

REVIEW

Folic Acid Treatment for Patients With Vascular Cognitive Impairment: A Systematic Review and Meta-Analysis

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Abstract

Background: As the life expectancy of elderly people has drastically increased, the incidence of cardiovascular and cerebrovascular diseases in this population has proportionally grown. Vascular cognitive impairment refers to all forms of cognitive disorder associated with cerebrovascular disease. Homocysteine has recently been recognized as a contributor to the pathomechanisms involved in cognitive impairment. B vitamins, such as folic acid, are known to be effective in lowering homocysteine levels.

Methods: We conducted a systematic review and meta-analysis of research on folic acid treatments for vascular cognitive impairment. Only randomized controlled trials studies that compared the efficacy of folic acid with placebo or other interventions were considered, irrespective of publication status, year of publication, and languages. Two independent reviewers searched the Medline via Ovid, EMBASE, and Cochrane Central Register of Controlled Trials (Central) journal databases up to July 2021 and independently appraised the included studies. We used mean difference outcome with 95% confidence intervals (CI) to calculate the change of Mini-Mental State Examination, cognitive function domain, and concentration of homocysteine.

Results: We found 3 studies comparing folic acid with placebo and 1 study comparing folic acid with other interventions. There is only slight evidence that the Mini-Mental State Examination score in patients who received folic acid increased 0.3 point higher compared with the placebo group after 24 months (95% CI = -0.12 to 0.37; $P = .31$). There is very strong evidence

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Significance Statement

- Folic acid is widely used as additional treatment for patients with cognitive impairment.
- Folic acid helps to reduce the concentration of the homocysteine level in plasma of patients with VCI.
- The change of cognitive function is not effectively shown for VCI patients who were treated with folic acid.

that the concentration of homocysteine in the folic acid group became 6.16 $\mu\text{mol/L}$ lower compared with the placebo group after 6 months (95% CI = 2.32 to 8.21 lower; $P < .001$).

Conclusions: Our review shows the effectiveness of folic acid in lowering the plasma homocysteine concentration after 6 months compared with placebo. However, this effect was not accompanied by improvement in cognitive function. Study registration: CRD42020199433 https://www.crd.york.ac.uk/prospero/export_details_pdf.php

Keywords: Alzheimer's disease, dementia, folic acid, homocysteine, vascular cognitive impairment

Introduction

Recently, due to the improvement of medical services and healthcare coverage, the number of elderly people has increased globally alongside the increment in life expectancy. The incidences of many diseases, including cardiovascular diseases, ischemia, and stroke, have proportionally increased. One of these diseases is vascular cognitive impairment (VCI), which refers to all forms of cognitive disorders associated with cerebrovascular disease that result in a wide range of cognitive deficits (Dichgans and Leys 2017). Vascular dementia (VaD) is the second most common subtype of dementia, after Alzheimer's disease, with 15% to 20% of dementia cases in North America and Europe. It is also estimated to reach approximately 30% in Asia and developing countries (Iadecola et al., 2019; Wolters and Ikram 2019).

Risk factor management and specific therapeutics approaches are the key factors in preventing disease progression. Homocysteine level has been recognized to contribute to the pathomechanism of neurodegeneration resulting in dementia. Clinical studies have shown that elevated homocysteine levels are associated with the development of dementia. In a mouse model of VCI, deficiencies in folate metabolism resulting in increased homocysteine levels yielded a metabolic profile that increases susceptibility to neurodegeneration (Dam et al., 2017). Several medications have been studied based on the pathomechanism of dementia, which include acetylcholinesterase inhibitors and memantine in patients with VaD. In patients with VaD, the occurrence of cholinergic dysfunction, which is also found in Alzheimer's disease, has been studied (Kalaria and Ballard 1999; Bär et al., 2007; Moretti et al., 2021). Other studies have analyzed the efficacy of donepezil, galantamine, and rivastigmine for Alzheimer's disease, which has also been studied in VaD. Other agents that have been studied and reported to have benefits in the prevention of cognitive decline in VaD or VCI patients are Ginkgo biloba, Gotu kola, and piracetam (Malinow et al., 1999; Birks et al., 2002). Folic acid is often prescribed to lower the concentration of homocysteine and prevent the decline of cognitive function. Folic acid is the most important dietary determinant of homocysteine, and daily supplementation of 0.5 to 5.0 mg could typically lower plasma homocysteine levels by 25%. The study also suggests vitamin B₁₂ supplementation of at least 0.4 mg/d could further lower homocysteine levels by approximately 7%, as well as vitamin B₆ supplements, which can decrease homocysteine after methionine loading (Flicker et al., 2001). Normal homocysteine

metabolism depends on adequate stores of folic acid, vitamin B₁₂ (cobalamin), and vitamin B₆ (pyridoxal phosphate). Folic acid is a substrate for cellular production of tetrahydrofolate, which is a precursor to 5-methyl-tetrahydrofolate that is required for normal methionine synthase enzyme activity and essential for basic cellular processes (Homocysteine Lowering Trialists' Collaboration 2005; Lonn, 2006).

Several studies reported that folic acid supplementation in patients with cognitive impairment, regardless of the causes (vascular or non-vascular), showed no significant improvement in cognitive function. However, most of the available findings were from low-quality studies, so the impact on cognitive function by delivering folic acid supplements could not be well established (Malouf and Evans 2008; Higgins et al., 2020).

Methods

Study Sample, Design, and Setting

We included patients who were clinically diagnosed with cognitive impairment and evidence of cerebrovascular disease proven by radiology imaging into our systematic review. Only randomized controlled trials and quasi-experimental trials that compared the efficacy of folic acid with placebo or other intervention were considered, irrespective of publication status, year of publication, and language.

Treatment Outcomes

As primary outcome, we aimed to evaluate the change of Mini-Mental State Examination (MMSE) score in patients who were treated with folic acid compared with placebo. We also aimed to evaluate the change of homocysteine concentration between those 2 groups.

Search Strategy and Literature Review

Two independent reviewers (A.G. and D.D.P.) searched the Medline via Ovid, EMBASE, and Cochrane Central Register of Controlled Trials (Central) journal databases until July 2021 (Figure 1). We also searched trials registries, such as WHOICTRP and clinicaltrials.gov, to look for ongoing trials. The reference lists of the retrieved articles were used for potentially relevant studies. Abstracts and other grey literature were also included

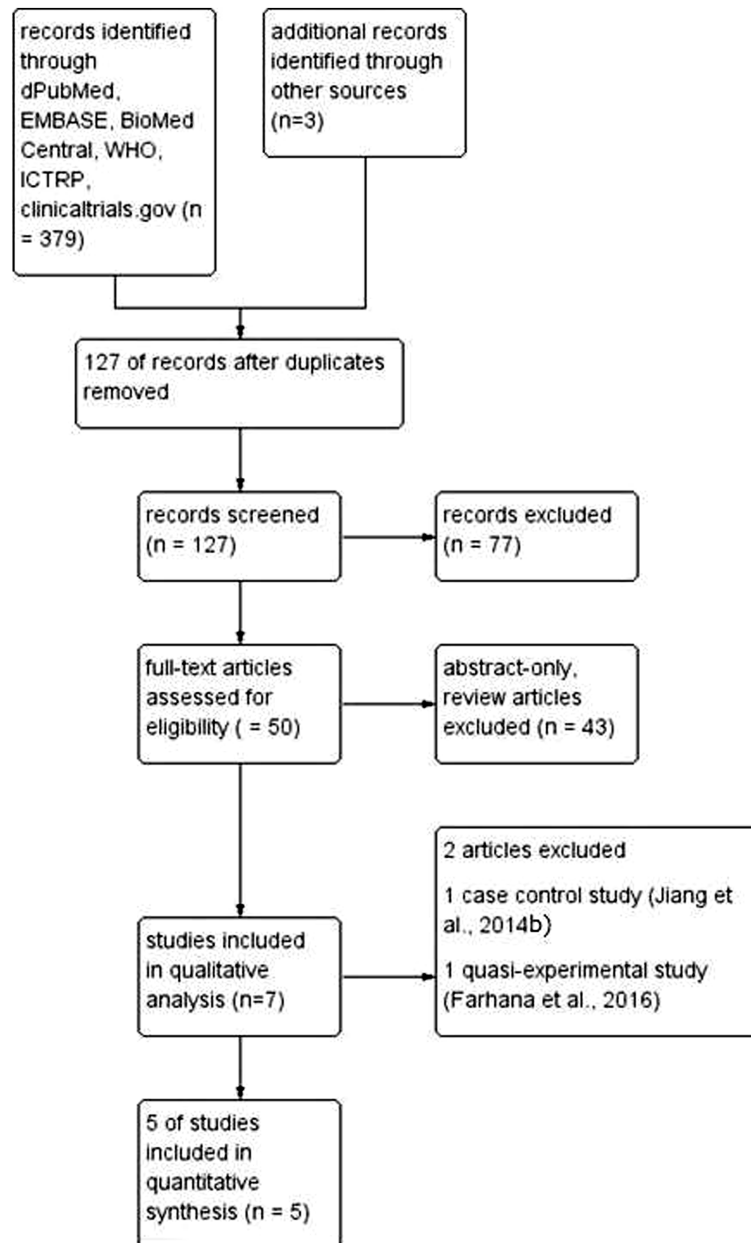


Figure 1. Study flowchart based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

through a manual and electronic search of the clinical trial registries and electronic databases, such as University of Sydney Library Database. If we found incomplete data, we sent emails to the related authors to ask for additional studies.

Selection of Study

Relevant studies, screened based on the title and abstract, were selected after conducting the electronic search. Studies on animals and review articles were excluded. Disagreement was resolved through discussion, failing which a third reviewer (M.H.) was consulted. The study selection process was plotted using a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram and were independently appraised using an Oxford Centre for Evidence-Based Medicine critical appraisal tool (OCEMB, 2011).

Assessment of Bias

Risk of bias was independently determined using the Cochrane risk-of-bias tool. The data were then included in a table. Risk of bias was classified as low, high, or unclear. Disagreement was resolved through discussion, failing which a third reviewer was consulted.

Statistical Analysis

We used mean difference outcome with 95% confidence intervals (CIs) to calculate the change of MMSE, cognitive function domain, and concentration of homocysteine. We performed statistical analysis following the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions and using Review Manager software (RevMan, V.5.3) (Higgins et al., 2020).

Table 1. List of Studies Comparing Combination of Folic Acid With Placebo/Regular Treatment

No	Authors	Design	Participants	Total participants	Intervention	Comparators	Outcome	Duration
1	Richard 2009	RCT, no blinding process	Alzheimer's patients with cerebrovascular lesions on neuroimaging	123	Acetylsalicylic acid 38–100 mg, pyridoxine 50 mg, and folic acid 0.5 mg (65 patients)	Regular care, 58 patients	Primary: IDDD Secondary: MMSE, RMBPC, total cholesterol, homocysteine concentration	24 mo
2	Kwok 2011	RCT	Chinese patients (>60 y old) with mild to moderate Alzheimer's or vascular dementia	140	1 mg methylcobalamin and 5 mg folic acid (70 patients)	Placebo, 70 patients	Primary: Mattis Dementia Rating Scale; Secondary: MDRS domain scores, MMSE, CNPI and CSSD	24 mo
3	Hankey 2013	RCT	Patients with recent stroke and cognitively impaired	481	Folic acid 2 mg; vitamin B6 25mg; vitamin B12, 500 µg (244 patients)	Placebo, 237 patients	Primary: new diagnosis of cognitive impairment (MMSE score <24 on ≥2 follow-up visits ≥6 mo after the qualifying stroke). Secondary: tHcy, mean MMSE, decline (from baseline, ≥6 mo after stroke) of ≥3 points in MMSE score on ≥2 follow-up visits (cognitive decline), and composite of cognitive impairment and decline.	6 mo and 24 mo
4	Stott et al., 2005	RCT	Patients with vascular disease	185	Folic acid plus vitamin B12, riboflavin, and vitamin B6 (23 patients)	Placebo, 24 patients	Telephone interview of cognitive status, homocysteine level	1 y
5	Jiang et al., 2014a	RCT	Patients with vascular cognitive impairment—no dementia (VCIND)	120	5 mg/d folic acid and 500 mg vitamin B12 3/d (60 patients)	Placebo, 60 patients	MoCA, P300, homocysteine level	24 wk
6	Jiang et al., 2014b	Case-control	Patients with VCIND	162	No intervention applied	None	MoCA, P300 homocysteine level	None
7	Farhana 2016	Quasi-experimental	Patients with VCI	48	Folic acid 3 mg/d	C. asiatica 750 and 1000 mg/d	MoCA	6 wk

Abbreviations: CNPI, Chinese version of neuropsychiatric inventory; CSSD, Cornell scale for depression in dementia; IDDD, interview for deterioration in daisy activities in dementia; MDRS, Mattis dementia rating scale; MMSE, mini mental state examination; MoCA, montreal cognitive assessment; RCT, randomized controlled-trial; RMBPC, revised memory and behavioral problems checklist; VCI, vascular cognitive impairment; VCIND, vascular cognitive impairment non-dementia.

A random-effects model was chosen a priori for all of the analyses as we expected heterogeneity across the studies. For the assessment of heterogeneity, we calculated the χ^2 and I^2 statistics. $P < .10$ or $I^2 > 50\%$ was considered to indicate substantial heterogeneity. A random-effects model was chosen a priori for the entire analysis. The χ^2 and I^2 statistics were calculated. $P < .10$ or $I^2 > 60\%$ was considered to indicate substantial heterogeneity. $I^2 > 40\%$ indicated moderate

heterogeneity. If we found heterogeneity across studies, we performed the subgroup analysis based on the dosage of folic acid.

Our initial intention was to perform a sensitivity analysis of heterogeneity found in the pooled studies through the exclusion of studies with low-quality results. However, this did not occur owing to a paucity of data. From our final 5 selected articles, 1 was excluded because it was a case-control study.

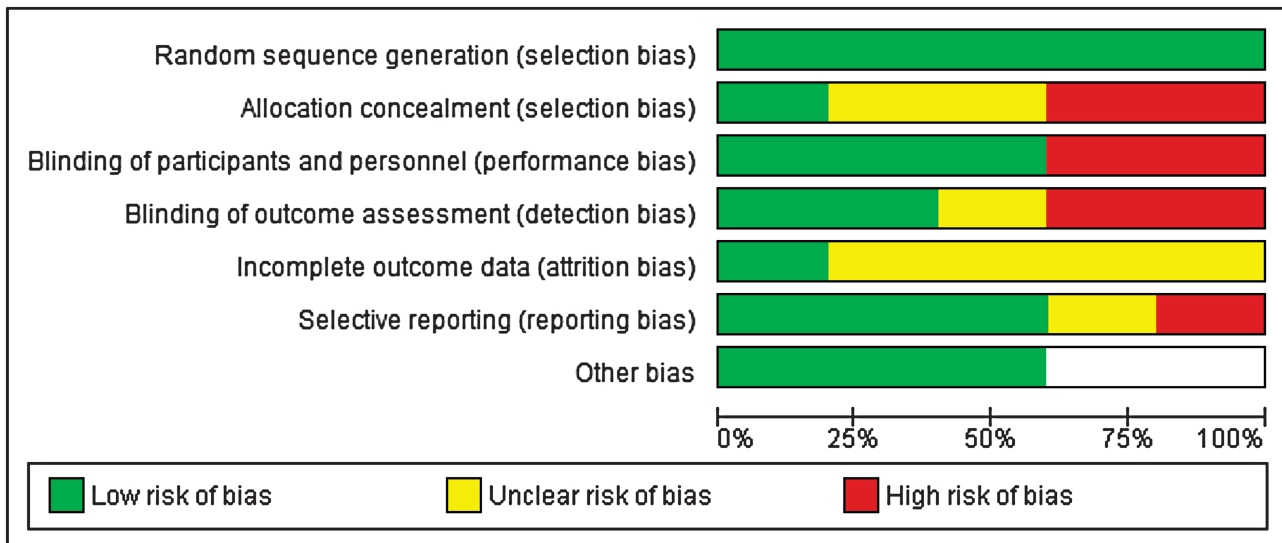


Figure 2. Risk of bias assessment.

Study Registration

The study protocol was registered on the International Prospective Register of Systematic Reviews CRD42020199433 https://www.crd.york.ac.uk/prospero/export_details_pdf.php.

RESULTS

Through our database search, we found 3 studies comparing folic acid with placebo and 1 study comparing folic acid with another intervention (Gotu kola). In studies comparing folic acid with placebo (Richard et al., 2009; Kwok et al., 2011; Hankey et al., 2013), there were 418 patients included, with the length of follow-up varied from 6 months to 24 months. In 1 study comparing folic acid with Gotu kola (Farhana et al., 2016), there were 48 patients included; length of follow-up was until 6 weeks. The summary of the included studies is listed on Table 1.

Risk of Bias Assessment

From the risk of bias assessment, we can see that there were concerns in random sequence, because 1 study is quasi-experimental, and 1 study did not mention the methods of randomization. Almost all of the studies did not mention the process of allocation concealment, and only 1 study (Richard et al., 2009) mentioned the process of allocation concealment; also, blinding was not performed. Two studies performed blinding sequence while conducting the trials (Kwok et al., 2011; Hankey et al., 2013). Lastly, 2 studies (Richard et al., 2009; Farhana et al., 2016) reported the negative outcomes of their trials, such as adverse events. Overall, we can conclude the quality of studies we included in our review varied from low to medium. (Figure 2). Furthermore, the quality of the included studies were assessed and presented in Figure 3.

Change of Cognitive Performance (6 Months and 24 Months)

Two studies reported change in cognitive performance after 6 months of treatment. There was no evidence of better cognitive performance in patients who received folic acid compared with the placebo group (mean difference = 0.75, 95% CI = -1.42 to 2.91; P = .5) (Figure 4).

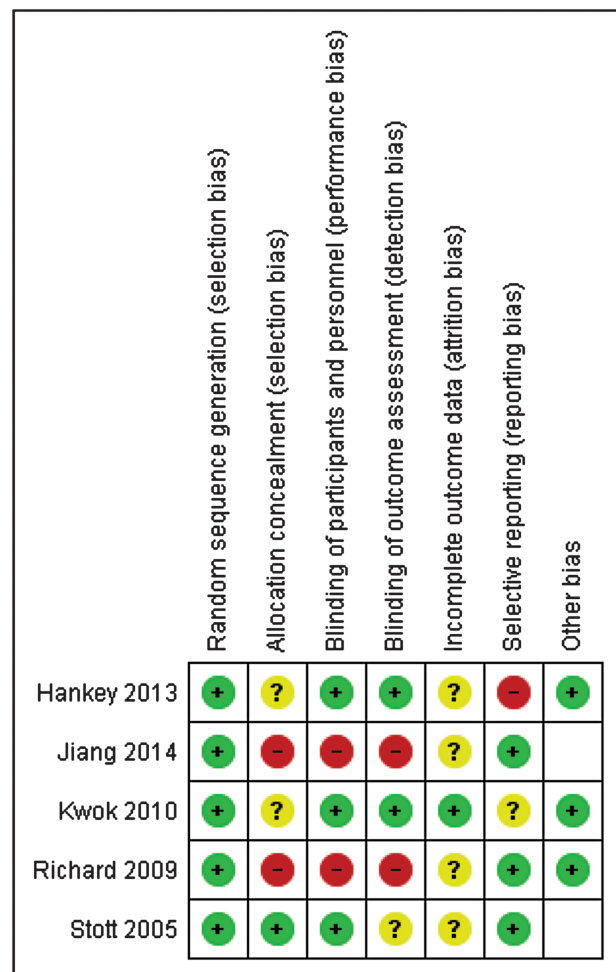


Figure 3. Quality of included studies.

Similarly, we also found better but non-significant difference in cognitive performance in patients who received folic acid compared with the placebo group after 24 months (mean

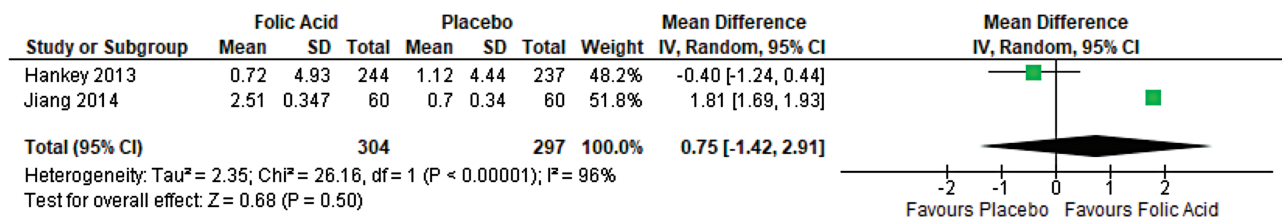


Figure 4. Cognitive performance folic acid vs placebo after 6 months.

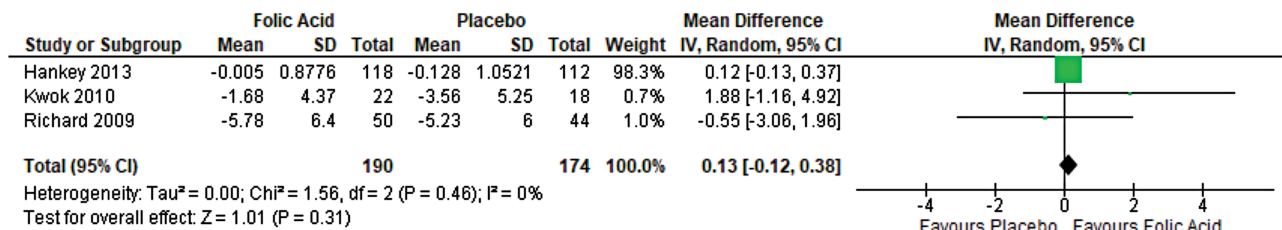


Figure 5. Cognitive performance folic acid vs placebo after 24 months.

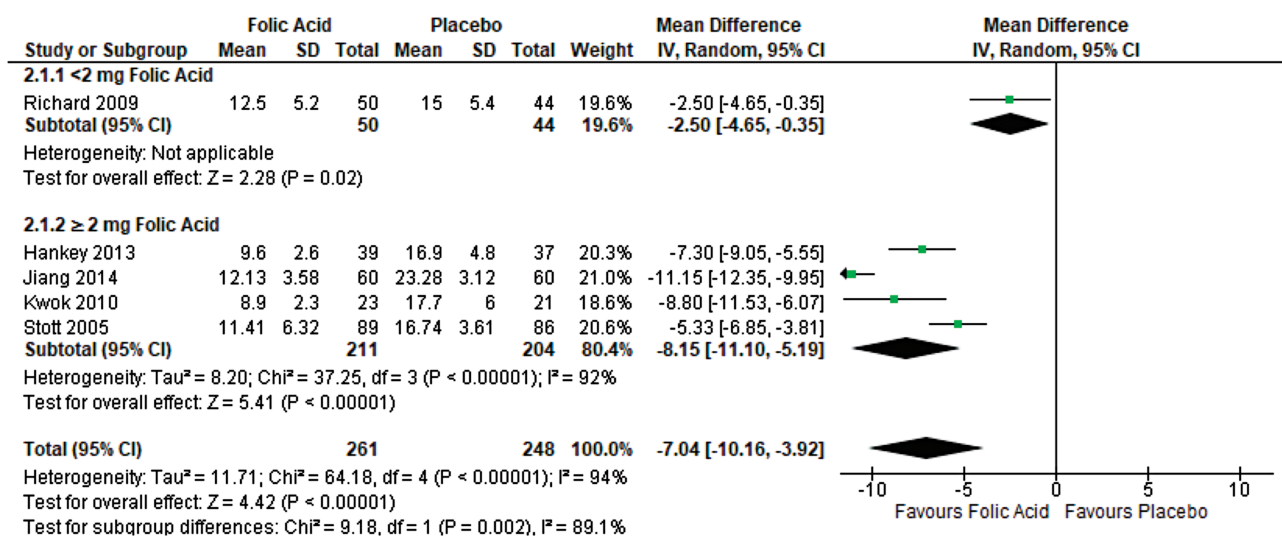


Figure 6. Homocysteine level folic acid vs placebo.

difference = 0.13; 95% CI = -0.12 to 0.38, P = .31). Additionally, there was no heterogeneity between subgroups (P = .46, I² = 0%) (Figure 5).

Change of Homocysteine Concentration

There is very strong evidence that folic acid treatment resulted in a lower homocysteine level. Patients in the folic acid group had lower homocysteine compared with the placebo group after more than 6 months of treatment (mean difference = -7.04; 95% CI = -10.16 to -3.92; P < .001). There was substantial heterogeneity between subgroups (P < .001, I² = 94%). Therefore, we performed a subgroup analysis for this outcome based on the dosage of folic acid (Figure 6).

In 1 study that used <2 mg folic acid, it was reported that the homocysteine level was 2.50 μmol/L lower in the treatment arm (P = .02; 95% CI = -4.65 to -0.35) (Figure 6).

In other studies that used ≥2 mg folic acid, patients in treatment group had 8.15 μmol/L lower homocysteine concentration compared with placebo (mean difference = -8.15; 95% CI = -11.10 to -5.19; P < .001) (Figure 6).

Discussion

Our study did not find the benefit of folic acid for VCI compared with placebo in terms of measurable improvement of cognitive function based on MMSE score. However, we did find conclusive evidence of improvement in lowering the homocysteine levels in patients with VCI after >6 months of folic acid treatment. It is known that homocysteine level influences the cognitive function as it modifies the risk of cerebrovascular events. It is believed that folate, vitamin B₁₂, and vitamin B₆ support the metabolic availability of methyl groups and thus facilitate the remethylation of homocysteine to methionine. Recent epidemiological and experimental studies have demonstrated folate deficiency increased homocysteine levels. Recent experimental studies showed that homocysteine causes oxidative stress, damages endothelium, and enhances thrombogenicity (Froese et al., 2019; Moretti and Peinkhofer, 2019; Moretti et al., 2021). Thus, elevated levels of homocysteine are often associated with several neurodegenerative conditions, including stroke, cognitive decline, Alzheimer's disease, VaD, and Parkinson's disease (Mahmood, 2014; Wang et al., 2015; Ma et al., 2016).

Folic Acid in Cognitive Function

From the review results, we showed that folic acid may improve cognitive function in some patients with VCI. It has been shown to ameliorate vascular dysfunction in cerebrovascular disease, particularly as an agent in the prevention of stroke. This finding is also similar to a previous systematic review that found the supplementation of vitamin B and folic acid could be beneficial for cognitive improvement in patients with mild cognitive impairment (Wang et al., 2007).

Limitations

Our study was able to assess only a small number of studies due to the strict protocol and paucity of data. Although 3 of the 4 studies included are randomized controlled trials, and one of them is an open label study, the other 2 studies were conducted with fewer blinding methods, and the remaining study used a quasi-experimental design.

Additionally, we used MMSE to define cognitive impairment and decline, although we know it is susceptible to ceiling effects in high-functioning populations and has a low sensitivity for cognitive impairment (Hankey et al., 2013).

Conclusions

Our study indicated there is high risk of bias among selected studies. All studies showed the effectiveness of folic acid in lowering plasma homocysteine concentration in >6 months compared with placebo/treatment. But this effect is not accompanied by improvement in cognitive function, that is, increased MMSE score.

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