.0259.

**Table 2.** Study Design Characteristics of 12 Randomized Controlled Trials of Folic Acid Supplementation\*

Source	Blinding	Intervention Group Folic Acid Dosage	Control	Grain Fortification	Duration of Intervention, mo
Baker et al, <sup>26</sup> 2002	Double	5 mg/d	Placebo	No	20
Schnyder et al, <sup>25</sup> 2002	Double	1 mg/d	Placebo	No	6
Righetti et al, <sup>24</sup> 2003	Open	5 mg/d or 15 mg/d	Usual care	No	12
Lange et al, <sup>22</sup> 2004	Double	1.2 mg/d	Placebo	No	6
Liem et al, <sup>23</sup> 2004	Open	5 mg/d	Usual care	No	12
Toole et al, <sup>21</sup> 2004	Double	2.5 mg/d	Placebo	Yes	24
Wrone et al, <sup>20</sup> 2004	Double	5 mg/d or 15 mg/d	Usual care	Yes	24
Liem et al, <sup>19</sup> 2005	Open	0.5 mg/d	Usual care	No	42
Bonaa et al, <sup>16</sup> 2006	Double	0.8 mg/d	Placebo	No	36
Lonn et al, <sup>17</sup> 2006	Double	2.5 mg/d	Placebo	Yes	60
Righetti et al, <sup>15</sup> 2006	Open	5 mg/d or 5 mg/ every other day	Usual care	No	29
Zoungas et al, <sup>18</sup> 2006	Double	15 g/d	Placebo	Yes	43

\*All trials were of parallel-group design except for Bonaa et al,<sup>16</sup> which was of factorial design.

obtain a single event rate for folic acid supplementation.

Both fixed-effects and DerSimonian and Laird random-effects models<sup>40</sup> were used to calculate the pooled RR for folic acid supplementation compared with control. Statistical testing for heterogeneity between studies was not significant. Although both models yielded similar findings, results from the random-effects models are presented herein because of the different preexisting conditions, intervention regimens, intervention durations, and dietary intakes of folic acid that were involved in the original trials. Prestated subgroup analysis was

conducted by type of precondition (CVD or ESRD). To assess the potential for publication bias, we constructed funnel plots for each outcome in which the log RRs were plotted against their SEs.<sup>41</sup> In addition, the Begg rank correlation test was used to examine the association between effect estimates and their variances, and the Egger linear regression test, which regresses *z* statistics on the reciprocal of the SE for each study, was used to detect publication bias.<sup>42,43</sup> We also conducted a sensitivity analysis in which each trial was excluded in turn to evaluate the influence of that trial on the pooled estimate. All analyses

were conducted in STATA version 8.2 (StataCorp, College Station, Tex). We attempted to conform to QUOROM (Quality of Reporting of Meta-analyses) guidelines in the report of this meta-analysis.<sup>44</sup>

## RESULTS

The characteristics of the study participants and design of the randomized controlled trials are presented in TABLE 1 and TABLE 2, respectively. Of the 12 trials, 2 were conducted primarily in the United States, 1 in Australia and New Zealand, 1 in Canada, and 8 in European countries. The number of participants ranged from 81 in a study by Righetti et al<sup>24</sup> to 5522 in the HOPE-2 (Heart Outcomes Prevention Evaluation 2) trial reported by Lonn et al.<sup>17</sup> All trials included both men and women. Among the 12 trials, 11 reported CVD events, 11 reported CHD events, 8 reported stroke events, and 10 reported total mortality. The dosage of folic acid in the intervention groups among trials ranged from 0.5 mg/d to 15 mg/d. Trials were primarily parallel group in design, with 1 factorial design. Seven of the 12 trials provided a placebo pill, while others used usual care as control. The duration of intervention and follow-up ranged from 6 months to 5 years.

Net change in blood homocysteine levels and RRs (95% confidence inter-

vals [CIs]) for CVD, CHD, stroke, and all-cause mortality are presented by study in TABLE 3. All trials showed a reduction in homocysteine levels, ranging from  $-1.5$  to  $-26.0$   $\mu\text{mol/L}$ . There was no statistically significant relationship between net change in homocysteine level and RR for any of the clinical outcomes.

FIGURE 2 depicts the results from random-effects models pooling the RRs for CVD, CHD, stroke, and all-cause mortality. Pooled RR estimates were not statistically significant for any outcome. The total proportion of events for CVD was 18.3% among 7755 participants and 19.2% among 6685 participants in the folic acid supplementation and control groups, respectively; for CHD, the total proportion was 11.4% among 8962 and 10.6% among 7915, respectively; for stroke, the total proportion was 4.7% among 7432 and 5.8% among 6374, respectively; and for all-cause mortality, the total proportion was 12.0% among 8020 and 12.3% among 6975, respectively.

In sensitivity analysis, no significant heterogeneity was present for trials reporting CVD outcomes ( $P = .33$ ), and exclusion of any single trial from the analysis did not alter the overall findings of no effect of folic acid supple-

mentation on CVD. For trials reporting CHD outcomes, there was no significant heterogeneity for testing ( $P = .15$ ), and the exclusion of any single study from the analysis did not alter the overall findings of no effect of folic acid supplementation on CHD. For trials reporting stroke outcomes, no significant heterogeneity was present ( $P = .27$ ). In sensitivity analysis, only the exclusion of the VISP (Vitamin Intervention for Stroke Prevention) trial, reported by Toole et al,<sup>21</sup> led to a significant protective effect of folic acid supplementation on stroke (RR, 0.76; 95% CI, 0.63-0.93). Finally, for all-cause mortality, heterogeneity was minimal ( $P = .87$ ) and exclusion of any single trial from the analysis did not alter the overall findings of no effect of folic acid supplementation on all-cause mortality. Exclusion of the 2 trials (Schnyder et al<sup>25</sup> and Lange et al<sup>22</sup>) that had follow-up of less than 12 months did not alter the overall findings. There was no evidence of publication bias in funnel plots or by rank correlation or regression testing.

In an analysis stratified by type of pre-existing condition (CVD or ESRD) and type of control group (placebo or usual care), all 95% CIs for pooled RR estimates crossed unity and no statisti-

cally significant heterogeneity was detected on testing (TABLE 4).

## COMMENT

To date, 12 randomized controlled trials have reported on the effects of folic acid supplementation on risk of CVD events and all-cause mortality. In our current meta-analysis, we found no significant benefit or harm of folic acid supplementation on the risk of CVD, CHD, stroke, or all-cause mortality among persons with a history of CVD or ESRD.

Some of the first evidence linking elevated homocysteine levels to the development of CVD came from observations of persons with genetic abnormalities of homocysteine metabolism. Cases of homocystinuria from an inherited deficiency of cystathionine synthase were associated with thrombosis and vascular disease as early as 1964.<sup>45</sup> A few years later, in 1969, McCully<sup>3</sup> related defects in homocysteine metabolism to atherosclerosis, eventually leading to the hypothesis that even mildly elevated homocysteine levels could contribute to atherosclerotic heart and cerebrovascular diseases.

Observational evidence relating homocysteine levels in blood and risk of CVD is abundant and has changed substantially over time with the accrual of

**Table 3.** Net Changes of Homocysteine Levels and Clinical Outcomes in 12 Randomized Controlled Trials of Folic Acid Supplementation

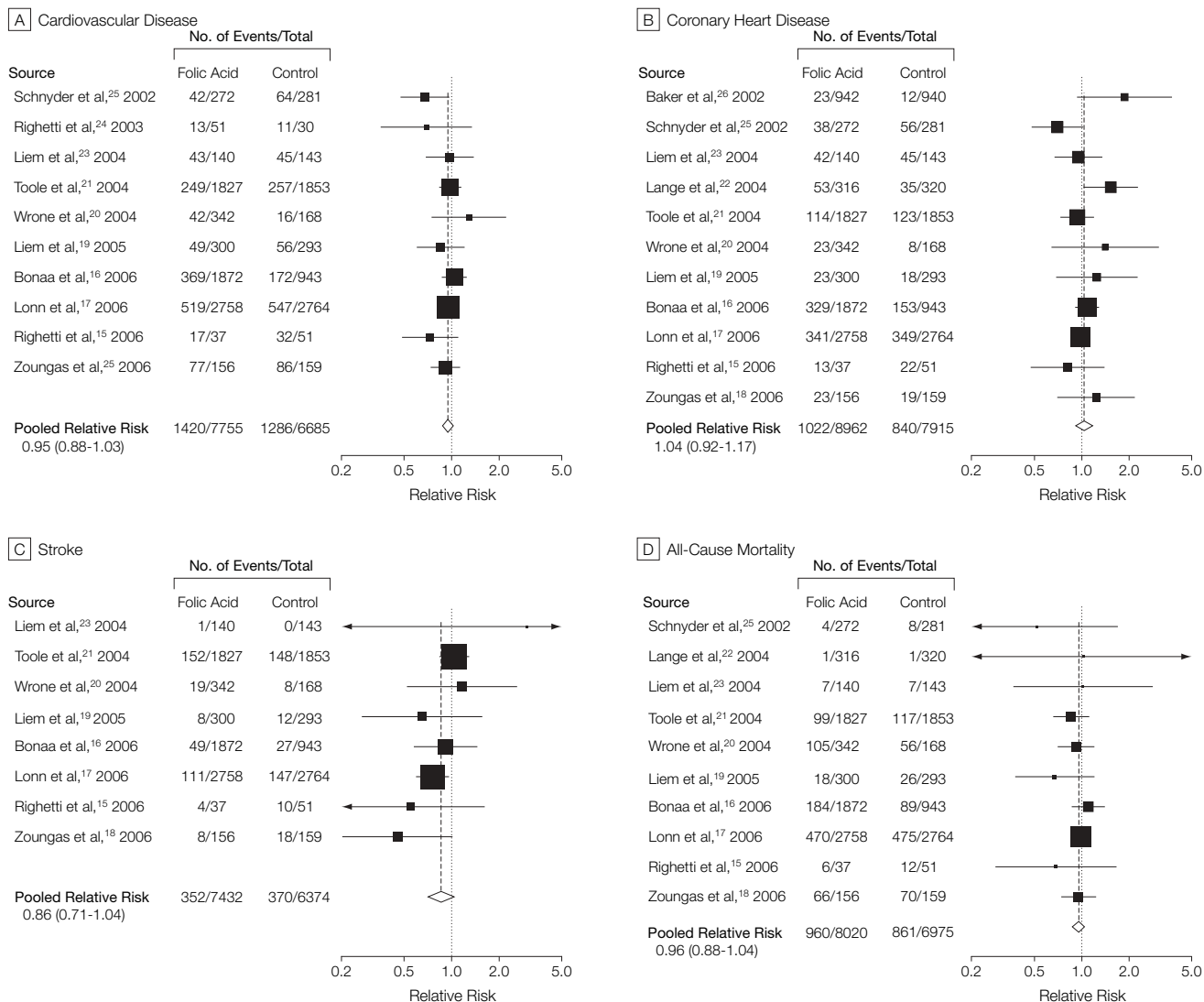
Source	Change in Homocysteine From Baseline		Relative Risk (95% CI)			
	Net, $\mu\text{mol/L}$ *	%	CVD	CHD	Stroke	All-Cause Mortality
Baker et al, <sup>26</sup> 2002	-1.5	-13.4	NR	1.91 (0.96-3.82)	NR	NR
Schnyder et al, <sup>25</sup> 2002	-2.9	-25.7	0.68 (0.48-0.96)	0.70 (0.48-1.02)	NR	0.52 (0.16-1.70)
Righetti et al, <sup>24</sup> 2003	-26.0†	-51.7	0.70 (0.36-1.35)	NR	NR	NR
Lange et al, <sup>22</sup> 2004	-3.6	-28.6	NR	1.53 (1.03-2.28)	NR	1.01 (0.06-16.12)
Liem et al, <sup>23</sup> 2004	NR	NR	0.98 (0.69-1.38)	0.95 (0.67-1.35)	3.06 (0.13-74.58)	1.02 (0.37-2.84)
Toole et al, <sup>21</sup> 2004	-2.1	-15.7	0.98 (0.84-1.16)	0.94 (0.73-1.20)	1.04 (0.84-1.29)	0.86 (0.66-1.11)
Wrone et al, <sup>20</sup> 2004	-3.6	-10.9	1.29 (0.75-2.22)	1.41 (0.65-3.09)	1.17 (0.52-2.61)	0.92 (0.71-1.20)
Liem et al, <sup>19</sup> 2005	-2.6	-21.5	0.85 (0.60-1.21)	1.25 (0.69-2.26)	0.65 (0.27-1.57)	0.68 (0.38-1.21)
Bonaa et al, <sup>16</sup> 2006	-3.8	-29.0	1.08 (0.92-1.27)	1.08 (0.91-1.29)	0.91 (0.58-1.45)	1.04 (0.82-1.32)
Lonn et al, <sup>17</sup> 2006	-3.2	-27.1	0.95 (0.85-1.06)	0.98 (0.85-1.13)	0.76 (0.59-0.96)	0.99 (0.88-1.11)
Righetti et al, <sup>15</sup> 2006	-15.1	-49.3	0.73 (0.49-1.10)	0.81 (0.47-1.40)	0.55 (0.19-1.62)	0.69 (0.28-1.67)
Zoungas et al, <sup>18</sup> 2006	-2.4	-8.9	0.91 (0.74-1.13)	1.23 (0.70-2.17)	0.45 (0.20-1.01)	0.96 (0.75-1.24)

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; NR, not reported.

\*Net change indicates (change in treatment group [preintervention - postintervention] - change in control group [preintervention - postintervention]); where information was only available for intervention (Baker et al<sup>26</sup>), net change denotes (preintervention - postintervention).

†Postintervention homocysteine level was estimated from a graph.

**Figure 2.** Relative Risk Estimates for Cardiovascular Disease, Coronary Heart Disease, Stroke, and All-Cause Mortality (Folic Acid Supplementation vs Control), by Trial and Pooled



Error bars indicate 95% confidence intervals (CIs). Size of data markers indicates each trial's contribution to the pooled estimate.

**Table 4.** Pooled Relative Risk of CVD, CHD, Stroke, and All-Cause Mortality, by Subgroups of Trials Defined by Characteristics of Participants and Study Design

	Relative Risk (95% CI)			
	CVD	CHD	Stroke	All-Cause Mortality
Preexisting 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)
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)
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)

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; ESRD, end-stage renal disease.

large studies. A 1995 meta-analysis of 29 epidemiologic studies indicated that elevated levels of homocysteine are related to CHD and stroke.<sup>46</sup> In 2002, an updated meta-analysis focusing on prospective observational studies confirmed this association, with an estimated 25% reduction (approximately 3 μmol/L) in homocysteine levels associated with 11% (95% CI, 4%-17%) lower risk of CHD and 19% (95% CI, 5%-31%) lower risk of stroke.<sup>47</sup> Observational studies may have overesti-

mated the effect size associated with folic acid supplementation on CVD. Clinical trials, if appropriately conducted, should provide the best evidence for a causal association.

The statistical power of clinical trials of folic acid supplementation and risk of CVD has been questioned in light of mandatory folic acid fortification of cereal grains in the United States and Canada and voluntary fortification of some foods in Australia and New Zealand.<sup>36</sup> Even in our meta-analysis with a total of 16 958 participants, we had only 84.2% statistical power to detect a 10% reduction in CVD risk and 64.1% power to detect a 10% reduction in total mortality. There are several large trials of folic acid supplementation ongoing, and their results will be pooled by the B-Vitamin Treatment Trialists' Collaboration.<sup>34</sup> A combined analysis of these trials with approximately 52 000 participants should have sufficient power to determine whether lowering homocysteine levels by approximately 25% reduces the risk of CHD by approximately 10%. In addition, it is important to note that in countries where food is fortified, the relative contributions of B vitamins to overall lowering of homocysteine levels may increase proportionally.

There are many factors that may contribute to the discrepancy in results of observational studies and clinical trials of folic acid supplementation for the secondary prevention of vascular disease. First among them is the possibility of confounding in observational studies. Despite the most comprehensive measurement and adjustment strategies, the uncontrolled or residual confounding in observational studies of dietary intake or supplementation is always a concern. Healthy lifestyle effects associated with dietary intake or supplement use cannot be completely adjusted for in observational studies. Second, it is possible that folic acid supplementation may have a protective effect in primary rather than secondary prevention. To date, trials have tested the effects of folic acid supplementation in secondary prevention

only. Third, it is possible that populations with specific genetic backgrounds, or populations with folate deficiency, may benefit from folic acid supplementation. Future clinical trials of folic acid supplementation are needed in special subgroups. Moreover, the duration of follow-up may also contribute to differences in the results of observational studies and clinical trials. The longest follow-up among trials included in this meta-analysis was 5 years.<sup>19</sup>

This meta-analysis has several important strengths. We found no evidence of heterogeneity or publication bias on testing, and our sensitivity analysis showed minimal influence on the combined results for any single trial. Finally, given that our meta-analysis draws on the results of randomized controlled trials, findings are less likely to be subject to confounding and bias than those from observational studies. One limitation of our study is the lack of data from multiple large trials that have yet to report results. While we are waiting for more data from ongoing large trials,<sup>27-34,47</sup> our findings that folic acid supplementation does not lower risk of CVD and all-cause mortality among persons with a history of vascular disease should be interpreted in the context of evolving evidence in this area.

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.

**Author Contributions:** Dr Bazzano had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Bazzano, Reynolds, He.

**Acquisition of data:** Bazzano, Holder.

**Analysis and interpretation of data:** Bazzano, Reynolds, He.

**Drafting of the manuscript:** Bazzano.

**Critical revision of the manuscript for important intellectual content:** Bazzano, Reynolds, Holder, He.

**Statistical analysis:** Bazzano, Reynolds.

**Administrative, technical, or material support:** He.

**Study supervision:** He.

**Financial Disclosures:** None reported.

**Funding/Support:** Dr Bazzano was supported by a Building Interdisciplinary Research Careers in Women's Health Scholarship (K12 HD43451) from the National Heart, Lung, and Blood Institute, National Institutes of Health (NIH). Dr Reynolds was partially supported by grant P20-RR17659 from the National Center for Research Resources, NIH.

**Role of the Sponsors:** The NIH had no role in the design and conduct of the study; the collection, analysis, and interpretation of the data; or the preparation, review, and approval of the manuscript.

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