BMJ

RESEARCH

Effects of vitamin E on stroke subtypes: meta-analysis of randomised controlled trials

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Cite this as: *BMJ* 2010;341:c5702
doi:10.1136/bmj.c5702

ABSTRACT

Objective To evaluate the effect of vitamin E supplementation on incident total, ischaemic, and haemorrhagic stroke.

Design Systematic review and meta-analysis of randomised, placebo controlled trials published until January 2010.

Data sources Electronic databases (Medline, Embase, Cochrane Central Register of Controlled Trials) and reference lists of trial reports.

Selection criteria Randomised, placebo controlled trials with ≥1 year of follow-up investigating the effect of vitamin E on stroke.

Review methods and data extraction Two investigators independently assessed eligibility of identified trials. Disagreements were resolved by consensus. Two different investigators independently extracted data. Risk ratios (and 95% confidence intervals) were calculated for each trial based on the number of cases and non-cases randomised to vitamin E or placebo. Pooled effect estimates were then calculated.

Results Nine trials investigating the effect of vitamin E on incident stroke were included, totalling 118 765 participants (59 357 randomised to vitamin E and 59 408 to placebo). Among those, seven trials reported data for total stroke and five trials each for haemorrhagic and ischaemic stroke. Vitamin E had no effect on the risk for total stroke (pooled relative risk 0.98 (95% confidence interval 0.91 to 1.05), P=0.53). In contrast, the risk for haemorrhagic stroke was increased (pooled relative risk 1.22 (1.00 to 1.48), P=0.045), while the risk of ischaemic stroke was reduced (pooled relative risk 0.90 (0.82 to 0.99), P=0.02). There was little evidence for heterogeneity among studies. Meta-regression did not identify blinding strategy, vitamin E dose, or morbidity status of participants as sources of heterogeneity. In terms of absolute risk, this translates into one additional haemorrhagic stroke for every 1250 individuals taking vitamin E, in contrast to one ischaemic stroke prevented per 476 individuals taking vitamin E.

Conclusion In this meta-analysis, vitamin E increased the risk for haemorrhagic stroke by 22% and reduced the risk of ischaemic stroke by 10%. This differential risk pattern is obscured when looking at total stroke. Given the relatively small risk reduction of ischaemic stroke and the generally more severe outcome of haemorrhagic stroke, indiscriminate widespread use of vitamin E should be cautioned against.

INTRODUCTION

Vitamin E is a lipid soluble antioxidant best known for its ability to inhibit lipid peroxidation by scavenging reactive oxygen species and to preserve cell membranes.[1] Cardiovascular disease is largely attributable to atherogenesis, and lipid peroxidation plays a central role in atherogenesis.[2] This has raised hopes that antioxidants including vitamin E may protect against cardiovascular disease. Data from observational studies support this view, suggesting a protective effect against coronary heart disease.[3-5] As a result, supplementation with vitamins has become popular, and more than half of the adult population in the United States is taking dietary supplements; including 12.7% taking vitamin E.[6]

A number of large, randomised, placebo controlled trials[7-14] and two meta-analyses[15 16] investigated the effects of vitamin E on incident cardiovascular disease. The results were largely disappointing, and no overall effect of vitamin E on main composite end points, including myocardial infarction, total stroke, or death due to cardiovascular disease, were found. In addition, concerns have been raised that high dose vitamin E may increase the risk for all cause mortality.[17]

Although randomised controlled trials are considered the ideal for investigating the effects of interventions on disease, the biological diversity of cardiovascular disease has not been adequately acknowledged in the available trials. There is evidence that the underlying pathophysiology is different for myocardial infarction and stroke. In addition, stroke does not represent a single well defined entity; the mechanisms underlying ischaemic and haemorrhagic events are different.[18 19] Thus, choosing composite main outcomes may dilute effects on individual outcomes. There is evidence for differential effects from the available trials. While results from most trials agree that vitamin E has no overall effect on myocardial infarction,[9 11 13 14] the evidence for stroke, including

stroke subtypes, is contradictory. There is some indication that vitamin E may be beneficial for incident ischaemic stroke[9 12] but detrimental for incident haemorrhagic stroke.[9 13]

As stroke remains a leading cause of death and disability[20] and vitamin E supplements are widely used and readily available, clarification of potential opposing associations of vitamin E with ischaemic and haemorrhagic stroke is of substantial public health importance. We therefore systematically searched the literature for randomised, placebo controlled trials of vitamin E that reported on incident stroke and stroke subtypes and performed a meta-analysis.

METHODS

Data sources and searches

We followed the guidelines for reports of meta-analyses of randomised controlled trials according to the PRISMA statement.[21] Two investigators (MS and TK) independently searched Medline and Embase (from inception to January 2010) as well as the Cochrane Central Register of Controlled Trials (CENTRAL) (issue 1, 2010), combining text terms and, where appropriate, MeSH terms for vitamin E ("vitamin E" or "alpha tocopherol") and stroke ("cerebrovascular disorders" or "cerebrovascular disease" or "stroke" or "intracranial hemorrhage" or "brain hemorrhage"). The search terms were combined with the "explode" feature. We limited our search to humans, clinical trials, randomised controlled trials, meta-analyses, and systematic reviews. We did not apply language restrictions. We also searched the reference lists of the identified articles.

Study selection

A priori, we defined the following inclusion criteria:

(1) Randomised, placebo controlled design with a follow-up of ≥1 year

(2) Investigating the effect of vitamin E on stroke incidence (total stroke or stroke subtypes)

(3) Trial participants must be selected on clinical grounds

(4) If multiple papers reported on a trial, we chose either the original report or the report that was most informative with regard to stroke and stroke subtypes.

We did not include trials of multivitamins or fixed vitamin combinations.

Two investigators (MS and TK) screened the titles and abstracts and identified and excluded all papers not meeting any of the prespecified criteria by consensus. The same investigators evaluated the remaining studies as full papers. Studies were excluded if they did not meet all criteria.

Data extraction

Two investigators (MS and PMR) independently extracted data and entered them in a customised database. Disagreements were resolved by consensus. Extracted data included authors and title of study, year of publication, country of origin, blinding strategy, participant age at enrolment and sex, inclusion criteria, treatment dose, method of statistical analysis, duration and completeness of follow-up, number of participants, and number of outcome events in each of the treatment groups. All data were extracted from the published papers; we did not contact the authors to collect further information.

Data synthesis and analysis

Within each study, we calculated the risk ratio as a measure for the relative risk and 95% confidence interval for total stroke, ischaemic stroke, and haemorrhagic stroke based on the reported events in the treatment and placebo groups.

We used a fixed effects model (Mantel-Haenszel method) and random effects model (DerSimonian and Laird method) to investigate the effect of vitamin E on stroke across the trials and calculated pooled relative risks and 95% confidence intervals.[22] We performed the Q test for heterogeneity[23] and also calculated the I^2 statistic.[24] We used meta-regression to evaluate to which extent heterogeneity between study results is related to blinding strategy (open label *v* double blind), morbidity status of participants (primary *v* secondary prevention), and vitamin E dose (≤200 mg/day *v* >200 mg/day; <200 mg/day *v* ≥200 mg/day; 50 mg/day *v* >50 mg/day). We used Galbraith plots to visually examine the impact of individual studies on the overall homogeneity test statistic.[25] We formally tested for small study effects (such as publication bias) by using Harbord's test.[26]

We considered a two tailed P value <0.05 as significant. All analyses were performed with Stata 10.1 (Stata, College Station, Texas, USA). Since we used only previously published data, we did not need approval of an ethics committee.

RESULTS

Fig 1 summarises the process of identifying eligible randomised controlled trials. After title and abstract evaluation, we were left with 22 articles. We excluded 14 more articles not meeting our inclusion criteria after evaluating the full text articles: eight articles presented subgroup or additional analyses of trials already included; one article was a meta-analysis; one article reported a follow-up of less than a year; one study did not have a placebo control group; two trials used tocopheryl nicotinate, not α-tocopherol (vitamin E); and one study was not a randomised controlled trial. We identified one additional article[7] by manually searching reference lists of included articles and reviews. Thus, nine trials were included in this analysis.[7-14 27]

Study characteristics

The characteristics of the included randomised controlled trials are summarised in the table. The total number of participants in the trials was 118 765 (59 357 randomised to vitamin E and 59 408 to placebo). One study did not specify the method of

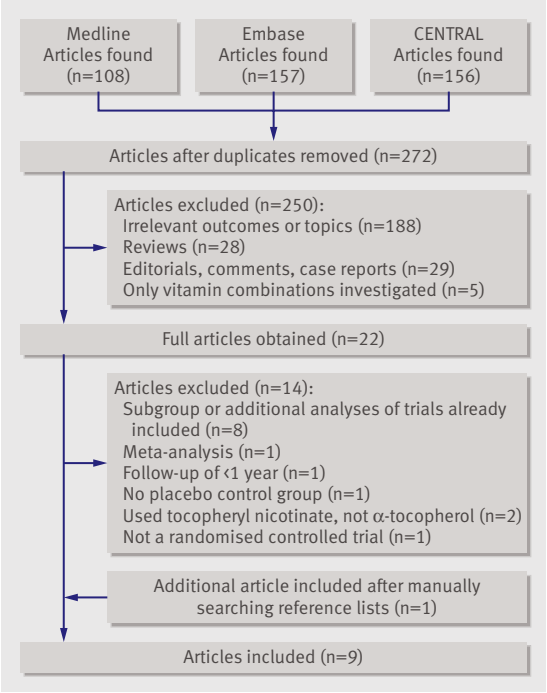

Fig 1 | **Flow chart of identifying and including trials**

analysis,[27] all other trials were analysed according to the intention to treat principle.

The Cambridge Heart Antioxidant Study (CHAOS) was a double blind, randomised controlled trial investigating the effect of vitamin E among 2002 patients with angiographically proved atherosclerosis.[7] Vitamin E significantly reduced the incidence of the primary end points non-fatal myocardial infarction (relative risk 0.23 (95% confidence interval 0.11 to 0.47)) and the composite of non-fatal myocardial infarction and cardiovascular death (relative risk 0.53 (0.34 to 0.83)).

The Gruppo Italiano per lo Studio dell Sopravivenza nell'Infarto miocardico (GISSI) Prevenzione trial was an open label, randomised controlled trial using a 2×2 factorial design to investigate the treatment of vitamin E and n-3 polyunsaturated fatty acids among 11 324 patients with recent myocardial infarction.[10] Patients randomised to vitamin E had no reduced risk for the primary composite end point of death, non-fatal myocardial infarction, and stroke (two way analysis: odds ratio 0.95 (0.86 to 1.05)).

The Secondary Prevention with Antioxidants of Cardiovascular Disease in Endstage Renal Disease (SPACE) trial was a double blind, randomised controlled trial of vitamin E among 196 patients receiving haemodialysis with a history of cardiovascular events.[27] Vitamin E reduced the risk for the primary composite end point of myocardial infarction, ischaemic stroke, peripheral vascular disease, and unstable angina (relative risk 0.46 (0.27 to 0.78)).

The Heart Outcomes Prevention Evaluation (HOPE) trial was a double blind, randomised controlled trial using a 2×2 factorial design to test the effects of ramipril and vitamin E among 9541 patients with high risk for cardiovascular disease.[14] Vitamin E had no apparent effect on the main composite outcome of myocardial infarction, stroke, and death from cardiovascular disease (relative risk 1.05 (0.95 to 1.16)).

The Alpha Tocopherol, Beta Carotene Cancer Prevention (ATBC) study was a double blind, randomised controlled trial to test α-tocopherol and β carotene among male smokers with no other previous serious illnesses. The analysis among 28 519 men free of cardiovascular disease suggested no overall effects of vitamin E on strokes.[12] However, the risk for ischaemic stroke was reduced (relative risk 0.86 (0.75 to 0.99)), whereas the risk for subarachnoid haemorrhages seemed elevated (relative risk 1.50 (0.97 to 2.32)).

The Primary Prevention Project (PPP) was an open label, randomised controlled trial among 4495 participants with cardiovascular risk factor but without overt cardiovascular disease, investigating the effect of aspirin and vitamin E with a 2×2 factorial design.[8] Vitamin E did not alter the risk for the main composite end point of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke (relative risk 1.07 (0.74 to 1.56)).

The Women's Health Study (WHS) was a double blind, randomised controlled trial with a 2×2 factorial design to test the effects of aspirin and vitamin E on cardiovascular disease and cancer among 39 876 apparently healthy women.[11] Vitamin E did not show a benefit on the main composite outcome of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death (relative risk 0.93 (0.82 to 1.05)).

The Women's Antioxidant Cardiovascular Study (WACS) was a double blind randomised controlled trial testing the effects of vitamin C, vitamin E, and β carotene in 8171 women at high risk for cardiovascular disease with a 2×2×2 factorial design.[9] Treatment with vitamin E did not change the risk for the composite primary end point of myocardial infarction, stroke, coronary revascularisation procedures, and cardiovascular death (relative risk 0.94 (0.85 to 1.04)).

The Physicians' Health Study II (PHS II) was a double blind randomised controlled trial with a 2×2 factorial design investigating the effects of vitamin E, vitamin C, a multivitamin, and β carotene on cardiovascular disease and cancer among 14 641 men.[13] Vitamin E did not change the risk for the main outcome consisting of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death (relative risk 0.90 (0.90 to 1.13)). However, the risk for haemorrhagic stroke was elevated (relative risk 1.74 (1.04 to 2.91)).

Effect of vitamin E on stroke

Seven clinical trials provided information about total stroke (fig 2).[8-14] None of the results from the individual trials suggested that vitamin E significantly alters the risk for total stroke. A total of 1438 strokes occurred among the 58 225 participants randomised to vitamin E, and 1475 strokes occurred among the 58 342 participants randomised to placebo (fixed effects model,

Characteristics of the nine randomised controlled trials of vitamin E on stroke outcomes

Trial	Study design	Participant details				Type of prevention	Vitamin E dose (source)	Follow-up details		Available data for stroke outcomes
		Total No	Age at enrolment (years)	Sex	Health status			Duration (years)	Completeness	
CHAOS 1996 (GB)[7]	Double blind RCT	2 002	Mean: 61.8	Mixed	Patients with angiographically proved coronary atherosclerosis	Secondary	400 or 800 IU daily (natural)	Median 1.4*	98%	Total (only fatal)
GISSI 1999 (Italy)[10]	Open label RCT	11 324	No limit	Mixed	MI within 3 months	Secondary	300 mg daily (synthetic)	3.4†	99.9%	Total
SPACE 2000 (Israel)[20]	Double blind RCT	196	40–75	Mixed	Haemodialysis patients with history of CVD events	Secondary	800 IU daily (natural)	Median 1.4*	Not stated	Ischaemic
HOPE 2000 (international)[14]	Double blind RCT	9 541	≥55	Mixed	High risk for CVD including previous CVD events, vascular disease, or diabetes	Secondary	400 IU daily (natural)	Mean 4.5	99.9% (mortality)	Total, haemorrhagic
ATBC 2000 (Finland)[12]	Double blind RCT	28 519	50–69	Men	Smokers, no cancer, no other serious illnesses, no previous stroke	Primary	50 mg daily (synthetic)	Median 6.0	100%	Total, fatal, ischaemic, haemorrhagic
PPP 2001 (Italy)[8]	Open label RCT	4 495	≥50	Mixed	≥1 CVD risk factor, no overt CVD event	Primary	300 mg daily (synthetic)	Mean 3.6, median 4.0	92.3% (overall); 99.3% (mortality)	Total, fatal, non-fatal
WHS 2005 (US)[11]	Double blind RCT	39 876	≥45	Women	No history of CVD, cancer, or other major disease	Primary	600 IU every other day (natural)	Mean 10.1	97.2% (morbidity); 99.4% (mortality)	Total, fatal, non-fatal, ischaemic, haemorrhagic
WACS 2007 (US)[9]	Double blind RCT	8 171	≥40	Women	High risk for CVD: history of CVD event or ≥3 cardiac risk factors	Secondary	600 IU every other day (natural)	Mean 9.4	93% (morbidity); 93% (mortality)	Total, fatal, non-fatal, ischaemic, haemorrhagic
PHS II 2008 (US)[13]	Double blind RCT	14 641	≥50	Men	Mostly healthy; 5.1% had prevalent CVD	Primary	400 IU every other day (synthetic)	Mean 8.0, median 7.6	99.9% (morbidity); 99.9% (mortality)	Total, fatal, non-fatal, ischaemic, haemorrhagic

RCT=randomised controlled trial; CVD=cardiovascular disease.
*Calculated as (No of days of follow-up)/365.25.
†Calculated as (person years)/(No of participants).

pooled relative risk 0.98 (0.91 to 1.05), P=0.53). There was no evidence for heterogeneity between the studies (I^2=12.8%; P for heterogeneity=0.33), and results were similar when we used a random effects model (pooled relative risk 0.98 (0.90 to 1.06), P=0.61). Accordingly, meta-regression did not suggest that blinding strategy (P=0.75), morbidity status of participants (P=0.96), or vitamin E dose (all P>0.2) were sources of heterogeneity. Formal investigation with Harbord's test gave no evidence for a small study effect (P=0.63). The results were similar for fatal and non-fatal total stroke (data not shown).

The effect of vitamin E analysed by type of stroke showed contrasting results. Results from five trials reported haemorrhagic stroke outcomes (fig 3).[9 11-14] All trials were double blinded. Although results of four trials suggested increases in the relative risks of haemorrhagic stroke among participants receiving vitamin E, only the results from the Physicians' Health Study II reached statistical significance.[13] In the pooled analysis, a total of 223 haemorrhagic strokes occurred among 50 334 individuals assigned to vitamin E and 183 haemorrhagic strokes occurred among the 50 414 individuals assigned to placebo (fixed effects model, pooled relative risk 1.22 (1.00 to 1.48), P=0.045). There was no evidence for heterogeneity among trials (I^2=0.0%; P for heterogeneity=0.44), and results were the same when using a random effects model (pooled relative risk 1.22 (1.00 to 1.48), P=0.048). Meta-regression did not suggest that morbidity status of participants (P=0.65) or vitamin E dose (all P>0.4) were sources of heterogeneity. Formal investigation with Harbord's test gave no evidence for a small study effect (P=0.56).

Reports from five trials allowed calculating effect estimates for ischaemic stroke (fig 4).[9 11-13 27] Results for three of the five individual trials indicated slightly reduced relative risks of ischaemic stroke among those assigned to vitamin E, but none of the results reached statistical significance. In the pooled analysis, a total of 884 ischaemic strokes occurred among the 45 670 participants randomised to vitamin E and 983 among the 45 733 randomised to placebo, translating into a significant 10% risk reduction (fixed effects model, pooled relative risk 0.90 (0.82 to 0.99), P=0.02). There was no evidence for heterogeneity (I^2=0.0%; P for heterogeneity=0.62), and results did not change with a random effects model (pooled relative risk 0.90 (0.82 to 0.99), P=0.02). Meta-regression did not suggest that morbidity status of participants (P=0.40) or vitamin E dose (all P>0.4) were a source of heterogeneity. Formal investigation with Harbord's test gave no evidence for a small study effect (P=0.97).

Absolute risks

Among participants randomly assigned to vitamin E, the incidence rates per 1000 were 24.7 for total stroke, 4.4 for haemorrhagic stroke, and 19.4 for ischaemic

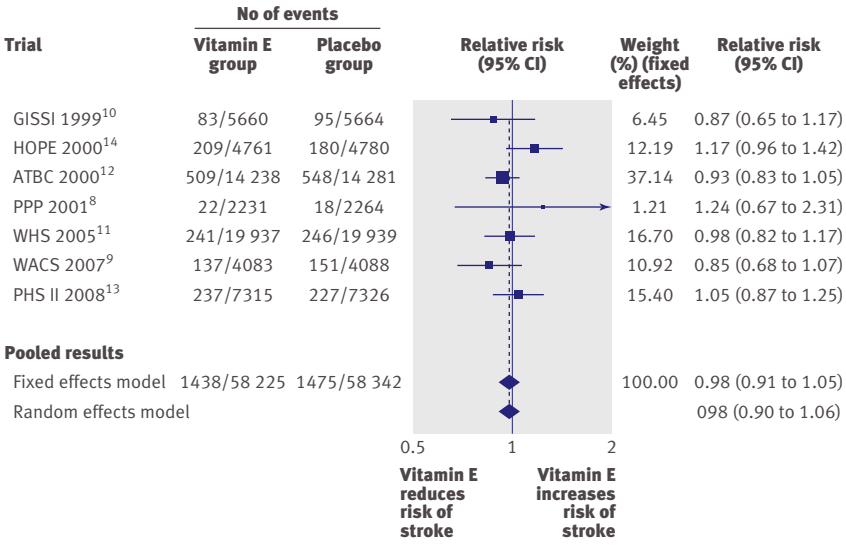

Fig 2 | Relative risks of the effect of vitamin E on total stroke for individual trials and for the pooled population

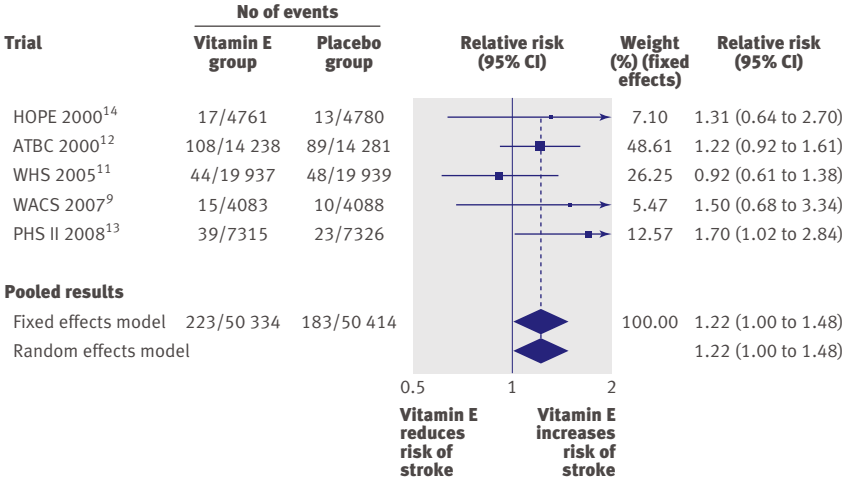

Fig 3 | Relative risks of the effect of vitamin E on haemorrhagic stroke for individual trials and for the pooled population

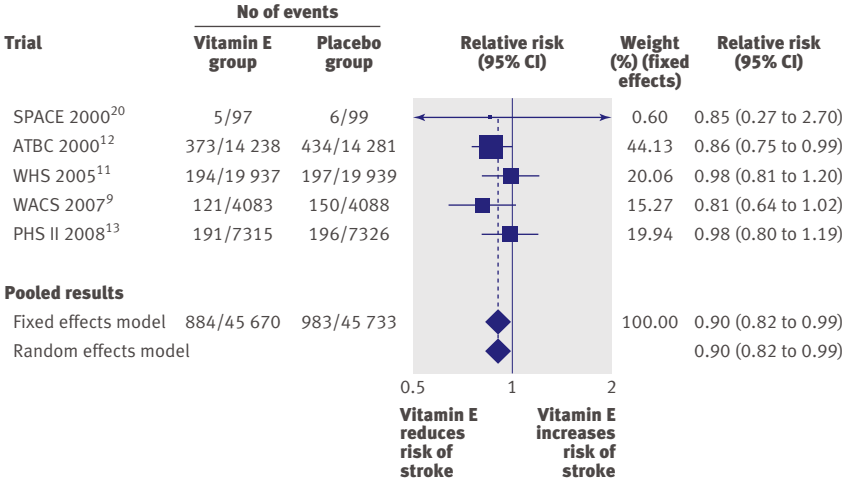

Fig 4 | Relative risks of the effect of vitamin E on ischaemic stroke for individual trials and for the pooled population

stroke. For participants randomised to placebo, the incidence rates per 1000 were 25.3, 3.6, and 21.5 respectively. This translates into a risk difference per 1000 treated people of 0.6 fewer total strokes, 0.8 more haemorrhagic strokes, and 2.1 fewer ischaemic strokes. In other words, for every 1250 individuals taking vitamin E, one haemorrhagic stroke occurs; whereas one ischaemic stroke is prevented for every 476 individuals treated.

Sensitivity analyses

By visually examining Galbraith plots, we did not identify trial results that fell outside the margins set by two standard deviations from the mean for all evaluated outcomes. For the analysis on ischaemic stroke, we excluded the trial that did not specify if the analysis was performed according to the intention to treat method.[27] This did not change the results (fixed effects model, relative risk 0.90 (0.82 to 0.99), P=0.02).

DISCUSSION

This meta-analysis of randomised controlled trials of vitamin E treatment reporting on stroke outcomes indicates that the risk of haemorrhagic stroke is significantly increased by 22% whereas the risk of ischaemic stroke is significantly reduced by 10%. These associations are obscured when total stroke is evaluated as the outcome.

Strengths and limitations of study

Strengths of our study include the thorough randomised, placebo controlled design of the individual included trials, the large number of trial participants for whom data on ischaemic and haemorrhagic stroke were available, and our adherence to the standardised guidelines on the reporting of systematic reviews according to the PRISMA statement.[21]

The following limitations of our meta-analysis should be considered. First, we decided a priori to include only trials that investigated the effect of "pure" vitamin E supplements on stroke and excluded those using fixed antioxidant vitamin combinations or multivitamins.[28] Trials of combinations preclude conclusions regarding the sole effect of vitamin E, since interactions between single components cannot be predicted.

Second, we considered randomised controlled trials irrespective of blinding and morbidity status of participants. This approach increases the total sample size and thus the power to detect a potential effect of vitamin E on stroke subtypes and also allows for greater flexibility at the analysis level by performing sensitivity analyses. Methodological quality is an important consideration when combining trials in a meta-analysis.[29] For example, larger effects have been reported in trials that were not double blinded compared with those that were double blinded.[30] Although quality scales for clinical trials are available, they are not generally recommended to assess quality in systematic reviews.[29] Meta-regression may be a better tool to investigate if methodological differences are a source of heterogeneity

among studies. Two of the trials in our meta-analysis were open label trials.[8 10] However, for the analysis of the effect of vitamin E on total stroke, there was no evidence for heterogeneity (I^2=12.8%; P for heterogeneity=0.33), and meta-regression did not identify blinding strategy as a significant source of heterogeneity (P=0.75). In addition, both trials did not provide data for stroke subtypes, so they did not affect the differential effect seen in our meta-analysis.

Third, intention to treat analysis is considered the optimum analysis approach for randomised controlled trials. One of the trials for the analysis on ischaemic stroke did not specify the method of analysis.[27] However, excluding this trial did not change the result. We also included trials irrespective of the participants' morbidity status. However, there is no a priori reason to believe that the effect of vitamin E should differ between people who are healthy, who have risk factors for cardiovascular disease, or who have experienced overt cardiovascular events. This is confirmed by our data as meta-regression did not indicate that morbidity status of trial participants is a source of heterogeneity (P=0.96 for total stroke, P=0.40 for ischaemic stroke, and P=0.65 for haemorrhagic stroke).

Fourth, there is some indication that biological effects may be even more complex than observed in our meta-analysis. One trial among male smokers presented results for haemorrhagic stroke stratified according to intracerebral and subarachnoid haemorrhage; these suggested that vitamin E particularly increased the risk for fatal intracerebral haemorrhage (relative risk 1.64 (95% confidence interval 0.93 to 2.90)) and fatal subarachnoid haemorrhage (relative risk 2.81 (1.37 to 5.79)).[12] However, the other trials did not report these subcategories, and we could not further investigate this in our systematic review.

Fifth, participants of clinical trials are selected based on certain inclusion and exclusion criteria, which reflect the risk status of only a subgroup of the general population. Hence, generalisability may be limited.

Lastly, vitamin E treatment differed by dosing regimen and source (see table). For example, natural source vitamin E (RRR stereoisomer of α-tocopherol) is more active than synthetic source vitamin E (racemic mixture of all stereoisomers of α-tocopherol).[31] However, meta-regression did not indicate that vitamin E dose is a source of heterogeneity among the studies.

Discussion of individual trials

Many large randomised controlled trials investigating the effect of vitamin E on incident major cardiovascular events were performed during the past two decades, but most did not find an overall significant effect.[8-14] Likewise, two recent meta-analyses did not find an effect on mortality from all causes, cardiovascular death, and stroke from all causes.[15 16] Our results of an overall null effect of vitamin E on total stroke agree with these earlier reports. However, the main outcome events in these previous trials—composites consisting of myocardial infarction, stroke, and death due to cardiovascular disease—may be too broad to capture the differential pathophysiology underlying ischaemic and haemorrhagic events.[18 19] Subgroup analyses from previous trials support this concept by pointing towards a beneficial effect of vitamin E on incident ischaemic stroke,[9 12] while suggesting a detrimental effect on incident haemorrhagic stroke.[9 13] The Alpha Tocopherol, Beta Carotene Cancer Prevention trial was the first, showing that in male smokers 50 mg/day of vitamin E increased the risk of haemorrhagic stroke.[12] This result was confirmed in the Physicians' Health Study II, which randomised 14 641 male physicians from the United States to 400 IU vitamin E on alternate days or placebo.[13] Results from the Women's Health Study, which randomised 39 876 apparently healthy women to 600 IU vitamin E on alternate days or placebo, however, do not indicate increased risk of haemorrhagic stroke in women.[11]

Potential biological mechanisms

The potential pathophysiological mechanisms explaining these results are undetermined. Evidence suggests that α-tocopherol inhibits platelet aggregation and adhesion in vitro, but it is not clear that these effects on platelet function are deleterious in normal healthy individuals at any dose.[32] Since results of the Women's Health Study indicate reduced risk of venous thromboembolism among women randomised to vitamin E,[33] an alternative hypothesis is that vitamin E interferes with activation of vitamin K dependent clotting factor and exerts an anticoagulant effect. Current research agrees on the antioxidant properties of vitamin E[1] and that lipid peroxidation plays a central role in atherogenesis.[2] However, it is not known if the vitamin E doses chosen in clinical trials are adequate to prevent lipid peroxidation in humans and if vitamin E plays an important role in preventing lipid peroxidation at all.[34] In addition, novel research indicates that vitamin E has important functions in the regulation of membrane bound enzymes, cellular trafficking, gene expression, and inflammatory responses.[35] The functional implications of these mechanisms are not well understood yet.

It is also unclear whether the propensity for bleeding is restricted to the intracranial cavity or whether it may be a general feature in vitamin E treatment. Data on adverse bleeding from the randomised controlled trials are scarce: one trial reported two cases of fatal bleeding in the intervention arm (2/97 given vitamin E *v* 0/99 given placebo),[27] and one reported non-fatal bleedings (16/2231 given vitamin E *v* 14/2264 given placebo).[8] Among three large trials recording any bleeding,[9 11 13] the Women's Health Study particularly focused on bleeding at multiple sites, and found no overall increased rate of bleeding but a small significantly increased risk for epistaxis among patients treated with vitamin E (relative risk 1.06 (95% confidence interval 1.01 to 1.11), P=0.02).[11]

Implications for clinical practice

While our data show a significantly reduced risk for ischaemic stroke and increased risk for haemorrhagic

stroke, the absolute effects are small (0.8 more haemorrhagic strokes and 2.1 fewer ischaemic strokes per 1000 treated persons). In addition, one has to keep in mind that other preventive strategies have far stronger effects on stroke.[36] For example, the 10% relative risk reduction for ischaemic stroke by vitamin E is negligible compared to the substantial risk reduction achieved by antihypertensive medication[37 38] or lipid lowering medication.[39] In addition, as living a healthy lifestyle, including abstinence from smoking, keeping a low body mass index, moderate alcohol consumption, regular exercise, and a healthy diet has been consistently associated with substantially reduced risk of ischaemic stroke,[40 41] intake of vitamin E supplements may not further add to the risk reduction. Because the consequences of haemorrhagic stroke in terms of morbidity and mortality are generally more severe than those of ischaemic stroke[42] and high doses of vitamin E supplements may increase all cause mortality,[17] a widespread and medically uncontrolled use of vitamin E should be cautioned.

Directions for future research

Further research is warranted to understand mechanisms of the observed diametric effects on stroke subtypes, in particular if and how the vitamin E effect is modified by additional risk factors for haemorrhagic and ischaemic stroke. We further need to understand whether subgroups of individuals exist for whom vitamin E confers a substantial increased risk or decreased risk for specific stroke subtypes. This may facilitate evaluation of an individual risk-benefit balance and help guiding physicians in the future. In addition, vitamin E supplementation may have a different effect on stroke and other cardiovascular disease events in developing countries where malnutrition may be found. This may be important since stroke burden and mortality is highest in low income countries.[43]

WHAT IS ALREADY KNOWN ON THIS TOPIC

Observational studies have suggested a protective effect of vitamin E intake on coronary heart disease

However, randomised controlled trials reported no effect of vitamin E on risk of cardiovascular disease. In addition, subgroup analyses suggested increased risk for haemorrhagic stroke

A meta-analysis raised concerns that high dose vitamin E may increase the risk for all cause mortality

WHAT THIS STUDY ADDS

Results from this meta-analysis suggest that vitamin E supplementation increases the risk for haemorrhagic stroke by 22%, but reduces the risk for ischaemic stroke by 10%. This differential effect is obscured when investigating total stroke

The absolute risks associated are moderate: among those taking vitamin E, one additional haemorrhagic stroke occurs per 1250 individuals, while one ischaemic stroke is prevented per 476 individuals

Given the relatively small risk reduction of ischaemic stroke and the generally more severe outcome of haemorrhagic stroke, indiscriminate widespread use of vitamin E should be cautioned against

Conclusion

In this meta-analysis of randomised trials, we found that vitamin E increased the risk for haemorrhagic stroke by 22% and reduced the risk of ischaemic stroke by 10%. Using total stroke as the outcome obscures these harms and benefits. However, given the relatively small reduction in risk of ischaemic stroke and the generally more severe outcome of haemorrhagic stroke, indiscriminate widespread use of vitamin E should be cautioned against.

Contributors: MS and TK conceived and designed the study, analysed the data, and drafted the manuscript. MS, PMR, and TK were responsible for the acquisition of the data. All authors interpreted the data, critically revised the draft for important intellectual content, and gave final approval of the version to be published. MS and TK are guarantors for the study. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.
Funding: No specific funding for this study.
Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: that for the specific matter of this research, no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.
Data sharing: No additional data available.

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Accepted: 25 August 2010