Research Article • DOI: 10.1515/tnsci-2015-0014 • Translational Neuroscience • 6 • 2015 • 150-156

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Translational Neuroscience

# META-ANALYSIS REVEALS PROTECTIVE EFFECTS OF VITAMIN B ON STROKE PATIENTS

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**Abstract**

Stroke is the loss of brain function due to a disturbance in the blood supply to the brain resulting from either ischemia or hemorrhage. Previous studies have evaluated the clinical importance of nutritional interventions such as vitamin B supplementation in the management of acute strokes. However, it is still inconclusive whether or not vitamin B supplementation will benefit patients with acute strokes. Therefore, a meta-analysis was performed to assess the efficacy of vitamin B supplementation in the treatment of stroke patients. Medline, Embase, Scopus, and Cochrane Library databases were searched (from 1960 to June 2015) and forest plots were generated to illustrate the treatment effects. A systemic review of the electronic databases yielded 12 eligible studies consisting of 7474 patients. Forest plots from the meta-analyses of the included studies illustrated that vitamin B supplementation significantly lowered the plasma concentration of total homocysteine (SMD = -0.82; 95% CI: -0.77; Z = -29.06, $p < 0.0001$) and resulted in significant reduction in stroke recurrence (OR = 0.86%; 95% CI: 0.76, 0.97; Z = -2.41; p = 0.016) as well as a combined incidence of vascular events, including recurrent strokes, myocardial infarctions and vascular deaths (OR = 0.87%; 95% CI: 0.79, 0.96; Z= -2.73; p = 0.0063).
Additionally, the nearly-symmetrical funnel plot (Egger's test, $t = -1.705$, p = 0.1224) indicated the absence of publication bias regarding the meta-analysis that examined the effect of vitamin B supplementation on the plasma levels of homocysteine in acute stroke patients. These findings suggested that vitamin B supplementation presents a potential addition to the armamentarium for the management of acute stroke patients.

**Keywords**

• Stroke • Vitamin B • Homocysteine • Meta-analysis

Received 17 March 2015
accepted 10 June 2015

## Introduction

Although considerable progress has been made in the management of stroke patients, stroke is still one of the leading causes of mortality and morbidity worldwide [1]. It can be classified into two major categories, ischemic or hemorrhagic stroke, which result either from obstruction of the blood supply or from rupture of a blood vessel, respectively [2]. Approximately 85-90% of strokes are ischemic in nature, with the majority being thromboembolic [1]. Compared with healthy subjects, patients who have suffered a recent ischemic stroke remain at an increased risk of additional major vascular events, including either a recurrent stroke, myocardial infarction, or vascular death [2].

Substantial epidemiological studies have demonstrated that elevated plasma level of total homocysteine is a common risk factor for both primary and recurrent strokes [3, 4]. As compared to placebo intervention, vitamin B (folic acid, vitamin $B_{12}$, and vitamin $B_6$) supplementation has been documented to effectively lower the plasma levels of total homocysteine and serves to reduce the risk of strokes in high-risk and healthy subjects [5]. Furthermore, multiple randomized, controlled trials have also documented the clinical efficacy of B-vitamin supplementation in decreasing the plasma concentrations of homocysteine [6-8] and in improving the clinical outcomes in patients with recent strokes [9, 10]. However, it is still inconclusive whether vitamin B supplementation is beneficial in treating stroke patients and improving the rehabilitation of those patients. In addition, most of the randomized controlled trials were mainly conducted on small populations, which may lack statistical power and thus lead to inconsistency among further studies.

For the time, both a systemic review of the literature was conducted and a meta-analysis of pooled data was performed of the randomized controlled trials to examine the effects of vitamin B supplementation in reducing the plasma levels of homocysteine of stroke patients and in improving the clinical outcomes, including recurrent vascular events such as recurrent strokes, myocardial infarction, and vascular death, in patients with recent strokes. These meta-analyses may provide novel insights into the management of stroke patients in the future.

## Methods

### Literature search to identify eligible studies

A comprehensive literature search of the electronic databases (from 1960 to 1 June, 2015), included Medline, Embase, Scopus, and Cochrane Library database, was carried out to identify all published studies that examined the association of vitamin B supplementation with the plasma levels of

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total homocysteine and the clinical outcomes of ischemic strokes, including recurrence of strokes, combined incidence of recurrent strokes, myocardial infarction, and vascular death. The following keywords were used for the literature search: stroke, homocysteine, B-vitamins, vitamin B, vitamin $B_{12}$, cobalamin, vitamin $B_6$, pyridoxine, folate, folic acid. Two investigators (L.W. and W.C.) performed the literature search independently. The search results were crosschecked and the final consensus was reached between the two investigators.

### Inclusion criteria

The articles that were included into this meta-analysis matched the following five criteria: (1) patients were clinically diagnosed with acute strokes, (2) studies that determined the effect of vitamin B supplementation on the plasma levels of homocysteine, (3) studies that evaluated the incidence of recurrent strokes following vitamin B supplementation, (4) studies that assessed the effect of vitamin B supplementation on the combined incidence of recurrent strokes, myocardial infarction, and vascular death. All the potentially eligible studies were reviewed and extracted by both investigators independently and inconsistencies were resolved by discussion until a consensus was reached.

### Data extraction

Two investigators (L. W. and W. C.) reviewed the abstracts of all relevant studies independently. A standardized data extraction form was used to retrieve the following data from the included full text articles: (1) demographic information including lead author, publication year, sample size, and mean age, (2) plasma levels of homocysteine, (3) doses of vitamin B supplementation, (4) clinical outcomes including vascular events (recurrent strokes, combined incidence of strokes, myocardial infarction, and vascular death).

### Definition and standardizations

Acute stroke patients recruited in the included studies were randomly assigned to receive either vitamin B supplementation or placebo intervention after given standard medical treatment for acute strokes. Patients in the two treatment groups were well-matched at baseline in terms of demographic variables, conventional vascular risk factors, and baseline laboratory values (including plasma homocysteine, fasting cholesterol, glucose, and creatinine). Patients were excluded from the randomized controlled studies if they fell into the following categories: (1) they were taking vitamin B subtances/complexes (folic acid, vitamin $B_6$, and vitamin $B_{12}$); (2) they were pregnant; (3) they had a limited life expectancy due to serious comorbidity.

### Statistical analysis

All statistical analyses were carried out using the statistical software R (version 3.0.2, R Foundation for Statistical Computing, Vienna, Austria) and the R package "meta" (written by Dr. Guido Schwarzer, Institute for Medical Biometry and Statistics, Freiburg, Germany). Standardized mean difference (SMD) and 95% confidence interval (CI) were calculated based on the inverse variance weighted fixed effect model to measure the difference in the plasma concentrations of homocysteine in patients with recent strokes following vitamin B supplementation or placebo intervention. To assess the effects of vitamin B supplementation on the recurrence of strokes or combined incidence of myocardial infarction, recurrent strokes and vascular death, the Mantel-Haenszel weighted fixed effect model was employed to estimate the odds ratio (OR) and 95% CI. Meanwhile, statistical heterogeneity among different studies was analyzed by Chi square-based Q and the $I^2$ statistics [11]. Heterogeneity was considered significant when $p < 0.05$ was observed in the Q test and $I^2$ was used to evaluate the degree of heterogeneity (0-40%: low heterogeneity; 30-60%: moderate heterogeneity; 50-90%: substantial heterogeneity; 75-100% considerable heterogeneity) [12].

To evaluate the publication bias concerning this meta-analysis, a funnel plot was generated in which asymmetry of the scatter plot would indicate publication bias [13]. Meanwhile, an Egger's test [14] was further performed to assess the asymmetry of the funnel plot.

## Results

### Characteristics of included studies

Initially, 1464 relevant studies were identified using the search strategies as described above. After extensively reviewing the titles and abstracts of those reports, 1384 articles were excluded as they lacked detailed clinical data, including the plasma levels of total homocysteine, major vascular events such as recurrence of strokes and combined incidence of myocardial infarction, recurrent strokes or vascular death. Eventually, the extensive literature search yielded a total of 12 studies consisting of 5701 patients for this meta-analysis [6-10, 15-21] (Figure 1). Among these reports, the effect of vitamin B supplementation on the plasma levels of total homocysteine was examined in ten studies [6-10, 15-19], whereas the influence of vitamin B supplementation on stroke recurrence or combined incidence of myocardial infarction, recurrent strokes, and vascular death was evaluated in four [9, 10, 20, 21] or three studies [9, 10, 21], respectively.

Notably, as summarized in Table 1, 61-78% of strokes occur in male patients and the mean age of stroke patients ranges from 62 to 70 years. Stroke patients in 11 of the 12 studies [6-10, 15-18, 20, 21] were randomly assigned to receive either vitamin B supplementation (2 mg or 2.5 mg folate, 0.5 mg or 0.4 mg $B_{12}$, 25 mg $B_6$, once daily) or placebo intervention after being given standard medical treatment for acute strokes while patients in one of the 12 studies were given a different dose of vitamin B supplementation (5 mg folate daily, 0.5 mg $B_{12}$, twice daily) [19] (Table 1). Additionally, there were no statistically significant differences in the baseline concentrations of homocysteine between the patients receiving vitamin B supplementation or placebo intervention in all included studies [6, 16, 18].

### B-vitamin supplementation reduces the levels of plasma homocysteine

Substantial evidence suggests that elevated plasma levels of total homocysteine are an independent risk factor for stroke [3, 22] and contribute to the inflammation and oxidative stress-induced neuronal cell death in stroke patients [23]. Therefore, a meta-analysis

was performed first on the 12 studies with 5701 patients that investigated the effect of vitamin B supplementation on the plasma concentrations of homocysteine in patients with acute strokes [6-10, 15-20]. As illustrated in the forest plot from the meta-analysis based on the inverse-variance weighted fixed effect model (Figure 2), vitamin B supplementation significantly reduces the levels of plasma homocysteine in stroke patients compared with placebo intervention (SMD = −1.34; 95% CI: −1.72, −0.97; Z = −7.079; p < 0.0001).

## B-vitamin supplementation reduces incidence of recurrent strokes

In light of the numerous observational studies that have implicated elevated levels of homocysteine in the development of cerebrovascular diseases [22, 24, 25], a fixed effect model meta-analysis was performed on four eligible studies [9, 10, 20, 21] using the Mantel-Haenszel method to examine if vitamin B supplementation decreases the incidence of recurrent strokes. As shown in Figure 3, supplementation with vitamin B significantly reduces the recurrence of strokes relative to placebo intervention (OR = 0.86; 95% CI: 0.76-0.97; Z = −2.4053; P = 0.0162) (Figure 3).

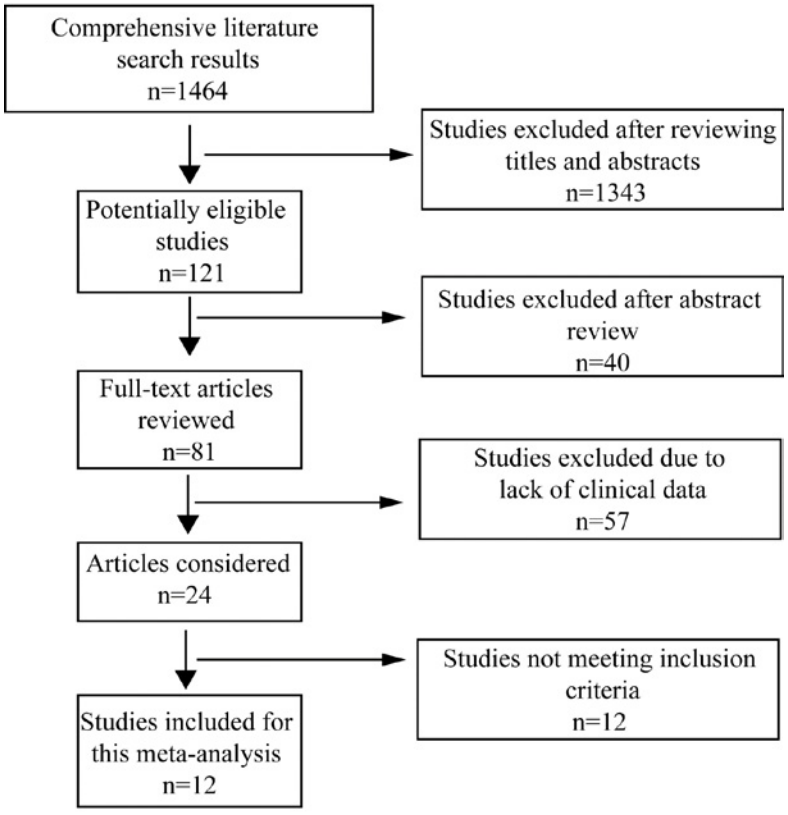


Figure 1. Flow diagram of the study selection process.

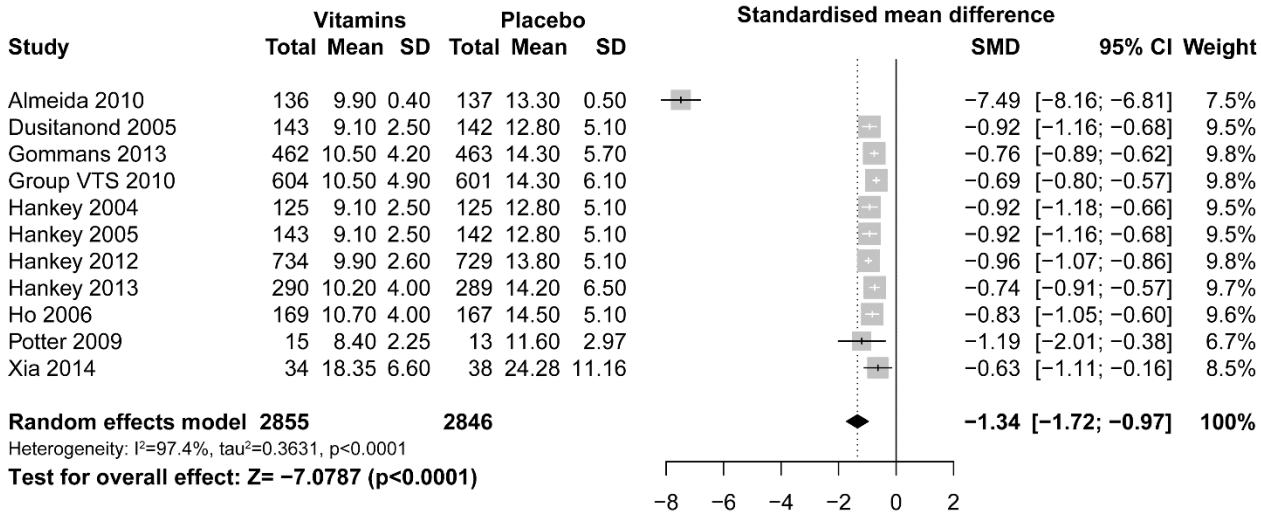


Figure 2. Forest plot showing that vitamin B supplementation significantly reduces the plasma levels of total homocysteine in acute stroke patients. Ten eligible studies were identified as described in the Methods section. Standardized mean difference (SMD) and 95% CI were calculated using the inverse variance method based on the fixed effect model. Meanwhile, tau² and I² statistic were used to measure the degree of heterogeneity among different studies. SD, standard deviation; CI, confidence intervals.

Table 1. Characteristics of included studies.

| Study | Pt No. | Mean age (years) | Sex (M) | Country | Intervention | Clinical outcomes | Baseline tHcy (Vit-B vs Placebo) | Follow-up time |
|---|---|---|---|---|---|---|---|---|
| Almeida (2010) | 273 | 63 | 68% | Australia | 2 mg folate, 0.5 mg $B_{12}$, 25 mg $B_6$ | tHcy Stroke recurrence | 11.7 ± 1.5 vs 11.1 ± 1.3 | 7 years |
| Arshi (2015) | 1773 | 65.9 | 61% | U.S.A. | 2.5mg folate 0.4 mg $B_{12}$ 25 mg $B_6$ | Stroke recurrence Combined incidence | NA | 2 years |
| Dusitanond (2005) | 285 | NA | NA | Australia | 2 mg folate, 0.5 mg $B_{12}$, 25 mg $B_6$ | tHcy | NA | 6 months |
| Gommans (2013) | 925 | 62.6 | 64% | New Zealand | 2 mg folate, 0.5 mg $B_{12}$, 25 mg $B_6$ | tHcy | 10 ± 3.2 vs 10 ± 3.5 | 3.4 years |
| Group VTS (2010) | 1205 | 62.6 | 64% | Australia | 2 mg folate, 0.5 mg $B_{12}$, 25 mg $B_6$ | tHcy Stroke recurrence Combined incidence | 14.4 ± 9.2 vs 14.2 ± 7.7 | 3.4 years |
| Hankey (2004) | 250 | NA | NA | Australia | 2 mg folate, 0.5 mg $B_{12}$, 25 mg $B_6$ | tHcy | 13.4 ± 8.5 vs 12.8 ± 5.1 | 6 months |
| Hankey (2005) | 285 | 65.3 | 65% | Australia | 2 mg folate, 0.5 mg $B_{12}$, 25 mg $B_6$ | tHcy | 13.4 ± 8.5 vs 12.8 ± 5.1 | 6 months |
| Hankey (2012) | 1463 | 62 | 64% | Australia | 2 mg folate, 0.5 mg $B_{12}$, 25 mg $B_6$ | tHcy Stroke recurrence Combined incidence | 13.7 ± 6.6 vs 13.4 ± 4.9 | 3.4 years |
| Hankey (2013) | 579 | 63 | 65% | Australia | 2 mg folate, 0.5 mg $B_{12}$, 25 mg $B_6$ | tHcy | NA | 6 months |
| Ho (2006) | 336 | 62 | 65% | Singapore | 2 mg folate, 0.5 mg $B_{12}$, 25 mg $B_6$ | tHcy | 13.7 ± 4.4 vs 14 ± 5.2 | 1 year |
| Potter (2009) | 28 | 70 | 78% | Australia | 2 mg folate, 0.5 mg $B_{12}$, 25 mg $B_6$ | tHcy | NA | 4 years |
| Xia (2014) | 72 | 68 | 61% | China | Folate (5 mg daily), $B_{12}$(0.5 mg twice daily) | tHcy | 26.8 ± 9.5 vs 25.9 ± 10.9 | 3 months |

## B-vitamin supplementation reduces the incidence of combined myocardial infarction, recurrent strokes and vascular death

A large body of evidence has suggested that increased plasma concentrations of total homocysteine is a common risk factor for other major atherothromboembolic vascular events, including myocardial infarctions, apart from recurrent strokes as described above [26, 27]. Data was then pooled from three studies [9, 10, 21] using the Mantel-Haenszel weighted fixed effect model to evaluate the clinical benefit of vitamin B supplementation in reducing the combined incidence of recurrent strokes, myocardial infarction and vascular death in patients with recent strokes. The pooled odds ratio from the meta-analysis suggests that vitamin B supplementation significantly reduced the combined incidence of recurrent strokes, myocardial infarction, and vascular death (OR = 0.87; 95% CI: 0.79-0.96; Z= −2.7322, P = 0.0063) (Figure 4).

## Publication bias

Since there have been a relatively small number of studies identified for the meta-analyses examining the impact of B-vitamin supplementation on the recurrence of strokes and the combined incidence of recurrent strokes, myocardial infarction and vascular death, the evaluation of the publication bias concerning these two meta-analyses were not performed. However, a funnel plot was generated from the eleven studies that examined the clinical benefit of B-vitamin

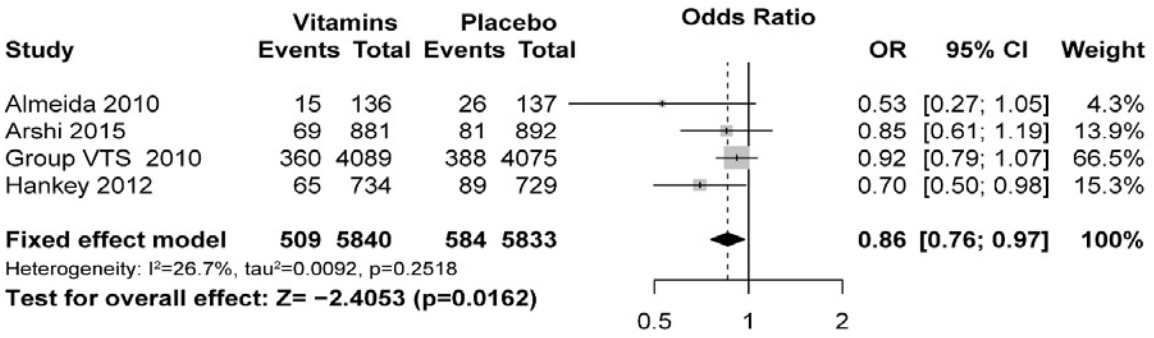


Figure 3. Forest plot showing that vitamin B supplementation significantly reduces stroke recurrence in acute stroke patients. Odds ratio (OR) and 95% CI were calculated from four eligible studies using the Mantel-Haenszel method based on the fixed effect model. Meanwhile, tau² and I² statistic were used to measure the degree of heterogeneity among different studies. OR, odds ratio; CI, confidence intervals.

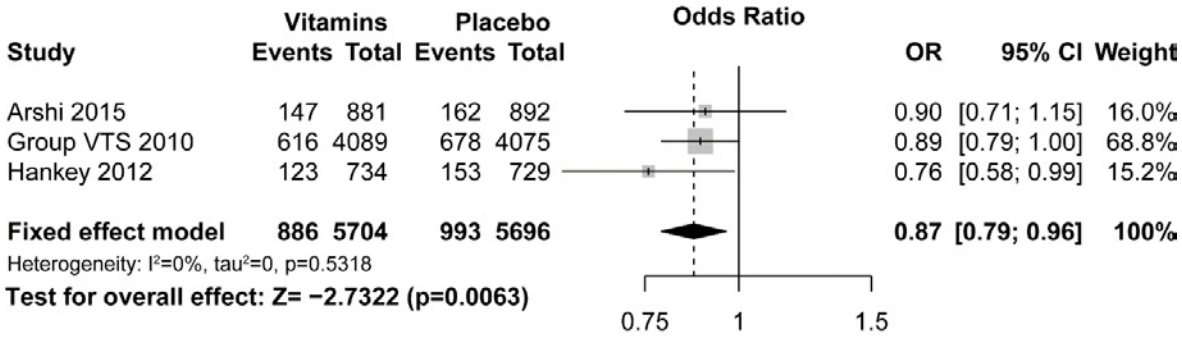


Figure 4. Forest plot showing that vitamin B supplementation significantly reduces combined incidence of major vascular events, including recurrent strokes, myocardial infarction, and vascular death. Odds ratio (OR) and 95% CI were calculated from three eligible studies using the Mantel-Haenszel method based on the fixed effect model. Meanwhile, tau² and I² statistic were used to measure the degree of heterogeneity among different studies. OR, Odds Ratio; CI, confidence intervals.

supplementation in lowering the plasma levels of total homocysteine. As shown in Figure 5, the nearly symmetrical funnel plot indicates absence of publication bias. The results from the Egger's regression test (t = −1.705, p = 0.1224) further confirmed that there was no significant asymmetry with respect to the funnel plot. These data suggested that there was no significant publication bias in the meta-analysis.

## Discussion

Stroke is the fourth leading cause of death and a major cause of adult disability in the United States [1]. Vitamin B supplementation has been shown to prevent cerebrovascular diseases, including strokes, in healthy subjects [5]. However, it is still not clear whether the supplementation with vitamin B has any clinical efficacy in treating stroke patients or to improve the clinical outcomes in these patients. In this meta-analysis study, it was found that vitamin

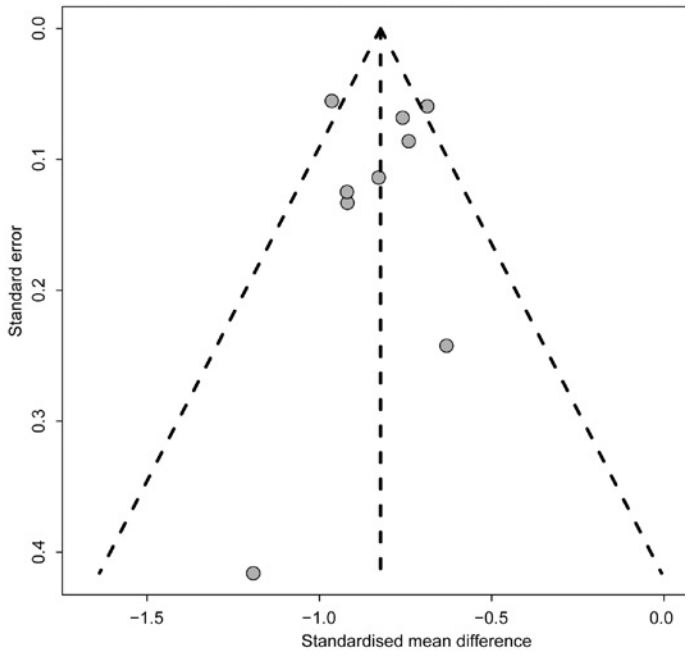


Figure 5. A funnel plot to examine the publication bias concerning this meta-analysis. The nearly symmetrical distribution of the scatter plot suggests absence of publication bias.

B supplementation significantly lowers the plasma levels of total homocysteine, reduces the recurrence of strokes, and decreases the combined incidence of myocardial infarction, recurrent strokes and vascular death in patients with recent strokes.

Intravenous administration of tissue plasminogen activator (tPA) remains the primary modality for the treatment of patients with acute ischemic stroke [28]. Intravenous tPA given within 6 hours of strokes, considerably improves the functional outcomes and increases the odds of survival and independency [28, 29]. However, there are still challenges that need to be addressed regarding the use of tPA for this purpose. As mentioned above, tPA must be administered to stroke patients within several hours after the onset of the ischemic stroke to dissolve the blood clot [29]. Additionally, treatment with intravenous tPA is associated with increased rates of intracranial hemorrhage, which may be fatal [29]. Thus, the relatively short therapeutic window and potential risks of intracranial bleeding considerably limit the clinical use of tPA in the management of stroke patients. Notably, the safety of dietary supplementation with folic acid, vitamin $B_{12}$ and vitamin $B_6$ in stroke patients has been well documented [30]. Furthermore, in this meta-analysis, the data showed that vitamin B supplementation effectively improves the clinical outcomes of stroke patients, as discussed earlier. These observations indicated that vitamin B supplementation might be an exciting addition to the armamentarium for the treatment of acute strokes in the future.

High levels of homocysteine in the plasma have been implicated in the generation of free radicals and subsequent oxidative stress-induced neuronal cell death in stroke patients [22, 23, 31]. B-vitamins (including folic acid, $B_6$, and $B_{12}$) are involved in the metabolism of homocysteine and thus function to maintain the plasma levels of homocysteine within the physiological range [32]. Consistent with these observations, vitamin B supplementation has been shown to enhance the antioxidant capacity, due to mitigation of oxidative damage and through the reduction of tissue inflammation in acute stroke patients [33-35]. These findings suggest that vitamin B may function to lower the plasma concentrations of total homocysteine and inhibit the generation of free radicals in the ischemic brain tissues, thereby improving the clinical outcomes of stroke patients.

One of the major limitations of this study is that eight out of the 12 selected reports that are included in this meta-analysis are sub-studies or a part of the VITAmins TO Prevent Stroke (VITATOPS) trial [6, 7, 9, 10, 15-17, 20]. It is also worth noting that differences in sampling protocols and methods of total homocysteine measurement may contribute to between-study heterogeneity, as observed in this meta-analysis of the effect of B-vitamin supplementation on the plasma levels of total homocysteine. Additionally, relatively small numbers of studies were identified for the analyses regarding the association of B-vitamin supplementation with recurrent strokes or combined incidence of recurrent strokes, myocardial infarction, and vascular death. These limitations indicate that additional independent studies that employ same sampling protocols and methods of homocysteine measurement are warranted to further increase statistical power and validate the findings discussed above. Since the majority of the included studies involve Caucasian populations, it will be necessary to extend the results of this meta-analysis to other ethnic populations such as African and Asian groups to assess whether these findings can be generalized across all ethnic groups.

Altogether, these meta-analyses suggest that B-vitamin supplementation compared with placebo protects patients with recent strokes against recurrence of vascular events, including strokes and myocardial infarctions, although further independent studies with larger sample size are needed to verify these beneficial effects in the future.

## Acknowledgment

*Conflict of interest statement:* The authors declare that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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