The role of vitamin E (tocopherol) supplementation in the prevention of stroke

A meta-analysis of 13 randomised controlled trials

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Summary

It was the objective of this work to systematically evaluate the role of vitamin E supplementation in the prevention of stroke. Eligible studies were identified from Medline, Embase and Cochrane Library. The efficacy data is the relative risk (RR) for the events of stroke. Thirteen randomised controlled trials (RCTs), with 166,282 participants in total, were analysed. The pooled results showed no significant benefit in the vitamin E group with respect to stroke of any type (RR 1.01; 95% confidence interval [CI]: 0.96, 1.07); ischaemic stroke (RR 1.01; 95% CI: 0.94, 1.09), haemorrhagic stroke (RR 1.12; 95% CI: 0.94, 1.33), fatal stroke (RR 0.94; 95% CI: 0.77, 1.14), and non-fatal stroke (RR 0.99; 95% CI: 0.91, 1.08). Administration of vitamin E 300 IU/day or more also gain no benefit (RR 0.99; 95% CI: 0.92, 1.06), as well as vitamin E less than 300 IU (RR 1.05; 95% CI: 0.96, 1.15). Vitamin E supplementation gained benefit of preventing stroke for neither healthy people (0.92; 0.83, 1.03) nor others at high risks in baseline (RR 1.05; 95% CI: 0.98, 1.12). Administration of synthetic vitamin E gain no benefit (RR 1.02; 95% CI: 0.96, 1.09), as well as the natural source vitamin E (RR 0.99; 95% CI: 0.89, 1.09). In conclusion, there is a lack of statistically significant or clinically important benefit of vitamin E supplementation in the prevention of stroke.

Keywords

Vitamin E, stroke, meta-analysis

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Introduction

Stroke is a leading cause of death in developed countries. It is also a major cause of long-term disability, and the economic burden of it will increase in the future (1). Any possible means to prevent stroke should be explored thoroughly. Higher consumption of fruits and vegetables has been related to lower risk of ischaemic stroke (2, 3). This may result from fruits and vegetables being rich in several antioxidants, which are known to be effective scavengers of free radicals (4). Antioxidants, such as vitamin E, may protect against atherogenesis by blocking oxidation of low-density lipoprotein cholesterol (5) and by favourably influencing plaque stability, vasomotor function, and tendency for thrombosis (6). Other mechanisms by which antioxidants could protect from stroke are reduction of platelet aggregation (7). An observational epidemiologic study in US (8) has shown that vitamin E did not seem to substantially reduce risk for stroke, while the Rotterdam Study (9) has shown high dietary intake of vitamin E in smokers reduces the risk of stroke. Nowadays, there are published well-designed large-scale registered controlled trials (RCTs) of the effectiveness of vitamin E in prevention of stroke. However, results of these studies are inconsistent and controversial. So we designed a meta-analysis in order to compare the incidence of stroke of any types in vitamin E supplementation groups versus the control groups, further ascertaining the role of vitamin E supplements in either primary or secondary prevention of stroke for participants with different health status.

Methods

Search strategy and selection criteria

Two reviewers independently searched relevant studies published before October 2010 including the following electronic databases:

Medline, Embase, and the Cochrane Library. Handsearches were performed. The search strategy used the following keywords: vitamin E or tocopherol, stroke. There was no language restriction. Studies were included if they met the following criteria: i) studying the effects of vitamin E in prevention of stroke; ii) the only difference between intervention and control group was the vitamin E supplementation, and not excluding intervention with multiple vitamin supplementation; iii) RCTs. We identified the relevant primary studies by the keywords in the titles or abstracts. We also searched references in relevant studies to confirm that no studies were missed. Authors of the eligible studies were requested to send any missing data if needed for further analysis and/or inclusion. Discordance in study inclusion between the two reviewers was subsequently reviewed and resolved through discussion.

Quality assessment of retrieved articles

Each included article was appraised by two reviewers independently. A critical review of the Cochrane handbook was used to appraise the RCTs (10).

Statistical analysis

Confirmed stroke was defined as a new neurologic deficit of sudden onset that persisted for more than 24 hours (h) or until death within 24 h. A confirmed transient ischaemic attack (TIA) was defined as a neurologic deficit of sudden onset that lasted less than 24 h. Strokes were classified as ischaemic or haemorrhagic when imaging (computed tomographic scans and magnetic resonance images) or necropsy findings were available. Stroke was considered fatal if any type of stroke led to death within 90 days from onset of attack. The endpoints used for this study were the relative risk (RR) for the events of stroke. They were calculated using Stata version 9.2 (Stata Corporation, College Station, TX, USA). A statistical test with a p-value less than 0.05 was considered significant. A RR > 1 reflects a favourable outcome in the vitamin E group; vice versa. Pooled estimates of efficacy were calculated using the Mantel-Haenszel fixed-effects model (11). But if there was heterogeneity; the following methods were used to deal with it: (a) subgroup analysis; (b) sensitivity analysis performed by excluding the trials which potentially biased the results. If the heterogeneity still potentially existed, the DerSimonian and Lair random-effects model was used. A test for heterogeneity, defined as variation

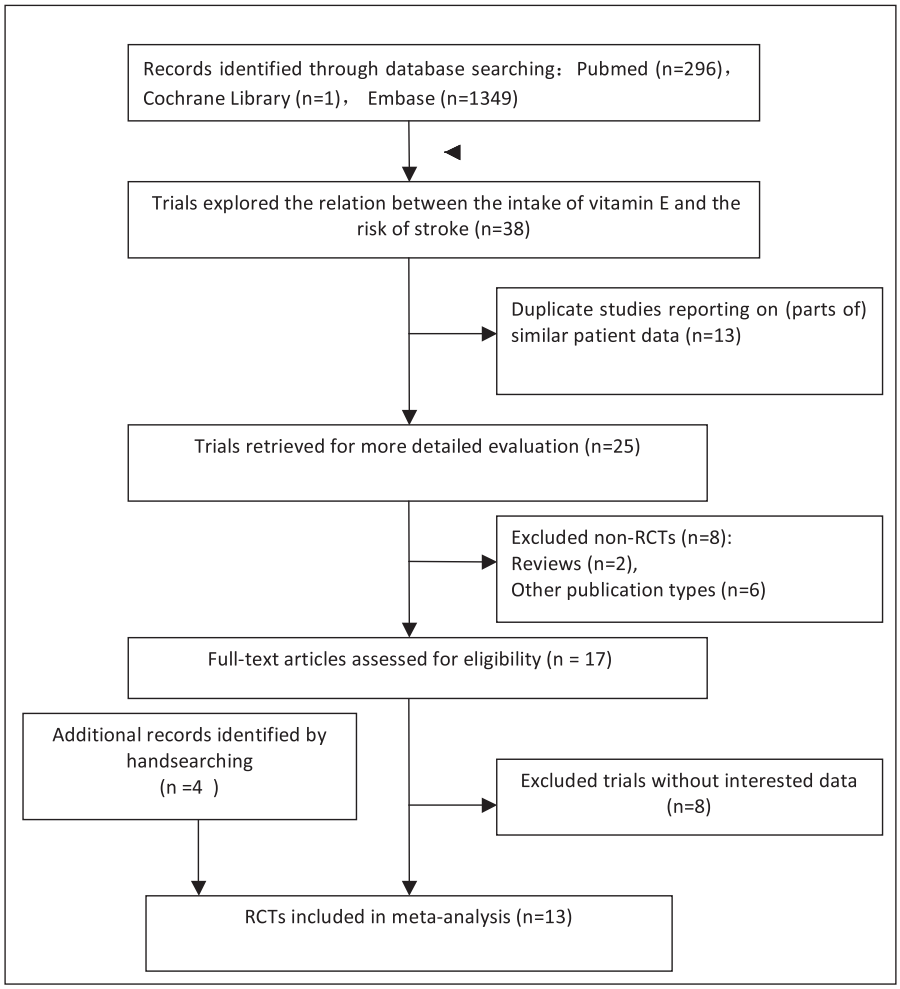

Figure 1: Flow diagram.

among the results of individual trials for a given treatment beyond that expected from chance, was used to assess whether the magnitude of a given treatment effect varied between the trials. The standard Q test was applied to investigate the statistical heterogeneity between trials and a p-value less than 0.1 was considered as heterogeneity. Intention-to-treat analyses were done. The presence of publication bias was evaluated by using the Begg and Egger tests (12, 13). A two-tailed p-value of less than 0.05 was judged as statistically significant.

Table 1: Characteristics of included studies.

Ref.	Study	Country	Multi-center	Intention-to-treat	Follow-up	Patient health status	Age range or mean age, years	Women%	Interventions
18	Milman U2008	Israel	no	1434	18 months	Over 55 years of age with the Hp 2–2 genotype	68.7	53	Natural source vitamin E(400 U/d) or placebo
14	Sesso HD 2008	US	no	14641	8 years	Healthy males except 754 men (5.1%) with prevalent cardiovascular disease	64.3	0	Synthetic vitamin E(400 IU)or placebo every other day and vitamin C(500 mg)or placebo daily.
15	Cook NR 2007	US	no	8171	9.4 years	Apparently healthy US women	60.6	0	Administration of 600 IU of natural-source vitamin E on alternate days
19	HOPE 2005	international	yes	9541	7 years	Patients at high risk for cardiovascular events.	66	26.5	Daily dose of natural source vitamin E (400 IU) or matching placebo.
16	Lee IM 2005	US	no	39876	10.1 years	Apparently healthy US women	54.6	100	Administration of 600 IU of natural-source vitamin E on alternate days.
20	ATBC-Törnwall 2004	Finland	no	24382	6.1 years	Without history of stroke. Heavy cigarette smoking	50–69	0	Synthetic vitamin E (50 mg/day),or beta-carotene (20 mg/day), both or placebo.
21	HPS 2002	UK	no	20536	5 years	With coronary artery disease, other occlusive arterial disease, or diabetes.	40–80	24.7	Synthetic vitamin E 600 mg/day, vitamin C 250 mg, and beta-carotene 20 mg daily, or matching placebo.
22	PPP 2001	Italy	yes	4495	3.6 years	With one or more of risk factors for cardiovascular disease.	64.4	57.5	Synthetic vitamin E (300 mg/day) or no vitamin E groups, and aspirin (100 mg/day) or no aspirin groups.
23	SPACE 2000	Israel	yes	196	519 days	Haemodialysis patients with pre-existing cardiovascular disease	40–75	31	Natural source vitamin E 800 IU/day,or matching placebo.
24	GISSI 1999	Italy	yes	11324	3.5 years	With recent (<3 months) myocardial infarction.	49–70	19.7	Synthetic vitamin E (300 mg daily), PUFA (1 g daily), both or none .
25	CHAOS 1996	UK	no	2002	510 days	With angiographically proven coronary atherosclerosis.	61.8	15.6	Natural source vitamin E (800 IU/day for first 546 patients, 400 IU/day for reminder), or matching placebo.
26	Steiner et al 1995	US	no	100	2 years	With history of temporary ischaemic attack, minor stroke, or residual ischaemic neurologic deficits	42–92	58	Aspirin (325 mg/day) and synthetic vitamin E (400 IU/day) or aspirin and matching placebo.

Results

Description of included trials

A total of 1,646 trials were identified from the literature databases. We screened 38 trials exploring the effectiveness of vitamin E on the risk of stroke. Duplicated reports were excluded. Finally, thirteen trials in total including 166,282 individuals were included. The process of study selection was shown in Figure 1. The details of included studies are provided in Table 1. The female rate ranged from 0 to 100%. The vitamin E dose varied between 50 mg/day to 800 mg/day. One trial (14) enrolled part of participants with prevalent cardiovascular disease, three trials (15–17) enrolled healthy participants, and the other 9 trials (18–26) enrolled those who were at high risks of stroke in baseline, namely patients with coronary artery disease, diabetes, or with history of TIA or residual ischaemic neurologic deficits or heavy cigarette smokers. The follow-up time ranged from 510 days to 10 years.

Quality assessment of the trials

Three trials (19, 23, 24) were judged to have reported an adequate randomisation procedure clearly. Ten trials (14–16, 18–24) were judged to have reported adequate allocation concealment, for the other three trials (17, 25, 26) the method was reported unclearly. Two trials (22, 24) did not use "double-blinding", and they were open-label studies, as depicted in *Methods*. All trials described main outcomes, and no missing data seemed to influence the results. All reports of the included studies were judged to be free of suggestion of selective outcome reporting. One trial (17) had a potential source of bias related to the specific study design (the subjects were randomly assigned to intervention groups according to a one-half replicate of a 2^4 factorial experimental design). Quality assessment of all the included studies is shown in Table 2.

Efficacy

Meta-analysis of thirteen trials assessing 166,282 participants showed no significant benefit in the vitamin E group with respect to stroke of any types (RR 1.01; 95% CI (0.96, 1.07); p=0.663; Fig. 2), with no heterogeneity between trials (p=0.366), and results were similar when we used a random-effects model (RR 1.02; 95% CI: 0.96, 1.08; p=0.518). According to the quality assessment of the trials, the estimated RR of seven high-quality trials (14–16, 18–21) indicated no significant benefit in the vitamin E group (RR 1.03; 95% CI: 0.97, 1.10; p=0.278; heterogeneity p=0.225). Subgroup analysis was done according to stroke subtypes, the doses or source of vitamin E and participants' health status. Pooled results of seven trials (14–16, 20, 21, 23, 26) found no significant benefit with vitamin E in the prevention of ischaemic stroke (RR 1.01; 95% CI: 0.94, 1.08; p=0.809; heterogeneity p=0.065), and results were similar when using a random-effects model (RR 0.98; 95% CI: 0.88, 1.10; p=0.759). Pooled results of six trials (14–16, 20, 21, 26) showed vitamin E had no effect on the risk for haemorrhagic stroke (RR 1.12 ; 95% CI: 0.94, 1.33; p=0.221; heterogeneity p=0.367), and results were similar when we used a random-effects model (RR 1.12; 95% CI: 0.92, 1.35; p=0.259). Pooled results of five trials (14–16, 21, 22) showed there was no significant difference between the vitamin E group and control group in terms of fatal stroke (RR 0.94 ; 95% CI: 0.77, 1.14; p=0.519; heterogeneity p=0.655), as well as non-fatal stroke (RR 0.99; 95% CI: 0.91, 1.08; p=0.846; heterogeneity p=0.223). Ten trials (14–16, 18, 19, 21–26)

Table 2: Quality assessment of the trials.

Studies	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?	Risk of bias
Milman U2008	unclear	yes	yes	yes	yes	yes	low
Sesso HD 2008	unclear	yes	yes	yes	yes	yes	low
Cook NR 2007	unclear	yes	yes	yes	yes	yes	low
HOPE 2005	yes	yes	yes	yes	yes	yes	low
Lee IM 2005	unclear	yes	yes	yes	yes	yes	low
ATBC-Törnwall 2004	unclear	yes	yes	yes	yes	yes	low
HPS 2002	unclear	yes	yes	yes	yes	yes	low
PPP 2001	unclear	yes	no	yes	yes	yes	potentially high
SPACE 2000	yes	yes	yes	yes	yes	yes	low
GISSI 1999	yes	yes	no	yes	yes	yes	potentially high
CHAOS 1996	unclear	unclear	yes	yes	yes	unclear	unclear
Steiner et al 1995	unclear	unclear	yes	yes	yes	unclear	unclear
Linxian, China 1993	unclear	unclear	unclear	yes	yes	no	potentially high

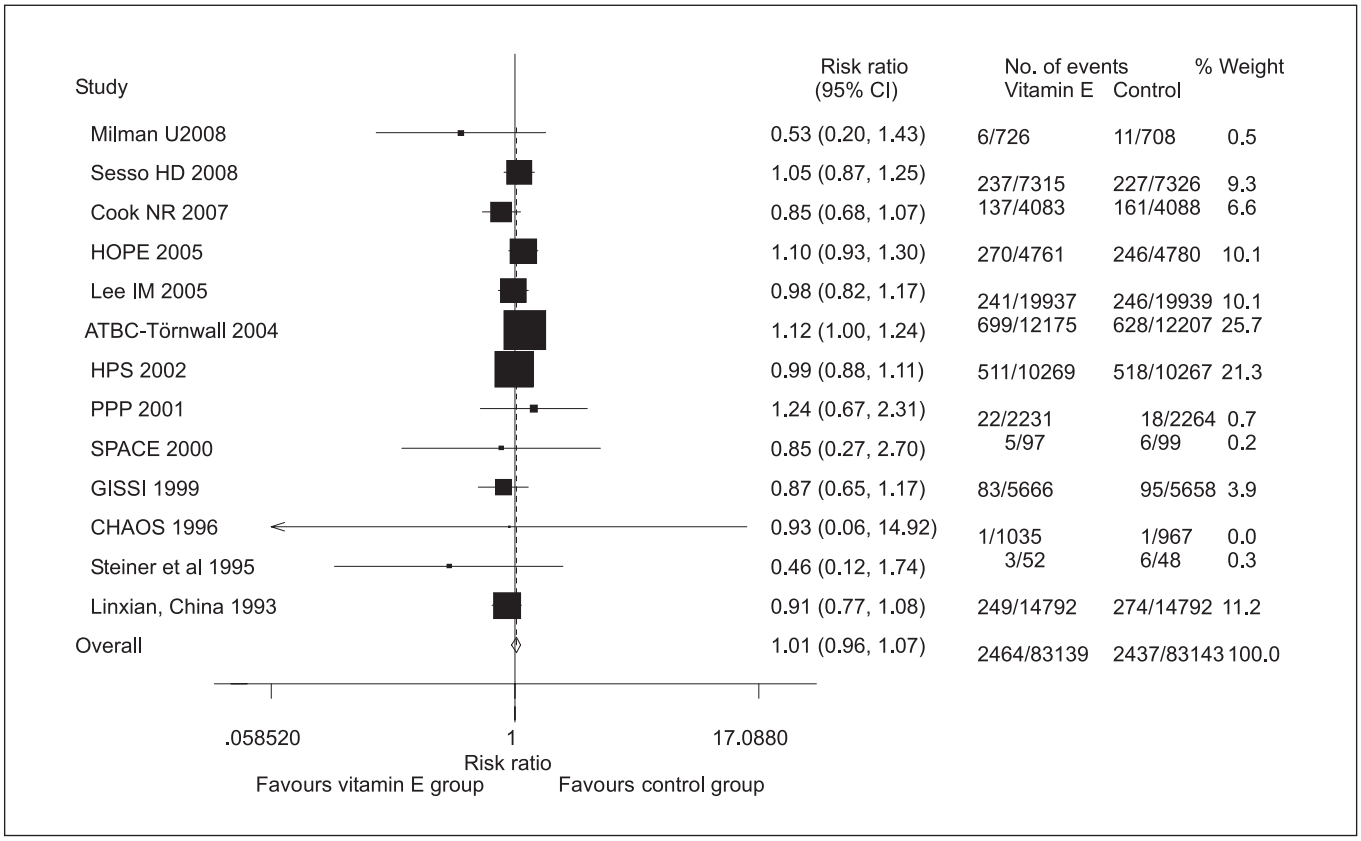

Figure 2: Relative risk (RR) of the frequency of total stroke in the 13 trials included in the meta-analysis using a fixed- effects model.

including 112,316 participants adopted the dose of vitamin E 300 IU or more. Pooled results showed there was no benefit in the vitamin E group (RR 0.99; 95% CI: 0.92, 1.06; p=0.741; heterogeneity p=0.654), as well as in vitamin E less than 300 IU sub-analysis (RR 1.05; 95% CI: 0.96, 1.15; p=0.857; a random-effects model was used). Vitamin E supplementation gained benefit of preventing stroke for neither healthy people according to the combined result from three trials (15–17) (RR 0.92; 95% CI: 0.83, 1.03; p=0.133; heterogeneity p=0.133) nor those at high risk in baseline according to the combined result from nine trials (18–26) (RR 1.05; 95% CI: 0.98, 1.12; p=0.179; heterogeneity p=0.442). Pooled RR of stroke of any type from trials administrating of synthetic vitamin E showed no difference between two groups (RR 1.02; 95% CI: 0.96, 1.09; p=0.496; heterogeneity p=0.252), as well as in the natural source vitamin E sub-analysis (RR 0.99; 95% CI: 0.89, 1.09; p=0.782; heterogeneity p=0.430). Table 3 shows the summary of results.

Publication bias

The tests for publication bias in the meta-analysis showed that there was no obvious publication bias (Begg's test, p=0.502; Egger's test, p=0.095; Fig. 3).

Discussion

This meta-analysis of 13 large-scale randomised controlled trials of vitamin E supplementation in prevention of stroke provides conclusive evidence of a lack of statistically significant or clinically important benefit or harm regarding **prevention of** any type of stroke or its subtypes.

Several reasons may explain why no beneficial effect of supplement use is found **in the present analysis**. High intake of fruits reportedly protects against stroke (3). However, supplement and diet are different types of intake of antioxidants, and they may have different effect on macrovascular disease. Secondly, it is necessary to pay attention to the fact that clinical trials usually involve persons with macrovascular diseases or at high risk; therefore, it is somehow reasonable that the non significant result of this meta-analysis is not in agreement with the protective effect reported in some observational epidemiologic studies. Interestingly, we did sub-analysis with three trials (15–17), in which apparently healthy participants were enrolled, but the pooled result also turned out to be disappointing. Thirdly, Steinberg hypothesised that the effect of antioxidants in atherosclerosis is exerted primarily on early lesions and may be difficult to detect in middle-aged and elderly individuals with advanced disease (27). Moreover, it has been suggested that the average Western diet may provide adequate supplies of vitamin E in a large proportion of individuals and that it may be difficult to observe benefits in this population with the use of additional

Outcomes	N of studies	N of participants	RR (95% CI)	Heterogeneity	P-value
Stroke of any types	13	166,282	1.01 (0.96, 1.07)	p = 0.366	p = 0.663
Pooled stroke of high quality trials	7	118,581	1.03 (0.97, 1.10)	p = 0.225	p = 0.287
Vitamin E 300 IU or more vs. control	11	112,316	0.99 (0.92, 1.06)	p = 0.654	p = 0.741
Vitamin E <300 IU vs. control*	2	53,966	1.05 (0.96, 1.15)	p = 0.044	p = 0.857
Healthy participants	3	77,631	0.92 (0.83, 1.03)	p = 0.618	p = 0.133
Participants at high risk of stroke	9	74,010	1.05 (0.98, 1.12)	p = 0.442	p = 0.179
Natural source vitamin E vs. control	6	61,220	0.99 (0.89, 1.09)	p = 0.430	p = 0.782
Synthetic vitamin E vs. control	7	105,062	1.02 (0.96, 1.09)	p = 0.252	p = 0.496
Ischaemic stroke	7	107,902	1.01 (0.94, 1.08)	p = 0.107	p = 0.809
Haemorrhagic stroke	6	107,706	1.12 (0.94, 1.33)	p = 0.367	p = 0.221
Fatal stroke	5	87,719	0.94 (0.77, 1.14)	p = 0.655	p = 0.519
Non-fatal stroke	5	87719	0.99 (0.91, 1.08)	p = 0.223	p = 0.846
Note: A fixed- effects model was used in almost all of these analysis of relative risks (RRs); * a random-effects model was used.					

Table 3: Summary of results.

supplemental vitamin E intake (28). In addition, for vitamin E, there have been suggestions that gamma tocopherol is a more powerful antioxidant. Supplementation with alpha tocopherol depletes gamma tocopherol, which may explain the lack of effect seen in vitamin E trials (29).

Noteworthy is the observation of no increase in haemorrhagic strokes with vitamin E in our meta-analysis, in contrast to a very recently published meta-analysis (30) regarding vitamin E and stroke prevention, which show an excess of deaths from such strokes. Schürks et al. included many of the same primary studies (14–16, 22–25) as ours, but we included several additional studies (17, 18, 21, 26). In addition, we had chosen more complete and newer studies when duplicate studies were found. For example, we chose the publication of the initial Heart Outcomes Prevention Evaluation [HOPE] trial in 2005 for the sake of longer follow-up time and more sufficient data, while they chose the one in 2000, and for the same reasons we chose the publication of the Alpha Tocopherol, Beta Carotene Cancer Prevention Study in 2004 instead of a more or less different publication in 2000. Thus, pooled results from more sufficient data turned out to be different with those of the study by Schürks et al. Alpha-tocopherol has effects on platelet function (31, 32), nevertheless, we suppose that this function should be somewhat limited to lead to excess haemorrhagic stroke, according to our meta-analysis. In addition, Schürks et al. found a relatively small risk reduction of

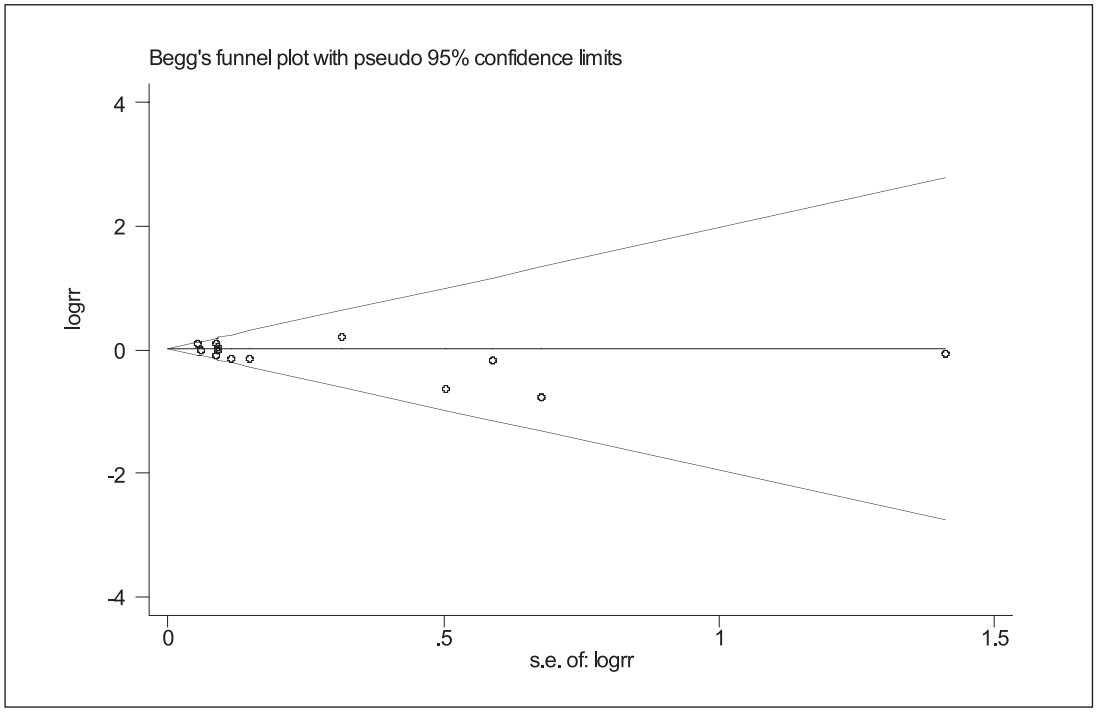

Figure 3: Publication bias.

ischaemic stroke with vitamin E pooling data from five trials, while we finally found there was no significant difference pooling data from seven trials. Furthermore, we did comprehensive subgroup analysis according to not only stroke subtypes, but also the doses or source of vitamin E and participants' health status. All results are non significant. The two main strategies of stroke prevention are the 'population' approach and the 'high risk' approach (33). Thus, the finding that vitamin E supplementation provides benefit neither for healthy people nor those at high risk further **supports that it has no future in the prevention of stroke**.

Several potential limitations of this meta-analysis merit consideration. We were not able to carry out a combined analysis of adverse events of vitamin E, because few studies reported according data in detail. It is worth mentioning that a much-noticed systematic review and meta-analysis (34) by Miller et al. concluded that high-dosage (>400 IU/day) vitamin E supplements may increase all-cause mortality and should be avoided. In addition, the patient health status and follow-up time varied among included studies, and different doses of vitamin E was adopted in these studies. The discrepancy may introduce clinical heterogeneity among studies, although no statistical heterogeneity is found.

In summary, this meta-analysis provides no support for the use of vitamin E supplements in the prevention of stroke. The article by Mente et al. reported for vitamin E supplements weak evidence in cohort studies and non-significant effects in RCTs but on the other hand they reported moderate evidence of associations for intake of dietary vitamin E (35). Therefore, questions concerning the complex nature of dietary effects on lipid peroxidation are worthy of further study.

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