Systematic Review and Meta-Analysis

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The effect of folic acid in patients with cardiovascular disease

A systematic review and meta-analysis

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Abstract

Background: The effectiveness of folic acid supplementation in stroke risk has been investigated, however, the available results are inconclusive and conflicting. The purpose of this systemic review and meta-analysis was to assess the effect of folic acid in patients with cardiovascular disease (CVD).

Methods: By searching the PubMed, EMBASE, and Cochrane library databases, we conducted a meta-analysis to evaluate effect of folic acid supplementation in patients with CVD. All-cause mortality, cardiovascular mortality, the risk of coronary heart disease (CHD) and stroke were summarized; hazard ratios (HR), the relative risk (RR) and its 95% confidence interval (CI) were also calculated. Fixed effects models were used to combine the data. A total of 12 randomized controlled trials, which involved 47,523 participants, met the inclusion criteria in this systematic review and meta-analysis.

Results: Our meta-analysis showed that cardiovascular patients who received folic acid therapy had significantly decreased risk of stroke (RR = 0.85, 95% CI = 0.77–0.94, $P_{heterogeneity} = .347$, $I^2 = 10.6\%$) compared with patients who received control treatment. However, no significant difference in all-cause mortality (HR, 0.97, 95% CI, 0.86–1.10, $P_{heterogeneity} = .315$, $I^2 = 15.4\%$), cardiovascular mortality (HR, 0.87, 95% CI, 0.66–1.15, $P_{heterogeneity} = .567$, $I^2 = 0$) and risk of CHD (RR, 1.04, 95% CI, 0.99–1.10, $P_{heterogeneity} = .725$, $I^2 = 0$) were found between the 2 groups.

Conclusion: This meta-analysis suggested that folic acid supplementation significantly reduced the risk of stroke in patients with CVD.

Abbreviations: CHD = coronary heart disease, CI = confidence interval, HR = hazard ratios, PRISMA = preferred reporting items for systematic reviews and meta-analyses, RCT = randomized controlled trial, RR = the relative risk.

Keywords: cardiovascular disease, folic acid, homocysteine, meta-analysis, systematic review

1. Introduction

Cardiovascular disease (CVD), a severe disease burden in both developed and developing countries, will be one of the most prominent global public health challenges in the 21st century.[1] In particular in developing countries the CVD burden is growing. Between 1990 and 2020, coronary heart disease (CHD) alone is anticipated to increase by 120% for women and by 137% for men in developing countries.[2] Numerous studies have suggested that homocysteine may be a modifiable risk factor for CVD. In experimental studies, homocysteine causes oxidative stress, damages endothelium, and enhances thrombogenicity.[3–5] In general, epidemiologic studies have shown an independent and graded association between homocysteine levels and cardiovascular risk.[6–9] The observational data suggest that even mild-to-moderate elevations in homocysteine increase cardiovascular risk; this observation is important, because such increases are common and can easily be corrected with safe and inexpensive therapy. Folic acid is the most important dietary determinant of homocysteine; daily supplementation with 0.5 to 5.0 mg typically lowers plasma homocysteine levels by approximately 25 percent.[10] A meta-analysis of observational studies showed that, with a 25% lower homocysteine level, the risk of ischemic heart disease and stroke could be reduced by 11% and 19%, respectively.[11]

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YW and YJ contributed equally to this work.

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The effectiveness of folic acid supplementation in stroke risk has been investigated by 2 previous meta-analyses[12,13]; however, the available results are inconclusive and conflicting. To comprehensively assess the effect of folic acid supplementation in CVD, we performed this systematic review and meta-analysis.

2. Methods

The present meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[14]

2.1. Search strategy

We searched for relevant studies that were published up to Nov. 2017 through the PubMed, Embase, and Cochrane Library databases with the following terms and their combinations: "folic acid", "cardiovascular", and "homocysteine". Two reviewers independently conducted the search and all disagreements about eligibility were resolved through discussion with the third expert. There were no search limitations concerning study design. Only publications in English language were considered. All scanned abstracts, studies, and citations were reviewed. Moreover, references of the retrieved manuscripts were also manually cross-searched for further relevant publications.

2.2. Selection criteria

The inclusion criteria included:

(1) patients with CVD;
(2) at least 2 comparison groups, where one received folic acid supplementation;
(3) randomized controlled trials (RCT);
(4) having at least 1 of following outcomes: all-cause mortality, cardiovascular mortality, the risk of CHD, and stroke.

The exclusion criteria included:

(1) The studies which used the same population or overlapping database;
(2) The studies with animal models.

2.3. Data extraction and quality assessment

Two investigators independently extracted all the available data from the included studies according to the descriptions provided by the authors of the included studies. Any disagreement was subsequently resolved by discussion with a third author. The following data from each study were extracted independently by 2 authors: first author's name, year of publication, study location, age and sex of the study population, interventions, follow-up time, sample size, and outcomes. We evaluated the quality of RCTs with the Cochrane Collaboration's tool for assessing the risk of bias.[15] The assessment included the following components: random sequence generation, allocation concealment, blinding of patients, and study personnel, blinding of outcome assessment, completeness of outcome data, selective reporting of outcomes, and other threats to validity (unequal treatment comparisons, early termination of trial, industry sponsor as author or involved in data handling and analysis).

2.4. Statistical analysis

The meta-analysis was conducted using Stata 12 (Stata-Corp, College Station, TX). We calculated hazard ratios (HR) of mortality or the risk ratio (RR) and 95% confidence intervals for all-cause mortality, cardiovascular mortality, the risk of CHD, and stroke. The heterogeneity of the studies was assessed using the Cochran's Q test (considered significant for $P < .10$) and was quantified by the I^2 statistic.[16] Primary analyses were performed using a fixed effects model (Mantel–Haenszel method), and if there was study heterogeneity ($P < .10$), a random effects model was used.[17] Relative influence from each study on the pooled estimate was assessed by omitting one study at a time for sensitivity analysis. Publication bias was evaluated by visual inspection of symmetry of funnel plot and assessment of Begg and Egger test ($P < .05$ was regarded as representative of statistical significance).[18]

3. Results

3.1. Study selection

As shown in Figure 1, we identified 628 studies from our electronic search. We found additional 4 records by hand searching reference lists from other relevant articles. According to inclusion criteria, 589 studies remained after removing the duplicates. Amongst these, 532 records that were screened for titles or abstracts, were excluded due to being irrelevant. Among the remaining 57 papers, 36 articles were excluded for letters, reviews and meta-analysis, whereas 21 remaining studies remained were evaluated in detail. Subsequently, 9 more studies were excluded; 3 that included the same patients, 4 that included patients with kidney diseases and 2 that not present the usable data. Finally, we identified 12 RCTs[19–30] including a total of 47,523 participants that fitted our inclusion criteria.

3.2. Characteristics of the studies

The 12 RCTs assessed 47,523 participants, including 24,585 participants who received folic acid supplementation and 22,938 controls. Study characteristics are summarized in Table 1. The included studies were published between 2002 and 2015. The mean age of patients in each study varied between 59.1 and 68.9 years old (Table 1). The 12 RCTs were also assessed qualitatively using tools recommended by the Cochrane Collaboration for the risk of bias. A graph and summary of selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias identified in each individual RCT is shown in Figure 2A and 2B.

3.3. Quantitative synthesis

All-cause mortality: there were four articles involving 25,282 participants which provided data on all-cause mortality. The heterogeneity test indicated there was no statistical heterogeneity ($P_{\text{heterogeneity}} = .315$, $I^2 = 15.4\%$), and the outcome showed that all-cause mortality was not significantly different between the 2 groups (HR, 0.97, 95% CI, 0.86–1.10, $P = .639$) (Fig. 3A).

Cardiovascular mortality: there were 3 articles involving 22,963 participants which provided data on cardiovascular mortality. The heterogeneity test indicated there was no statistical heterogeneity ($P_{\text{heterogeneity}} = .567$, $I^2 = 0$), and the outcome showed that cardiovascular mortality was not significantly

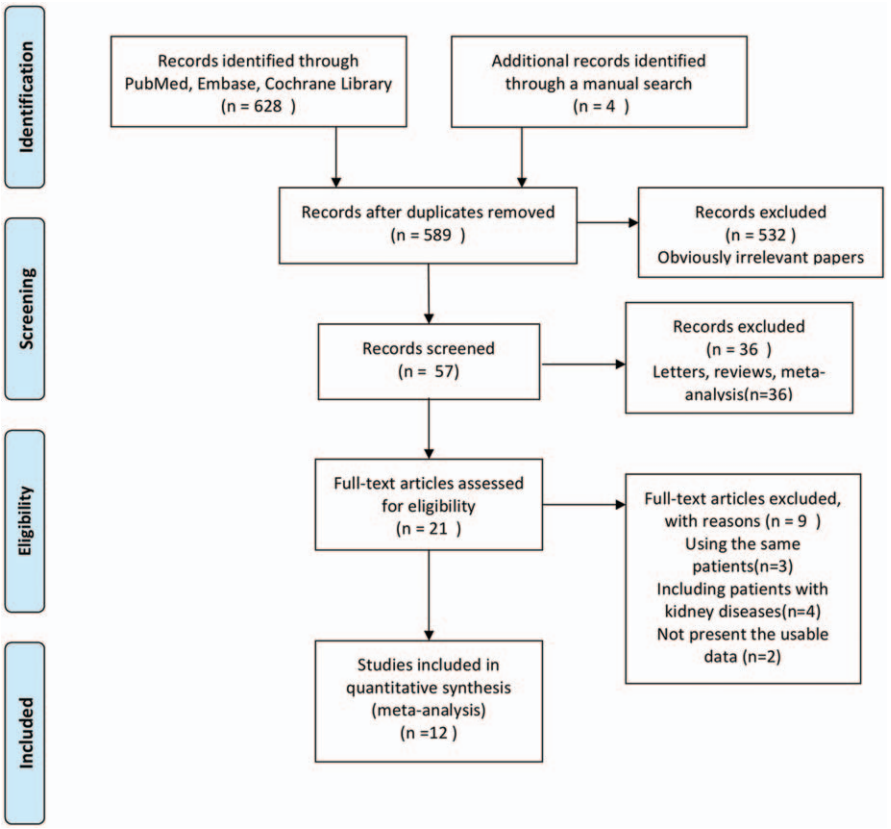

Figure 1. Flow diagram of studies identification.

Table 1

Characteristics of the studies included in this meta-analysis.

Authors/year of publication	Country	Male (%)	Mean age	Folic acid (mg/day)	If plus other Vitamin B	Intervention		Follow-up	Outcomes assessed
						Folic acid	Control		
Schnyder/2002[19]	Switzerland	FA:79 Con:82	FA: 63.4±10.6Y; Con:61.8±11Y	1	Yes	272	281	6–12 mo	All cause mortality, cardiovascular mortality, CHD
Lange/2004[20]	Netherlands	FA:24 Con:30	FA: 61.4±9.8Y; Con:61.3±10.8Y	1.2	Yes	316	320	7 mo	CHD
Liem/2004[21]	Netherlands	FA:69 Con:70	FA: 59Y; Con:59Y	5	No	140	143	12 mo	CHD, stroke
Liem/2005[22]	Netherlands	FA:76 Con:80	FA: 64.9±9.9Y; Con:65.5±9.7Y	0.5	No	300	293	42 mo	CHD, stroke
Bonaa/2006[23]	Norway	FA:74 Con:75	FA: 63.4±11.7Y; Con:62.6±11.4Y	0.8	No	1872	943	40 mo	CHD, stroke
Lonn/2006[24]	Canada	FA:71.1 Con:72.4	FA: 68.8±7.1Y; Con:68.9±6.8Y	2.5	Yes	2758	2764	60 mo	CHD, stroke
Righetti/2006[25]	Italy	FA:64.9 Con:49	FA: 63.9±1.6Y; Con:65.1±1.9Y	2.5	Yes	37	51	29 mo	CHD, stroke
Ebbing/2008[26]	Norway	FA:80.8 Con:76.5	FA: 61.5±10.1Y; Con:62±9.9Y	0.8	Yes	1540	779	38 mo	All cause mortality, CHD, stroke
Imasa/2009[27]	Philippines	FA:58.6 Con:57.3	FA: 59.1Y; Con:59.6Y	1	Yes	116	124	6 mo	CHD
Armitage/2010[28]	UK	82.9	64.2±8.9Y	2	Yes	6033	6031	80 mo	CHD, stroke
Lamas/2013[29]	USA	FA:83 Con:82	FA: 65Y; Con:65Y	0.8	Yes	853	855	60 mo	All cause mortality, cardiovascular mortality, CHD, stroke
Huo/2015[30]	China	FA:41 Con:41.1	FA: 60±7.5Y; Con:60±7.6Y	0.8	No	10348	10354	60 mo	All cause mortality, cardiovascular mortality, CHD, stroke

CHD = coronary heart disease, Con = Control, FA = Folic acid, M = months, NA = Not available, Y = years.

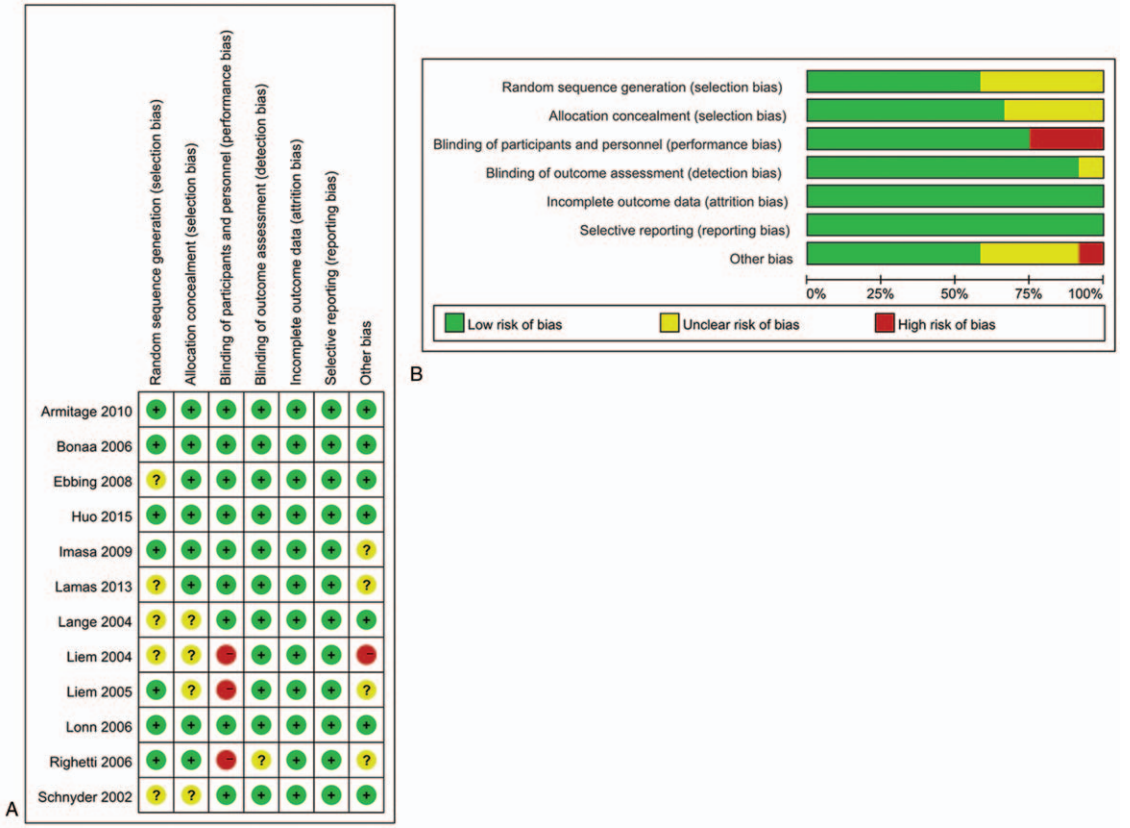

Figure 2. Risk of bias assessments for the randomized trials included in the meta-analysis. (A) Risk of bias summary; (B) Risk of bias graph. *Symbols*. (+): low risk of bias; (?): unclear risk of bias; (-): high risk of bias.

different between the 2 groups (HR, 0.87, 95% CI, 0.66–1.15, $P=.321$) (Fig. 3B).

Risk of CHD: There were 12 articles involving 47,523 participants which provided data of risk of CHD. The heterogeneity test indicated there was no statistical heterogeneity ($P_{heterogeneity}=.725$, $I^2=0$), and the outcome showed that risk of CHD was not significantly different between the 2 groups (RR, 1.04, 95% CI, 0.99–1.10) (Fig. 3C). We probed into detailed results from subgroup analyses stratified by intervention regimen (folic acid only or plus B vitamins) (Figure S1A, http://links.lww.com/MD/D234), daily folic acid dosage (<2 mg/day, or ≥2 mg/day) (Figure S1B, http://links.lww.com/MD/D234), and follow-up time (<40 months, or ≥40 months) (Figure S1C, http://links.lww.com/MD/D234). All subgroup results were totally consistent with the overall results.

Risk of stroke: There were nine articles involving 46,094 participants which provided data on risk of stroke. The heterogeneity test indicated there was no statistical heterogeneity ($P_{heterogeneity}=.347$, $I^2=10.6\%$), and the outcome showed that risk of stroke was significantly reduced in folic acid group compared with control groups (RR, 0.85, 95% CI, 0.77–0.94) (Figure 3D). When stratified by intervention regimen, a significantly reduced risk of stroke was found only in folic acid group (RR, 0.80, 95% CI, 0.70 to 0.93, $P_{heterogeneity}=.750$, $I^2=0\%$) (Figure S2A, http://links.lww.com/MD/D234), but not in plus B vitamins group. When stratified by daily folic acid dosage, a significantly reduced risk of stroke was found in dosages <2 mg/day group (RR, 0.79, 95% CI, 0.69–0.91, $P_{heterogeneity}=.841$, $I^2=0\%$) (Fig. S2B, http://links.lww.com/MD/D234), but not in dosages ≥2 mg/day group. With reference to follow-up time, subgroup analysis revealed a significantly reduced risk of stroke with follow-up time ≥40 months (RR, 0.86, 95% CI, 0.78–0.95, $P_{heterogeneity}=.182$, $I^2=33.9\%$) (Fig. S2C, http://links.lww.com/MD/D234), but not with follow-up time <40 months.

3.4. Sensitivity analysis

Sensitivity analyses were performed to assess the influence of individual dataset on the pooled RRs by sequentially removing each eligible study. As seen in Figure 4, any single study was omitted, while the overall statistical significance for all-cause mortality (Figure 4A), cardiovascular mortality (Figure 4B), CHD (Figure 4C), stroke (Figure 4D) did not change, indicating the statistical robustness of the obtained results.

3.5. Publication bias

Begg funnel plot and Egger test were performed to assess publication bias among the literatures. As shown in Figure 5, there was no evidence of publication bias for all-cause mortality (Begg test $P=1.000$; Egger test $P=.932$) (Figure 5A), cardiovascular mortality (Begg test $P=1.000$; Egger test $P=.555$) (Figure 5B), risk of CHD (Begg's test $P=.537$; Egger's test $P=.754$) (Figure 5C) and stroke (Begg test $P=.754$; Egger test $P=.446$) (Figure 5D).

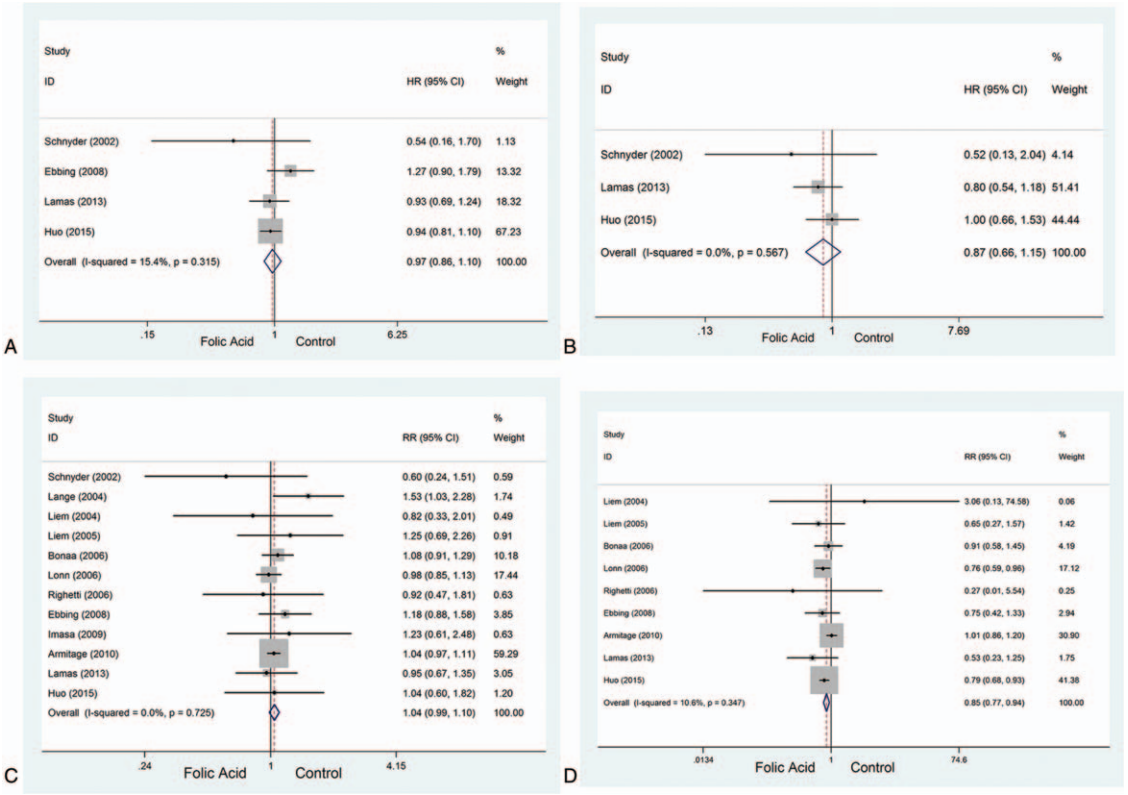

Figure 3. The effect of folic acid in patients with cardiovascular disease. (A) All-cause mortality; (B) Cardiovascular mortality; (C) Coronary heart disease; (D) Stroke.

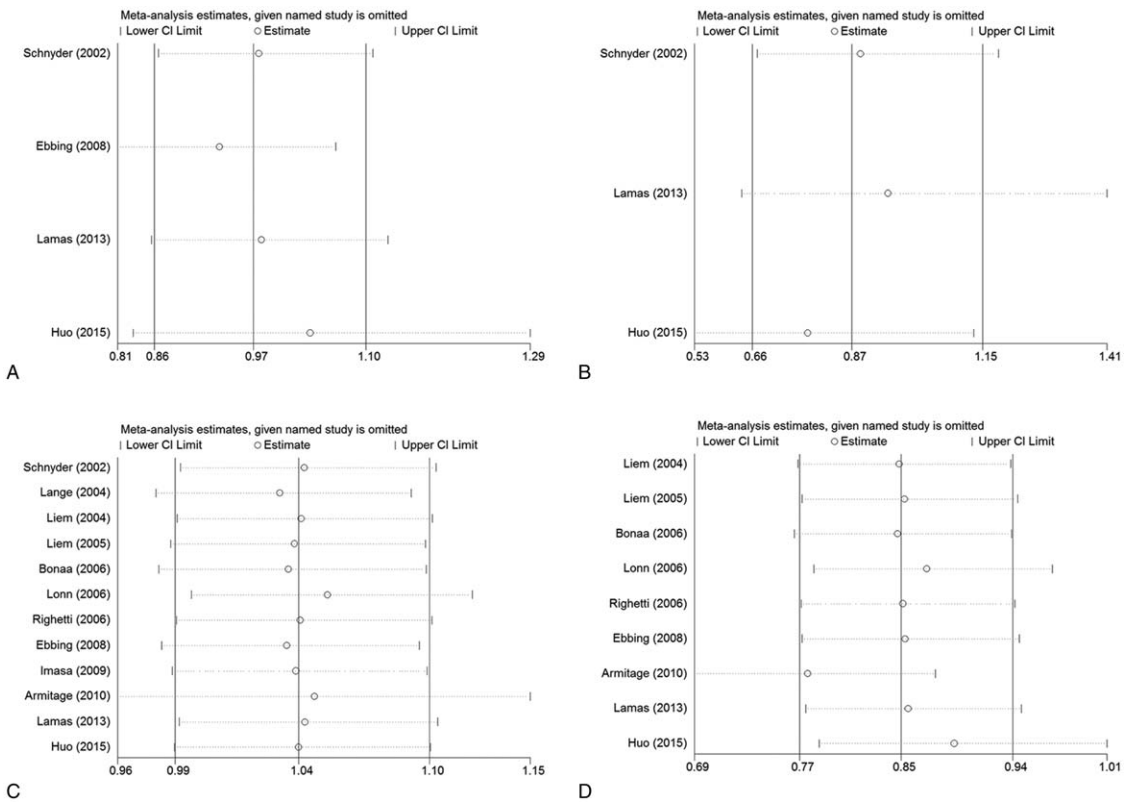

Figure 4. Sensitivity analysis of the effect of folic acid in patients with with cardiovascular disease. (A) All-cause mortality; (B) Cardiovascular mortality; (C) Coronary heart disease; (D) Stroke.

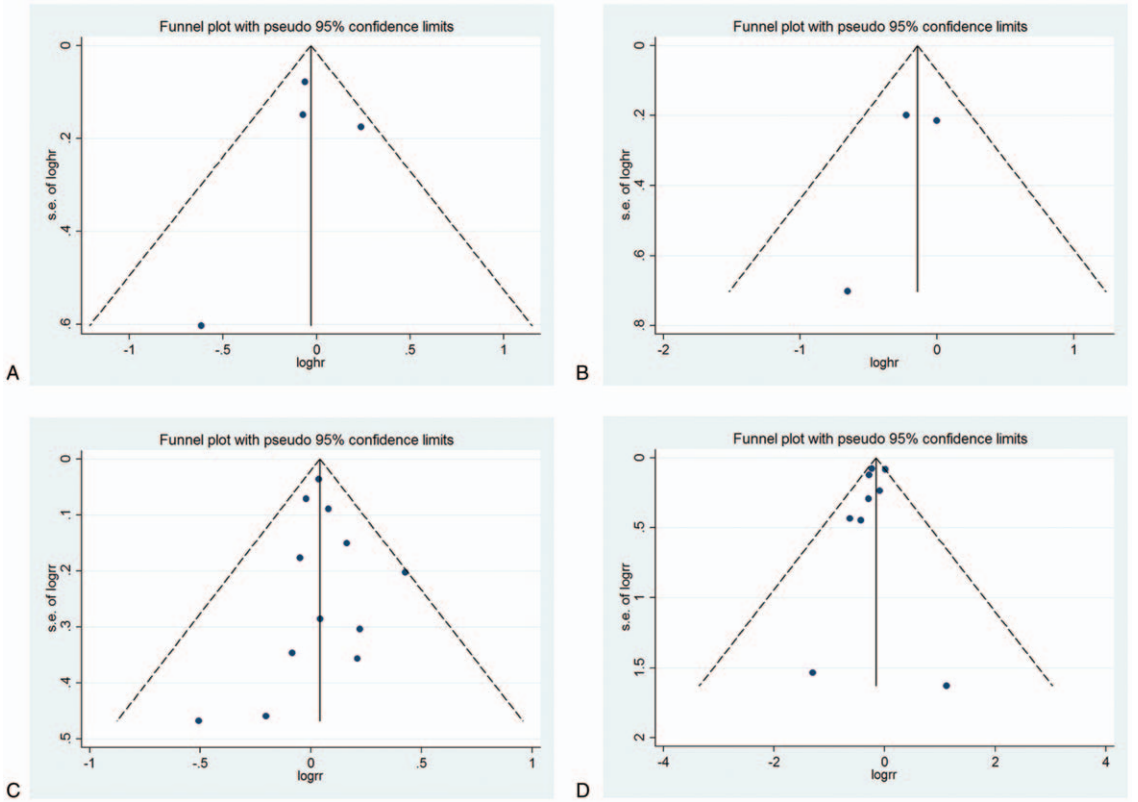

Figure 5. Funnel plot for publication bias test. Each point represents a separate study for the indicated association. (A) All-cause mortality; (B) Cardiovascular mortality; (C) Coronary heart disease; (D) Stroke.

4. Discussion

In this study, we evaluated the efficacy and safety of folic acid supplementation in patients with CVD by systematic review and meta-analysis. To the best of our knowledge, this is the largest comprehensive meta-analysis assessing the effect of folic acid supplementation in patients with CVD, which involved 47,523 participants from 12 RCT studies. Our meta-analysis showed that cardiovascular patients who received folic acid therapy had significantly decreased risk of stroke compared with patients who received control treatment. However, there were no significant differences in all-cause mortality, cardiovascular mortality and risk of CHD between the 2 groups.

The effectiveness of folic acid supplementation in stroke prevention is not well established.[31] Clarke et al[12] have reported a meta-analysis based on 7 trials identifying no significant benefit of folic acid supplementation on stroke risk. Our systematic review and meta-analysis, which included 12 RCTs and 47,523 participants, found that folic acid supplementation significantly reduced the risk of stroke. The varying strength of the association between folic acid supplementation and stroke risk across different trials may be due to differences in study design and study participant characteristics. Li et al[13] have performed a meta-analysis of folic acid supplementation and risk of CVD, reveling a 10% lower risk of stroke with folic acid supplementation, which is consistent with our study. Compared with their work, we focused on patients with CVD, while Li et al have analyzed a variety of patients, including heart transplant, esophageal dysplasia, end-stage renal disease, and atherosclerosis, etc. Recently, Tian et al[32] conducted a meta-analysis based on 11 RCT involving 65,790 patients with CVD and found that the incidence of stroke was significantly reduced in patients with preexisting CVD, RR 0.90 (95% CI 0.84–0.97, $P=.005$). Another meta-analysis conducted by Zhao et al[33] found that folic acid supplementation could reduce the stroke risk in regions without folic acid fortification, particularly in trials using a relatively low dosage of folic acid and with low vitamin B12 levels.

Meanwhile, some limitation of this meta-analysis should be pointed out. First, the characteristics of participants, the duration and intensity of treatment, and other design features varied across studies, which could have influenced the results, thereby limiting comparability to some extent. Second, because pooled data that were either published or provided by individual study authors were used in the analysis, and data from individual patients or original data were unavailable, our attempts to perform more detailed relevant analysis and to obtain more comprehensive results were restricted. Third, the definitions of the CVD outcomes were somewhat heterogeneous in the selected trials, and that could have influenced the interpretation of the results; therefore, we examined the effect of folic acid supplementation on stroke and CHD separately. Finally, several studies had small sample sizes and short follow-up periods which could have reduced the statistical power.

5. Conclusions

In summary, our results demonstrated that the folic acid supplementation significantly reduced the risk of stroke in patients with CVD. However, further well-designed large studies might be necessary to clarify the risk of stroke in folic acid group compared with control.

Author contributions

Conceptualization: Yuan Wang, Yang Jin.
Data curation: Yuan Wang, Yang Jin, Yao Wang, Li Li, Yanhong Liao, Dan Yu.
Formal analysis: Yao Wang, Li Li, Yanhong Liao, Yun Zhang.
Resources: Yun Zhang.
Writing – original draft: Yuan Wang, Yang Jin, Dan Yu.

References

[1] Lopez AD, Mathers CD, Ezzati M, et al. Global Burden of Disease and Risk Factors. New York: Oxford University Press; 2006.
[2] Leeder S, Raymond S, Greenberg H, et al. A Race Against Time: The Challenge of Cardiovascular Disease in Developing Economies. New York: The Centre for Global Health and Economic Development, Columbia University; 2004.
[3] Welch GN, Loscalzo J. Homocysteine and atherothrombosis. N Engl J Med 1998;338:1042–50.
[4] Harker LA, Harlan JM, Ross R. Effect of sulfinpyrazone on homocysteine-induced endothelial injury and arteriosclerosis in baboons. Circ Res 1983;53:731–9.
[5] Harker LA, Slichter SJ, Scott CR, et al. Homocystinemia. Vascular injury and arterial thrombosis. N Engl J Med 1974;291:537–43.
[6] Eikelboom JW, Lonn E, Genest JJr, et al. Homocyst(e)ine and cardiovascular disease: a critical review of the epidemiologic evidence. Ann Intern Med 1999;131:363–75.
[7] Boushey CJ, Beresford SA, Omenn GS, et al. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. Probable benefits of increasing folic acid intakes. JAMA 1995;274:1049–57.
[8] Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. BMJ 2002;325:1202.
[9] Klerk M, Verhoef P, Clarke R, et al. MTHFR 677C–>T polymorphism and risk of coronary heart disease: a meta-analysis. JAMA 2002;288: 2023–31.
[10] Ciaccio M, Bivona G, Bellia C. Therapeutical approach to plasma homocysteine and cardiovascular risk reduction. Ther Clin Risk Manag 2008;4:219–24.
[11] Collaboration HSHomocysteine and risk of ischemic heart disease and stroke: a meta-analysis. JAMA 2002;288:2015–22.
[12] Clarke R, Halsey J, Lewington S, et al. Effects of lowering homocysteine levels with B vitamins on cardiovascular disease, cancer, and cause-specific mortality: Meta-analysis of 8 randomized trials involving 37 485 individuals. Arch Intern Med 2010;170:1622–31.
[13] Li Y, Huang T, Zheng Y, et al. Folic acid supplementation and the risk of cardiovascular diseases: a meta-analysis of randomized controlled trials. J Am Heart Assoc 2016;5:
[14] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264–9. w264.
[15] Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[16] Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Ann Intern Med 1997;127:820–6.
[17] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
[18] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
[19] Schnyder G, Roffi M, Flammer Y, et al. Effect of homocysteine-lowering therapy with folic acid, vitamin B12, and vitamin B6 on clinical outcome after percutaneous coronary intervention: the Swiss Heart study: a randomized controlled trial. JAMA 2002;288:973–9.
[20] Lange H, Suryapranata H, De Luca G, et al. Folate therapy and in-stent restenosis after coronary stenting. N Engl J Med 2004;350:2673–81.
[21] Liem AH, van Boven AJ, Veeger NJ, et al. Efficacy of folic acid when added to statin therapy in patients with hypercholesterolemia following acute myocardial infarction: a randomised pilot trial. Int J Cardiol 2004;93:175–9.
[22] Liem A, Reynierse-Buitenwerf GH, Zwinderman AH, et al. Secondary prevention with folic acid: results of the Goes extension study. Heart 2005;91:1213–4.
[23] Bonaa KH, Njolstad I, Ueland PM, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. N Engl J Med 2006;354:1578–88.
[24] Lonn E, Yusuf S, Arnold MJ, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. N Engl J Med 2006;354: 1567–77.
[25] Righetti M, Serbelloni P, Milani S, et al. Homocysteine-lowering vitamin B treatment decreases cardiovascular events in hemodialysis patients. Blood Purif 2006;24:379–86.
[26] Ebbing M, Bleie O, Ueland PM, et al. Mortality and cardiovascular events in patients treated with homocysteine-lowering B vitamins after coronary angiography: a randomized controlled trial. JAMA 2008;300: 795–804.
[27] Imasa MS, Gomez NT, Nevado JB Jr. Folic acid-based intervention in non-ST elevation acute coronary syndromes. Asian Cardiovasc Thorac Ann 2009;17:13–21.
[28] Armitage JM, Bowman L, Clarke RJ, et al. Effects of homocysteine-lowering with folic acid plus vitamin B12 vs placebo on mortality and major morbidity in myocardial infarction survivors: a randomized trial. JAMA 2010;303:2486–94.
[29] Lamas GA, Boineau R, Goertz C, et al. Oral high-dose multivitamins and minerals after myocardial infarction: a randomized trial. Ann Intern Med 2013;159:797–805.
[30] Huo Y, Li J, Qin X, et al. Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China: the CSPPT randomized clinical trial. JAMA 2015;313:1325–35.
[31] Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45:3754–832.
[32] Tian T, Yang K-Q, Cui J-G, et al. Folic acid supplementation for stroke prevention in patients with cardiovascular disease. Am J Med Sci 2017;354:379–87.
[33] Zhao M, Wu G, Li Y, et al. Meta-analysis of folic acid efficacy trials in stroke prevention: insight into effect modifiers. Neurology 2017;88: 1830–8.