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α-tocopherol in the prevention of ischemic or hemorrhagic stroke: A meta-analysis

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Abstract. Stroke remains a leading cause of disability and mortality worldwide, and the preventive role of antioxidants is of great clinical interest. The present study aimed to clarify the relationship between circulating α-tocopherol and stroke by performing a meta-analysis of prospective studies. The Web of Knowledge, Embase, Scopus, Cochrane Library and PubMed databases were searched through January 2026 for relevant studies. Risk ratios (RRs) and the corresponding 95% confidence intervals (CIs) were extracted to estimate the association of circulating α-tocopherol with stroke risk. In total, six cohort studies involving 104,209 participants and 2,194 events were identified. The results indicated that a high circulating α-tocopherol level was associated with a 22% lower stroke risk (RR, 0.78; 95% CI, 0.70-0.87). Additionally, a higher circulating α-tocopherol level was associated with a reduced stroke risk in the ischemic stroke (RR, 0.80; 95% CI, 0.72-0.90), body mass index >25 (RR, 0.80; 95% CI, 0.72-0.89), physical activity adjusted (RR, 0.69; 95% CI, 0.57-0.84) and physical activity not adjusted (RR, 0.83; 95% CI, 0.73-0.94) subgroups, but not for the hemorrhagic stroke (RR, 0.65; 95% CI, 0.41-1.01) subgroup. Dose-response analysis indicated that each 5 mg/l increment in circulating α-tocopherol was associated with an average 8% lower stroke risk (RR, 0.92; 95% CI, 0.85-0.98). In conclusion, the findings of the present meta-analysis indicates that an increased circulating α-tocopherol level may be related to lower ischemic but not hemorrhagic stroke risk. Notably, while physical activity is a critical determinant of stroke risk, the protective association of α-tocopherol remains significant and is further strengthened after accounting for this factor. This suggests that α-tocopherol may play a vital role in stroke prevention, particularly within the context of active lifestyle management.

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Introduction

Stroke is a primary cause of disability and mortality (1) and the medical costs for stroke remain at a high level. Therefore, new approaches are required to lower the incidence rate of this condition globally. Accumulating evidence has shown that dietary habits influence the incidence of stroke (2,3); for instance, several studies have revealed that the intake of olive oil, nuts and vegetables (all foods abundant in vitamin E) is related to a lower incidence of stroke (4-6). To date, eight isomers of vitamin E have been confirmed; among these eight isomers, α-tocopherol, which is absorbed by the digestive system and directly released into the blood circulation, is regarded as the predominant form of vitamin E (7).

Vitamin E influences the process of low-density lipoprotein (LDL) oxidation (8), which is one of the notable initial steps in the pathogenesis of atherosclerosis. However, prospective cohort studies have indicated that the relationship between circulating α-tocopherol and stroke is inconsistent (9-14). Additionally, randomized controlled trials (RCTs) regarding vitamin E supplementation and cardiovascular disease (CVD) have yielded conflicting results (15,16). While some early trials suggested a protective effect of vitamin E supplementation on CVD (17,18), subsequent large-scale trials and meta-analyses failed to demonstrate notable benefits for major cardiovascular events (16,19,20). Notably, some evidence even suggested potential risks, such as an increased incidence of cerebral hemorrhage at high doses (21). These discrepancies underscore the importance of evaluating circulating α-tocopherol, which accurately reflects the net effect of dietary intake and individual metabolism.

The primary aim of the present study was to quantitatively evaluate the association between circulating α-tocopherol levels and the risk of stroke. Specifically, the study sought to determine whether this relationship varies across different stroke types and populations. To achieve this, subgroup analyses for circulating α-tocopherol and stroke risk according to stroke subtypes (ischemic versus hemorrhagic), body mass index (BMI), age, follow-up duration and physical activity were also performed.

Materials and methods

Search strategy. The present meta-analysis was performed according to the PRISMA guidelines. A literature search was conducted for all cohort studies reporting the relationship between circulating α-tocopherol levels and stroke. The electronic Web of Knowledge (https://www.webofscience.com), Embase (https://www.embase.com), Scopus (https://www.scopus.com), Cochrane Library (https://www.cochranelibrary.com) and PubMed (https://pubmed.ncbi.nlm.nih.gov) databases were searched through to January 2026. The following key words and search strategies were used: 'tocopherol' or 'vitamin E'; and 'stroke' or 'ischemic stroke' or 'hemorrhagic stroke' or 'cerebrovascular disease' or 'intracranial hemorrhage' or 'brain hemorrhage'; and 'serum' or 'circulating' or 'plasma'; and 'cohort'. Additionally, any potential publications were retrieved from the references of relevant reviews.

Study selection. The inclusion criteria were as follows: i) cohort studies; ii) circulating α-tocopherol levels were measured; iii) the outcome was stroke or its subtypes; and iv) risk ratio (RR) of the incidence of stroke was reported. Estimates with maximum adjustment for confounders were used. Experimental studies, conference abstracts and studies that did not report stroke risk estimates were excluded.

Data extraction. The following study characteristics and data were extracted from the included articles: The first author, publication year, area, participant age range, number of events and participants, follow-up duration, quality score and the RRs and corresponding confidence intervals (CIs). Data were independently extracted in duplicate by two investigators. Any disagreement was resolved by consultation with an arbitral author.

Evaluation of study quality. Publication quality was assessed according to the scoring principles of the Newcastle-Ottawa Scale (NOS) (22). Studies awarded seven or more stars were considered high quality.

Primary and subgroup analyses. The relationship between circulating α-tocopherol levels and the total stroke risk was investigated. Subgroup analyses according to stroke subtype (ischemic versus hemorrhagic), BMI, age (≥65 vs. <65 years), follow-up duration (>10 vs. ≤10 years) and physical activity (adjusted or not) were conducted. The cut-offs for the specific subgroup analyses (such as a BMI of 25, an age of 65 and a follow-up of 10 years) were based on the median values from the included studies.

Dose-response analysis. A dose-response meta-analysis was performed according to previously reported methods (23,24). For each study, the mean level of circulating α-tocopherol for each category and its corresponding RR were extracted for analysis. When the mean circulating α-tocopherol level was unavailable, the midpoint of the lower and upper boundaries was used as the average level for that category. For the upper exposure category, 1.2-fold of its lower limit was used.

Meta-regression and sensitivity analyses. To explore potential sources of heterogeneity, meta-regression analyses were performed for follow-up duration and age (both as continuous variables), as well as physical activity adjustment status (adjusted vs. not adjusted). Additionally, a leave-one-out sensitivity analysis was conducted to evaluate the stability of the pooled results.

Statistical analysis. The summary RRs were obtained by the inverse-variance method using the random-effects model (25,26). Between-study heterogeneity was assessed by I^2 statistics (26); heterogeneity between studies was defined as I^2>50% or a significance level of P<0.10. Publication bias was determined using Egger's test and the risk of publication bias was ascertained when P<0.05. The present meta-analysis was conducted using Review Manager (RevMan) software, version 5.4 (The Cochrane Collaboration). To further explore potential sources of heterogeneity and assess the stability of the results, meta-regression and leave-one-out sensitivity analysis were performed using R Project for Statistical Computing, version 4.5.2 (RStudio, Inc.) with the 'meta' (https://CRAN.R-project.org/package=meta) and 'metafor' (https://CRAN.R-project.org/package=metafor) packages.

Results

Results of the literature search. In total, 856 potential studies were retrieved by the initial literature search. A flow chart summarizing the study selection is shown in Fig. 1. At first, 132 duplicated articles were excluded, then 668 studies were excluded after a review of the abstract and title. Subsequently, 56 potentially relevant studies underwent full-text evaluation. Finally, 6 studies (9-14) on circulating α-tocopherol were included in the present meta-analysis. These studies involved 104,209 individuals and 2,194 stroke outcomes. In total, 2 studies (9,11) were awarded 7 stars and 4 studies (10,12-14) were awarded 8 stars according to the NOS. Additionally, 4 included studies (9,10,12,13) contained relevant data for dose-response analysis.

Study characteristics. The characteristics of the 6 cohort studies are shown in Table I. The publication year ranged from 1999 to 2020. In total, 3 studies (9,11,12) were from Finland, 1 (10) was from the United States, 1 (14) was from Sweden and 1 (13) was from Japan. All 6 prospective studies reported the risk estimates for circulating α-tocopherol with maximum-adjusted confounders.

Circulating α-tocopherol and stroke risk. A meta-analysis of the 6 studies showed that a higher level of circulating α-tocopherol was related to a 22% lower stroke risk (RR, 0.78; 95% CI, 0.70-0.87; I^2=0; P<0.01; Fig. 2). Furthermore, circulating α-tocopherol was associated with ischemic stroke risk reduction (RR, 0.80; 95% CI, 0.72-0.90; P<0.01) but not hemorrhagic stroke risk reduction (RR, 0.65; 95% CI, 0.41-1.01; P=0.06).

Subgroup analyses for the association of circulating α-tocopherol with stroke risk. Subgroup analyses according to BMI and age are shown in Fig. 3. Subgroup analyses according to follow-up

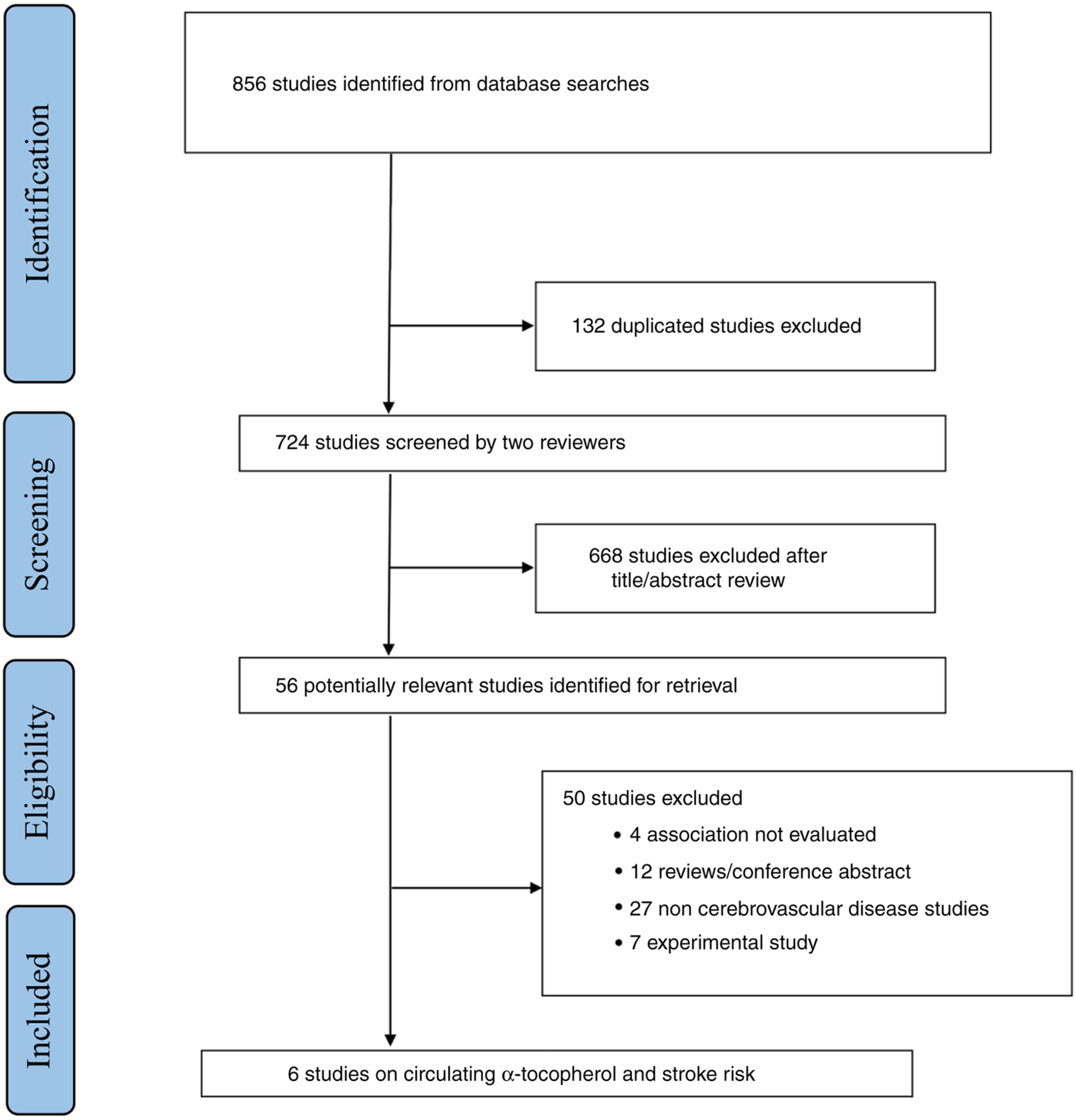

Figure 1. Flow chart of study selection. This diagram illustrates the systematic process of literature search, screening and the inclusion/exclusion criteria used to identify the final studies for the meta-analysis.

duration and physical activity are shown in Fig. 4. A high circulating α-tocopherol level was associated with a reduced stroke risk in the BMI <25 (RR, 0.57; 95% CI, 0.34-0.95; P=0.03), BMI >25 (RR, 0.80; 95% CI, 0.72-0.89; P<0.01), age ≥65 years (RR, 0.75; 95% CI, 0.59-0.95; P=0.02), age <65 years (RR, 0.73; 95% CI, 0.60-0.90; P<0.01), follow up duration ≤10 years (RR, 0.78; 95% CI, 0.68-0.89; P<0.01), physical activity adjusted (RR, 0.69; 95% CI, 0.57-0.84; P<0.01) and physical activity not adjusted (RR, 0.83; 95% CI, 0.73-0.94; P<0.01) subgroups. However, circulating α-tocopherol was not associated with a reduced stroke risk in the follow-up duration of >10 years subgroup (RR, 0.73; 95% CI, 0.49-1.09; P>0.05). The I^2 values were 15, 4 and 25% for the follow-up duration ≤10 years, follow-up duration >10 years and age >65 years subgroups, respectively. The I^2 values were 0 in the remaining subgroups.

Dose-response analysis. In total, 4 studies and 90,863 participants were included in the random-effects linear dose-response analysis. The results of this analysis showed that circulating α-tocopherol was associated with a reduced stroke risk (P-value for heterogeneity=0.55; P=0.015). Furthermore, each 5 mg/l increment of circulating α-tocopherol was related to an average 8% lower risk of stroke (RR=0.92; 95% CI, 0.85-0.98) (Fig. 5). Additionally, the models were checked for non-linearity; however, the results demonstrated no significant non-linearity (P>0.05).

Meta-regression, sensitivity and publication bias analyses. The meta-regression showed that follow-up duration (P=0.185), age (P=0.942) and physical activity (P=0.133) were not significant sources of heterogeneity (Fig. 6). Subgroup analyses

Table I. Characteristics of the studies on circulating α-tocopherol and stroke.

Author, year	Location	Age, years	Stroke events	Participants	Follow-up duration, years	RR (95% CI), high vs. low	Maximum adjustment	Quality score	(Refs.)
Leppälä *et al*, 1999	Finland	Range, 50-69	1057 TS 85 SAH 112 ICH 807 IS	28,519 M	8	SAH: 1.10 (0.53-2.31) ICH: 0.47 (0.23-0.93) IS: 0.70 (0.55-0.89)	Age, BMI, SBP, serum total and HDL cholesterol, smoking, alcohol consumption, diabetes, heart disease, education, physical activity, and α-tocopherol and β-carotene supplementation.	7	(9)
Hak *et al*, 2004	USA	Range, 40-84	297 IS	22,071 M	13	IS: 0.67 (0.36-1.26)	Age, smoking, BMI, total and HDL cholesterol, triglycerides, levels of other tocopherols, history of hyper-tension, diabetes mellitus, and parental history of MI before the age 60; frequency of vigorous exercise, alcohol and assignment to aspirin or β-carotene treatment or placebo.	8	(10)
Marniemi *et al*, 2005	Finland	Range, 65-99	70 TS	755 M and F	10	TS: 0.60 (0.31-1.18)	Age, sex, smoking, functional capacity and weight- adjusted energy intake.	7	(11)
Nagao *et al*, 2012	Japan	Range, 40-79	530 TS 302 IS 210 ICH	39,242 M and F	13	M: TS: 0.81 (0.41-1.60) IS: 0.83 (0.35-2.00) HS: 0.97 (0.25-3.77) F: TS: 0.35 (0.16-0.77) IS: 0.47 (0.14-1.52) HS: 0.26 (0.07-0.97)	BMI, smoking, alcohol drinking, history of hypertension and diabetes mellitus, walking, sports, total cholesterol and high-density lipoprotein cholesterol.	8	(13)
Karppi *et al*, 2012	Finland	Range, 46-65	67 TS 50 IS	1,031 M	12.1	TS: 1.08 (0.48-2.44) IS: 1.09 (0.44-2.73)	Age, examination year BMI, SBP, smoking, serum LDL cholesterol, diabetes and history of stroke	8	(12)

Table I. Continued.

Author, year	Location	Age, years	Stroke events	Participants	Follow-up duration, years	RR (95% CI), high vs. low	Maximum adjustment	Quality score	(Refs.)
Lind *et al*, 2020	Sweden	PIVUS: mean ± SD, 70.1±0.1 ULSAM: mean ± SD, 71.2±0.6 TwinGene: mean ± SD, 68.3±8.2	173 IS	12,591 M and F	4.3	IS: 0.83 (0.73-0.95)	Age, sex, systolic blood pressure, diabetes, smoking, LDL- and HDL-cholesterol, BMI and atrial fibrillation	8	(14)

BMI, body mass index; CI, confidence interval; CVD, cardiovascular diseases; F, females; HDL, high-density lipoprotein; HS, hemorrhagic stroke; ICH, intracerebral hemorrhage; IHD, ischemic heart disease; IS, ischemic stroke; M, males; MI, myocardial infarction; PIVUS, prospective investigation of the vasculature in uppsala seniors; Q, quartile; RR, relative risk; SAH, subarachnoid hemorrhage; SBP, systolic blood pressure; TS, total stroke; ULSAM, uppsala longitudinal study of adult men.

revealed low-to-moderate heterogeneity in specific groups (I^2 was 15, 4 and 25% for duration ≤10-year, duration >10-year and age ≥65-year subgroups, respectively). The sensitivity analysis showed that the summary results for circulating α-tocopherol and stroke risk remained robust when leaving any single study out; the summary RRs ranged between 0.70 and 0.81 (Fig. 7). Symmetrical characteristics were confirmed through visual inspection of the funnel plot, and no publication bias was detected (P>0.05) following Egger's test (Fig. 8).

Discussion

The novelty of the present study lies not in the general association between vitamin E and stroke, which has been previously documented (27,28), but rather in the specific analysis of circulating α-tocopherol levels and the implementation of comprehensive subgroup and dose-response analyses. Unlike prior research detailed stratifications by stroke type, BMI, age, follow-up duration and physical activity were conducted to identify specific susceptible populations. Furthermore, a rigorous dose-response analysis of circulating α-tocopherol was performed to clarify its physiological threshold. While a recent meta-analysis of RCTs suggested that vitamin E supplementation may help prevent ischemic stroke (28), it is notable that consumption at non-recommended doses might increase the risk of intracerebral hemorrhage (21). By focusing on circulating levels, the present study provides a more precise perspective to reconcile these conflicting findings.

Circulating α-tocopherol is the primary fat-soluble antioxidant; its abilities involve scavenging free radicals, protecting lipids from peroxidation and inhibiting LDL cholesterol oxidation; these abilities contribute to inhibiting atherosclerosis (29). Accumulating evidence also shows that tocopherols inhibit platelet aggregation and atherothrombosis (30,31).

All of the six studies (9-14) included in the present study reported associations between circulating α-tocopherol and overall stroke risk. Notably, three studies (9,13,14) showed that circulating α-tocopherol was associated with a lower overall stroke risk, whereas the remaining studies (10-12) showed that circulating α-tocopherol was not associated with overall stroke risk. Additionally, four included studies (9,10,12,13) examined ischemic stroke risk, whereas two included studies (9,13) examined hemorrhagic stroke risk. In the present study, the subgroup analysis results showed that a high circulating α-tocopherol level was related to a 43% lower stroke risk in the BMI-adjusted subgroup and a 20% lower stroke risk in the BMI-not-adjusted subgroup. A previous antioxidant study showed that a concoction of antioxidants (containing 800 IU of vitamin E, 10 mg of carotene and 500 mg of vitamin C) could lower exercise-induced lipid hydroperoxide levels in overweight adults compared with the placebo-treated overweight group (32). Oxidative stress can result in the excessive production of reactive oxygen species, which play essential roles in stroke-related neuronal injury (33).

In the present study, the subgroup analysis results also showed that a high circulating α-tocopherol level was related to a 31% lower stroke risk in the physical activity-adjusted subgroup and a 17% lower stroke risk in the physical activity-not-adjusted subgroup. Previous evidence shows that physical activity is a modifiable risk factor for stroke risk and that moderate physical

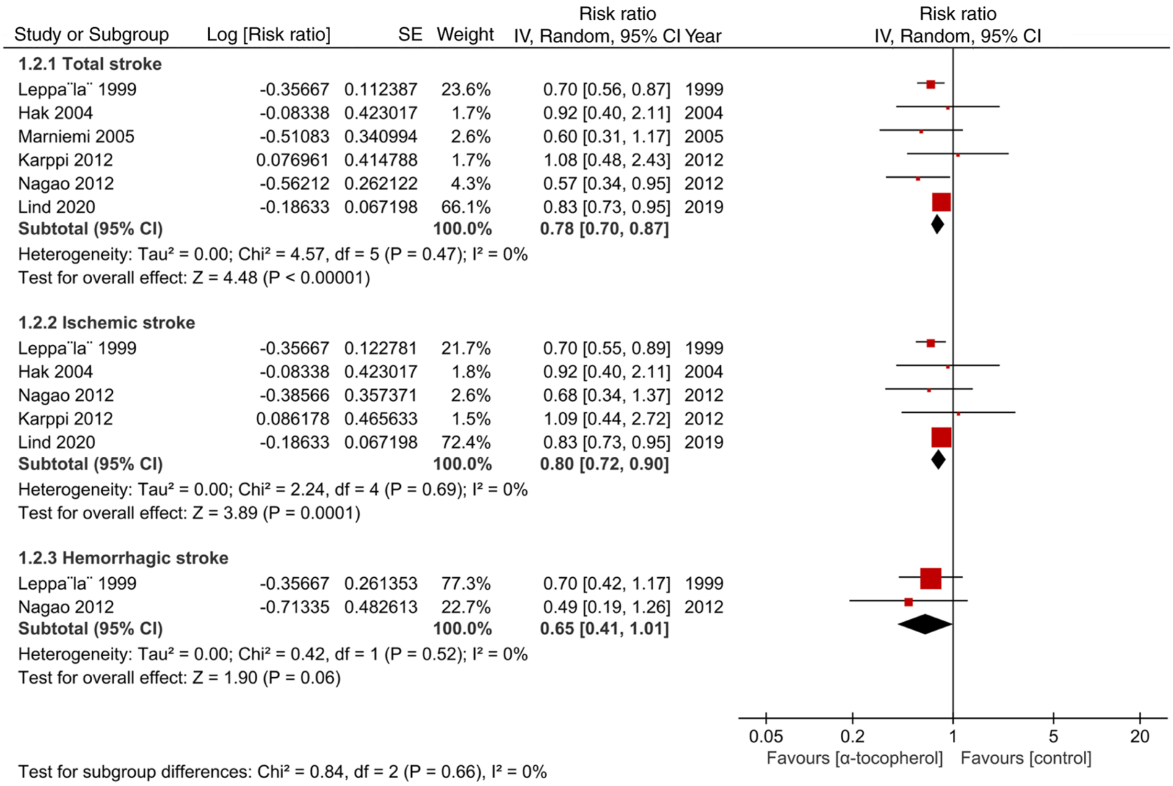

Figure 2. Meta-analysis of circulating α-tocopherol with stroke risk, ischemic stroke, and hemorrhagic stroke risk. The forest plots present the pooled risk ratios and 95% CIs. Statistical significance was set at P<0.05. CI, confidence interval.

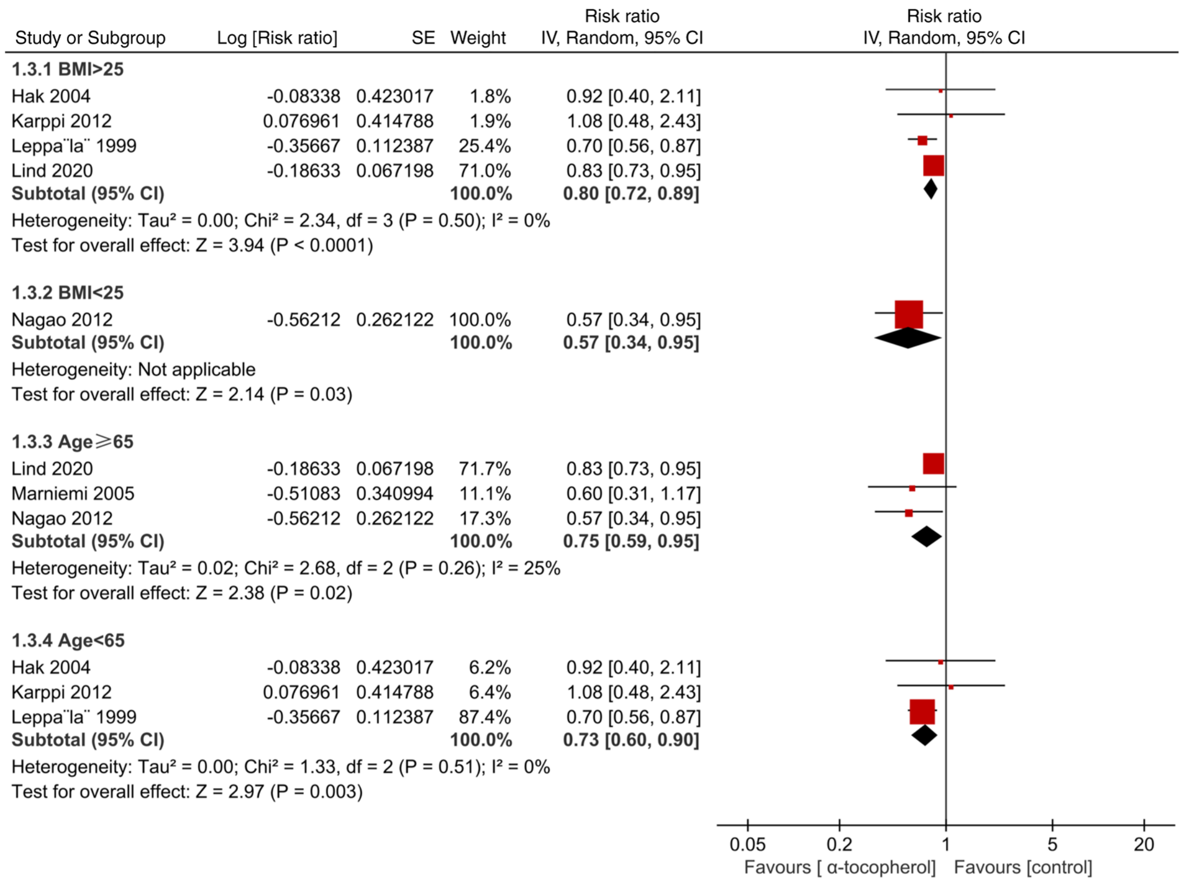

Figure 3. BMI and age subgroups analyses. These subgroup analyses evaluate whether the association between circulating α-tocopherol and stroke risk remains consistent across different BMI categories and age groups. Results are presented as risk ratios (RRs) and 95% CIs. BMI, body mass index; CI, confidence interval.

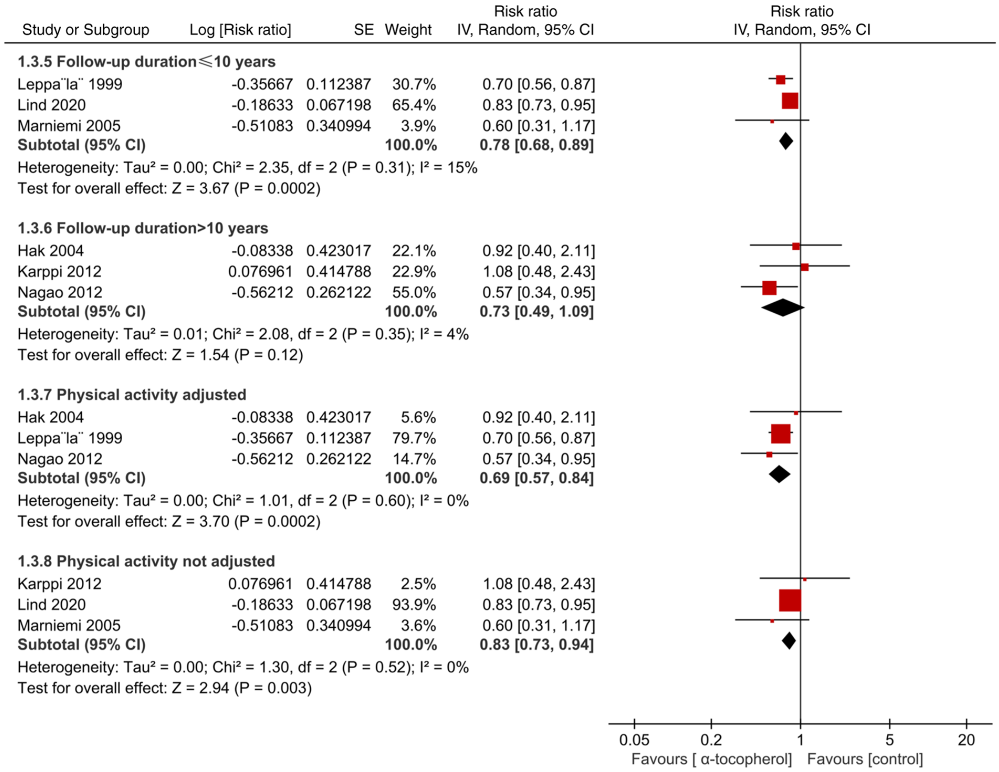

Figure 4. Follow-up duration and physical activity subgroups analyses. These subgroup analyses evaluate whether the association between circulating α-tocopherol and stroke risk is influenced by the length of follow-up or adjustments for physical activity. Results are presented as risk ratios and 95% CIs. CI, confidence interval.

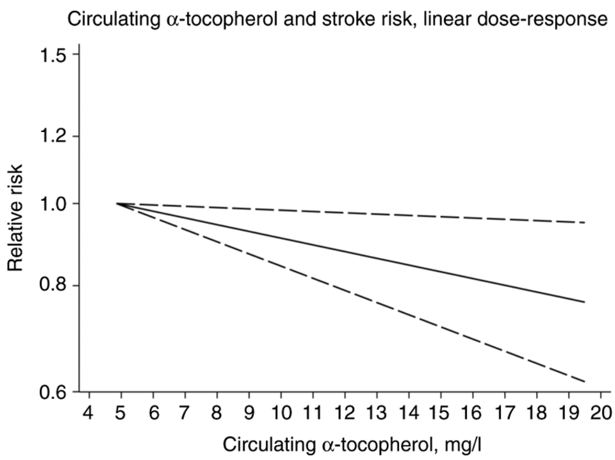

Figure 5. Circulating α-tocopherol and stroke risk. Dose-response analysis of circulating α-tocopherol levels and stroke risk. Summary estimates were calculated using a random-effects model (P=0.015). The solid and long-dashed lines represent the estimated relative risks and their 95% confidence intervals, respectively.

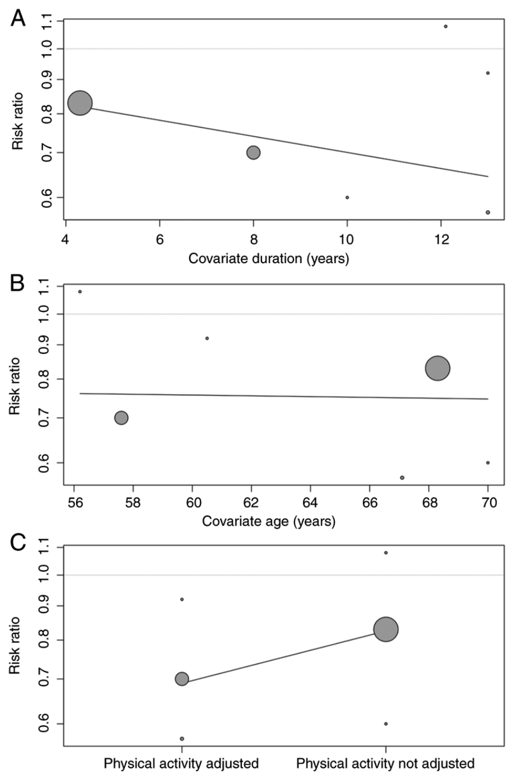

Figure 6. Meta-regression plots of potential moderators. (A) Follow-up duration (P=0.185); (B) age (P=0.942); (C) physical activity (analyzed as a dichotomous variable: adjusted vs. non-adjusted, P=0.133). In panel (C), the individual bubbles for the six studies are distributed into two columns based on their adjustment status. The size of each bubble represents the study's weight, and the P-values indicate no statistically significant moderating effects.

activity helps reduce stroke risk (34). Moreover, the subgroup analysis results indicated that follow-up duration affected the association of circulating α-tocopherol with stroke risk. As such, there may be a critical period for circulating α-tocopherol to achieve stroke risk reduction. However, the subgroup analysis results showed that the association between a high circulating α-tocopherol level and stroke risk was not markedly affected by age; a high circulating α-tocopherol level was related to a 25% lower stroke risk in the age ≥65 years subgroup and a 27% lower

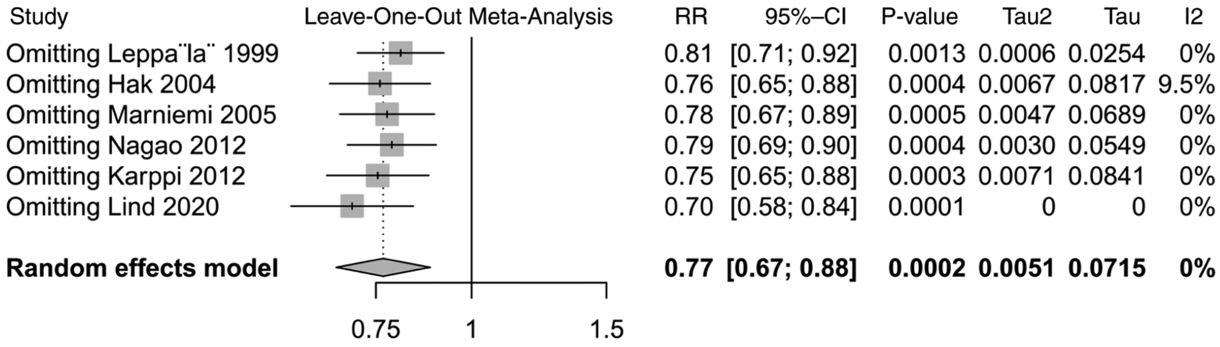

Figure 7. Leave-one-out sensitivity analysis of the association between circulating α-tocopherol levels and stroke risk. The vertical dashed lines represent the overall pooled RR and its 95% CI. This plot demonstrates that no single study significantly altered the summary results. RR, risk ratio; CI, confidence interval.

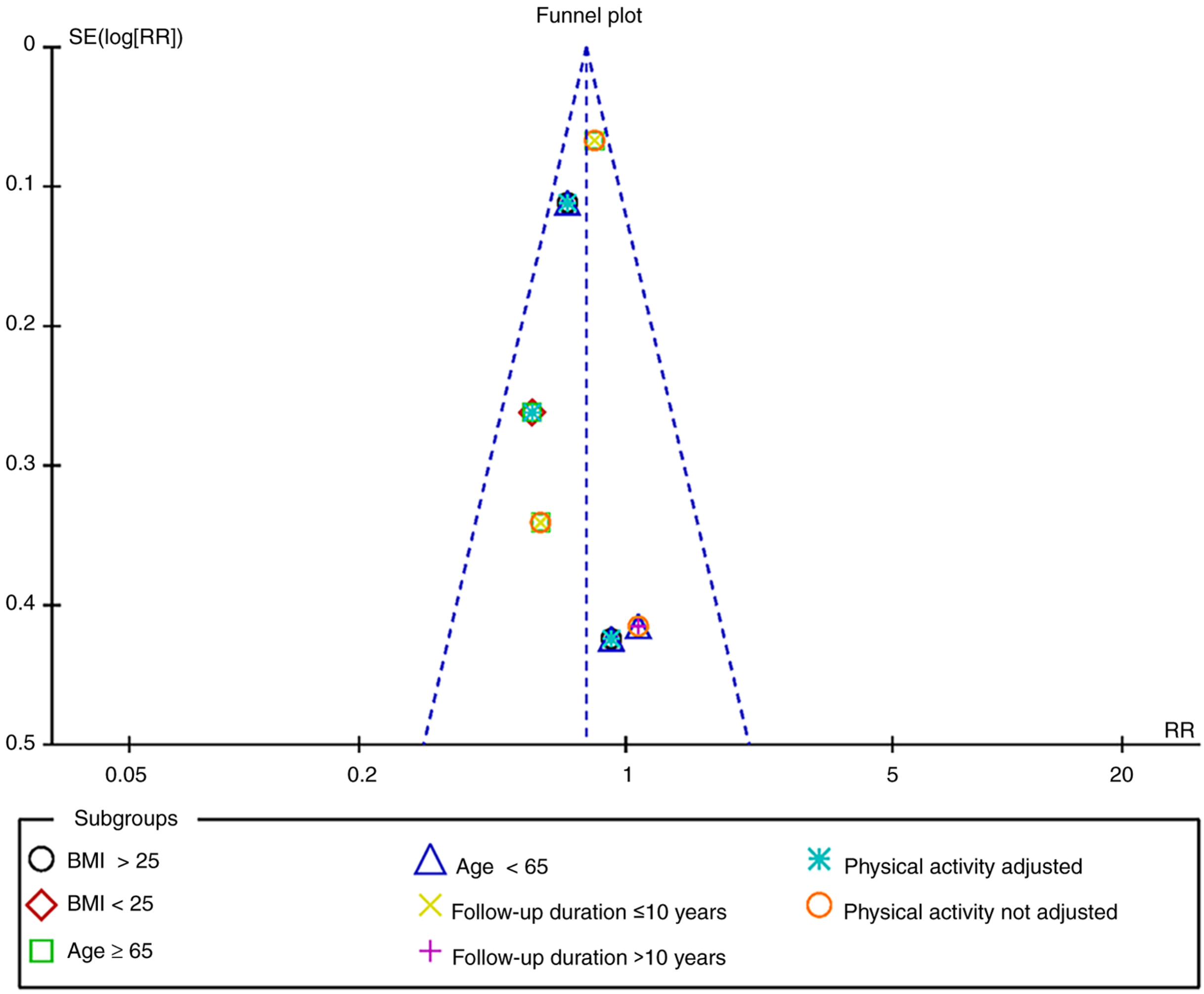

Figure 8. Funnel plot of circulating α-tocopherol and stroke risk. Different symbols and colors are used to distinguish study subgroups, including BMI, physical activity, age and follow-up duration. No significant publication bias was detected (Egger's test, P>0.05). BMI, body mass index; RR, risk ratio.

stroke risk in the age <65 years subgroup; the subgroup analysis results for follow-up duration >10 years were not significant. It is notable that the point estimate (RR=0.73) was similar to that of the other subgroups, but the CI was wide, likely due to reduced power.

The studies included in the present study reported that the vitamin E consumption was mainly derived from foods such as olive oils, nuts and vegetables. No adverse effects were reported for high or low dietary vitamin E intake. In total, two included studies (11,13) reported that an individual's average vitamin E intake was <10 mg/day. Previous evidence has demonstrated that the methods of cooking foods typically influence the absorption of vitamin E (27).

Several limitations of the present study should be acknowledged. Firstly, the subgroup analysis results should be interpreted cautiously due to the limited sample size and the number of cases. Secondly, the interpretation of the BMI subgroup results should be approached with caution as only one included study (13) provided an RR for individuals with a mean BMI <25; a meaningful summary RR for these individuals could not be calculated from a single study. Thirdly, only one included study (9) reported the relationship between circulating α-tocopherol and subarachnoid stroke; thus, the summary RRs for subarachnoid stroke could not be estimated. The results of the meta-regression analyses showed that follow-up duration, age, and physical activity adjustment status were not the sources of heterogeneity between studies. Given the relatively small number of studies included (n=6) the power of the meta-regression to detect true moderators was low. The I^2 statistic value for the primary analysis (total stroke) was 0. However, the I^2 values were 15, 4 and 15% for the follow-up duration ≤10 years, follow-up duration >10 years and age >65 years subgroups, respectively. Thus, low heterogeneity may exist due to the varied follow-up durations and ages of the patients. Finally, besides the subgroups, the limitation of the overall small number of included studies may have influenced the outcomes. In the present study, meta-regression and sensitivity analysis were utilized to assess the robustness of the findings. Although the overall heterogeneity was negligible (I^2=0.00%), the fluctuations observed in subgroup analyses (ranging from 4-25%) suggest that varied follow-up durations and patient ages may influence outcomes. Given the small number of studies (n=6), the statistical power of the meta-regression should be interpreted with caution. However, the consistent results across the leave-one-out analysis (RR range: 0.70-0.81; all P<0.05) further confirm the reliability and robustness of the observed effect.

In conclusion, the results of the present meta-analysis indicate that a higher circulating α-tocopherol level may be related to lower ischemic but not hemorrhagic stroke risk. Notably, while physical activity is a critical determinant of stroke risk, the protective association of α-tocopherol remains significant and is further strengthened after accounting for this factor. This suggests that α-tocopherol may play a vital role in stroke prevention, particularly within the context of active lifestyle management.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

PX conceived and designed the study, analyzed and interpreted the data and performed the primary meta-analysis. PC performed the meta-regression and sensitivity analysis, wrote the initial draft, and edited the manuscript. Both PX and PC participated in the proofreading and verification of the final manuscript. PX and PC confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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