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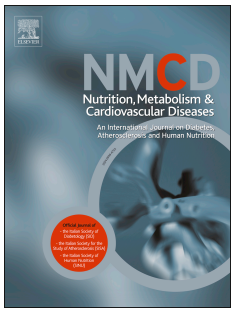

Supplementation with vitamin e alone is associated with reduced myocardial infarction: a meta-analysis

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SUPPLEMENTATION WITH VITAMIN E ALONE IS ASSOCIATED WITH REDUCED MYOCARDIAL INFARCTION: A META-ANALYSIS.

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[5]Supplemental Table 1 is available as Online Supporting Material with the online posting of this paper at http://jn.nutrition.org

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[6]*Conflicts of Interest: All the Authors approved the submitted version of this manuscript and declare that no conflict of interest exists.*

[7] *This review was conducted and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) Statement.*

[8]Abbreviations list - ROS:reactive oxidant species RCTs: randomized clinical trials

Abstract

Background and Aims: Previous meta-analyses of interventional trials with vitamin E provided negative results but it remains unclear if this vitamin has some influence on cardiovascular events when supplemented alone. The aim of this study was to compare the effect of vitamin E alone or in combination with other antioxidants on myocardial infarction.

Methods and Results: Pubmed, ISI Web of Science, SCOPUS and Cochrane database were searched without language restrictions. We investigated randomized clinical trials studying the effect of vitamin E supplementation on myocardial infarction. Sixteen randomized controlled trials of vitamin E treatment were analyzed in this meta-analysis. The dose range for vitamin E was 33 to 800 IU. Follow-up ranged from 0.5 to 9.4 years. Compared to controls, vitamin E given alone significantly decreased myocardial infarction (3.0% vs 3.4%) (random effects R.R.: 0.82; 95% C.I., 0.70-0.96; p=0.01). This effect was driven by reduction of fatal myocardial infarction (random effects R.R.: 0.84; 95% C.I., 0.73-0.96; p=0.01).

Conclusions: When supplemented alone, vitamin E reduces myocardial infarction in interventional trials while it appears ineffective when associated with other antioxidants.

Keywords: vitamin E, atherosclerosis, myocardial infarction, cardiovascular events.

INTRODUCTION

The oxidative stress theory of atherosclerosis is based on the assumption that the initial phase of atherosclerosis is dependent upon oxidative modification of LDL. Thus, LDL accumulates within the arterial wall with ensuing LDL uptake by monocyte-macrophages *via* the scavenger receptors[1]. Even if recent experimental studies further reinforced the role of reactive oxidant species (ROS) on atherosclerosis [2, 3], a cause-effect association between ROS and plaque destabilization is still elusive. Furthermore, the role of ROS in favoring atherosclerotic damage has been recently questioned because interventional trials with antioxidants in humans provided inconclusive results[2]. Among the antioxidants used in the interventional trials, vitamin E, which inhibits lipid peroxidation, has been the most investigated molecule. The strong interest for this antioxidant was based on observational studies suggesting that in subjects following a diet rich in vitamin E the incidence of cardiovascular events was significantly reduced[3]. Meta-analyses of interventional trials with vitamin E reached conclusions apparently in contrast with observational studies as they consistently failed to show any beneficial effect of vitamin E but even revealed some potentially harmful effects including increase of all-cause mortality[4, 5] or hemorrhagic stroke[6]. These meta-analyses, however, included trials in which vitamin E was used alone or in combination with other antioxidants such as ascorbic acid or carotenoids[4-6][7]. As potentially negative interaction between vitamin E and other antioxidants cannot be excluded[8], we investigated if analysis of trials in which only vitamin E was supplemented would have provided different findings. Therefore, we performed two distinct meta-analyses separating the effect of vitamin E in trials where it was supplemented alone with trials where it was supplemented in combination with other antioxidants to evaluate the effect of vitamin E on myocardial infarction.

METHODS

ELIGIBILITY CRITERIA.

Types of studies: Randomized clinical trials (RCTs) studying the effect of vitamin E supplementation on myocardial infarction. No language, publication date, or publication status restrictions were imposed.

INFORMATION SOURCES.

The studies were identified by searching electronic databases. This search was applied to Pubmed, ISI Web of Science, SCOPUS and Cochrane library. The last search was run on December 4th 2014. Reference lists of all studies included in the present systematic review were screened for potential additional eligible studies.

SEARCH.

Two investigators (L.P. and L.L.) independently searched in the electronic databases combining the following text terms and MeSH terms:

("Vitamin E" [Mesh]AND (("cardiovascular system"[MeSH Terms] OR cardiovascular[Text Word]) AND events[All Fields]) OR "myocardial infarction"[All Fields] AND "Vitamin E/therapeutic use" [Mesh] filtered randomized controlled trials - clinical trials.

We limited our search to humans.

STUDY SELECTION.

Two authors (L.L., L.P.) independently reviewed titles and abstracts generated by search. Studies were excluded if the title and/or abstract showed that the papers did not meet the selection criteria of our meta-analysis. For potentially eligible studies or if the relevance of an article could not be excluded with certitude we procured the full text. Disagreements were resolved by discussion between L.L. and L.P.; if no agreement reached, a third author (F.V.) decided.

Studies not including a control group drawn from the same population, animal studies, or trials that exclusively reported clinical outcomes other than cardiovascular were excluded. Case reports, editorials, commentaries, letters, review articles, guidelines were also excluded from the analysis.

We defined the following inclusion criteria:

(1) Randomised, placebo controlled design with a follow-up of ≥6 months

(2) Investigating the effect of vitamin E on myocardial infarction.

(3) If multiple papers reported on a trial, we chose either the original report or the report that was most informative about the main outcome of myocardial infarction.

Main analysis

We investigated the association between supplementation of vitamin E given alone or vitamin E plus other antioxidants on myocardial infarction, fatal or non-fatal myocardial infarction.

We conducted all analyses according to the intention-to-treat principle. For trials with a 2 factorial design, we based main results on 2-way analyses, that is, all trial participants receiving vitamin E given alone or in association with other antioxidants were compared with the group of participants who not received vitamins. For factorial randomized trials that evaluated two or more interventions, according to Mc Alister et al. [9] we performed an "inside the table" analysis. This analysis was performed to avoid the possibility of unrecognized interactions between treatments [9] and evaluates their efficacy comparing the outcomes of these treatments vs patients who did not receive them [9].

To be included RCTs had to report the efficacy of vitamin or antioxidant supplements for the prevention of myocardial infarction.
The total overall effect was calculated combining the data of the group A (where supplementation with vitamin E was given alone) with group B (where supplementation with vitamin E was given with other antioxidant agents).

Quality assessment

This review was conducted and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) Statement issued in 2009[10].

Types of allocation concealment

Types of allocation concealment were described according Cochrane Handbook[11].

• Adequate, if the allocation of patients involved a central independent unit, on-site locked computer, identically appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed envelopes.

• Unclear, if the trial was described as randomised, but the method used to conceal the allocation was not described.

• Inadequate, if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised.

Statistical analysis

To evaluate the effect of vitamin E supplementation on cardiovascular events, we allocated the results of each randomized controlled trial as dichotomous frequency data. We considered a P value <0.05 as significant. Risk ratios (RR) and 95% confidence intervals (CIs) were calculated. These data were pooled using a randomised-effect model. Statistical heterogeneity was calculated by the I^2 [12]. The I^2 value estimates the amount of variance across studies due to heterogeneity rather than chance. We considered the following scores: I^2 25% for mild heterogeneity, 50% for moderate heterogeneity, and 75% for high level of heterogeneity[13]. To reduce the probability of committing a type I error due to the high number of subgroup comparisons, an adjustment for multiple comparisons was considered following the Sidak method[14].

The software Comprehensive Meta Analysis (version 2.2.064, USA, 2011) supported the analysis.

The presence of publication bias was evaluated by using the Begg's[15] and Egger's[16] tests (reporting the 1-tailed p-value).

Results

Study identification

A total of 16 studies[17-34] met the inclusion criteria and were included in this meta-analysis (Table 1).

The study identification and selection progression is summarized in Figure 1.

All studies were written in English. The 16 studies ranged in size from 100 to 39,876 patients (Table 1). Allocation concealment of the RCT is reported in Table 1.

The meta-analysis was performed after identification of two typologies of interventional trials: Supplementation A= supplementation with vitamin E alone, supplementation B= supplementation with vitamin E plus other antioxidant agents (e.g. multivitamins[35], vitamin A[36], vitamin C[35, 37], beta carotene[38], n-3 polyunsaturated fatty acids (PUFA)[39], ramipril[40], selenium[41]).

Further analyses, in patients treated with Vitamin E (any kind of supplementation) vs control, were performed to examine: type of cardiovascular prevention (primary vs secondary studies) and vitamin E dosage (low <400 IU vs high dosage ≥400 IU) (Supplemental Table 2).

STUDY POPULATION

Clinical characteristics of the study populations are illustrated in Table 1. All the trials included subjects with an average age >50 years. Men and women were almost equally distributed in all trials with the exception of four trials where three recruited only women (WAVE[29], WHS[30] and WACS[21]) and two only men (ATBC[23] and PHS[28]). To avoid the possible influence of hormone replacement therapy and probucol on cardiovascular events, patients randomized to these therapy in the WAVE[29] and MVP study[27], were excluded.

META-ANALYSIS OF INTERVENTIONAL TRIALS

As a result of widespread heterogeneities among trials we decided to present the analysis with random effects pooling.

Myocardial Infarction

Sixteen studies assessed the effect of vitamin E on myocardial infarction (Figure 2, Panel A). The total overall effect did not show difference between antioxidant-treated subjects and controls. However, significant differences were observed when supplementations A and B were separately analysed. Compared with control, supplementation group A showed a significant reduction of myocardial infarction (3.0% vs 3.4%) (random effects R.R.: 0.82; 95% C.I., 0.70-0.96; p=0.01) (Figure 2) and was associated with an absolute risk reduction (ARR) of 0.36%. No significant reduction was observed comparing subjects treated with a combination of antioxidants (supplementation B) versus controls (Figure 2, Panel A). The p value for difference between groups A and B was 0.03. The heterogeneities among trials were: I^2=40 (p=0.02) for total overall effect, I^2=59 (p=0.02) for group A and I^2=8 (p=0.36) for group B. No evidence of publication bias was observed (Begg's test, p=0.276; Egger's test, p=0.09).

Subgroup meta-analysis by vitamin E dosage, showed that a significant reduction of myocardial infarction was observed in A group only for high dosage (≥400 IU) of vitamin E (Figure 2 Panels B and C) (random effects R.R.: 0.68; 95% C.I., 0.50-0.93; p=0.01)(Figure 2 Panel C).

Fatal Myocardial Infarction

Twelve studies assessed the effect of vitamin E on fatal myocardial infarction. Compared with control, supplementation group A showed a significant reduction of fatal myocardial infarction (1.1% vs 1.3%) (random effects R.R.: 0.84; 95% C.I., 0.73-0.96; p=0.01) (Figure 3) with an absolute risk reduction (ARR) of % 0.17. No significant reduction was observed comparing group treated subjects with controls in group B (Figure 3). The p value for difference between A and B groups was 0.16. The heterogeneities among trials were: I^2=17 (p=0.27) for total overall effect, I^2=0 (p=0.66) for group A and I^2=24 (p=0.24) for group B. No evidence of publication bias was observed (Begg's test, p=0.28; Egger's test, p=0.09).

Non Fatal Myocardial Infarction

Twelve studies assessed the effect of vitamin E on non-fatal myocardial infarction. Compared with control, no significant reduction was observed in supplementation studies A and B (Figure 4). The p value for difference between A and B groups was 0.70. The heterogeneities among trials were: I^2=36 (p=0.08) for total overall effect, I^2=64 (p=0.01) for group A and I^2=0 (p=0.69) for group B. No evidence of publication bias was observed (Begg's test, p=0.29; Egger's test, p=0.15).

Further subgroups analysis for myocardial infarction, fatal myocardial infarction and non-fatal myocardial infarction did not show significant differences according to the type of cardiovascular prevention (primary vs secondary studies), and vitamin E dosage (low <400 IU vs high dosage ≥400 IU) (see supplemental material, table 1).

DISCUSSION

This study provides evidence that vitamin E supplementation in a range of 400-800 IU/daily is able to decrease myocardial infarction.

In contrast with observational studies showing an inverse association between dietary intake of vitamin E and cardiovascular events[3], supplemental trials with this vitamin provided un-conclusive results. Reviews or meta-analyses of interventional trials consistently showed negative and even harmful effects[6, 42, 43]; in a few cases positive results were reported but they were limited by several methodological shortcomings [7, 44]. Meta-analyses usually included interventional trials which examined the effect of vitamin E without excluding the interventional trials in which vitamin E was combined with other antioxidants. The use of a cocktail of antioxidants has been based on the assumption that a combination of antioxidants could exert a synergistic activity which ultimately leads to an antioxidant activity higher than that potentially achievable by a single antioxidant[8]. However, this assumption has never been supported by any experimental study[8]. Conversely, a cocktail of molecules with different antioxidant properties may negatively influence the activity of a single antioxidant and offset its potentially beneficial effect because of deleterious side effects. For instance, as vitamin C has been shown to exert pro-oxidant activity when administered “per os” to humans[8, 45], it cannot be excluded that this “paradox” effect has limited the antioxidant property of vitamin E. Also more relevant is the demonstration that beta-carotene supplementation is associated with a significant increase of total mortality, which could counteract potential beneficial effects of vitamin E[46]. Therefore, based on this putative negative interaction, we reasoned that it should be more appropriate to examine the beneficial effects, if any, of vitamin E, in trials where it was administered not in combination with other antioxidants.

The novelty of the present meta-analysis is the demonstration of a different efficacy of vitamin E when used alone or in combination with other antioxidants. In particular, we found that vitamin E supplementation significantly reduced myocardial infarction by about 20%. Such clinical efficacy was essentially driven by a reduction of fatal myocardial infarction while no effect was observed for nonfatal myocardial infarction. A similar finding has been shown by Myung et al[7], who found a significant reduction of myocardial infarction in patients treated with vitamin E. At variance with this report a reduction of MI was detected only when vitamin E was given alone while no significant changes were detected in patients given a mixture of antioxidants, vitamin E included.

The meta-analysis also provides information on the impact of different vitamin E dosage on myocardial infarction; thus, a beneficial effect could be observed only with vitamin E dose ≥400 IU/day while lower dosage was ineffective.

Different mechanisms may account for the reduction of myocardial infarction by vitamin E supplementation. In addition to its anticoagulant and antiplatelet effects, vitamin E has been shown to limit atherosclerotic progression in many but not all experimental studies[47, 48]. Human studies supported the anti-atherosclerotic activity of vitamin E. Thus, in patients undergoing carotid endo-arterectomy, injection of I^{125}-labeled autologous LDL resulted in LDL accumulation within macrophages of atherosclerotic plaque, a phenomenon which was significantly reduced by vitamin E pre-treatment[49]. This prompted the suggestion that vitamin E may exert an anti-atherosclerotic effect by preventing LDL accumulation within the vessel wall via an oxidative stress-mediated mechanism[49]. It should be underlined, however, that the antioxidant effect could not be the only mechanism accounting for the anti-atherosclerotic property as vitamin E possesses other anti-inflammatory activities such as inhibition of muscle cell proliferation, monocyte-endothelial adhesion and inflammatory cytokine release[50-52], which are independent from inhibition of oxidative stress.

This study has several implications and limitations. The fact that vitamin E, which is a known antioxidant, reduced the clinical *sequelae* of atherosclerotic disease may suggests the oxidative stress theory is still valid and that modulation of oxidative stress should be an important future goal to achieve to reduce atherosclerosis.

Our meta-analysis included study populations with different degree of vascular events as both primary and secondary prevention trials were analyzed. However, most of these were secondary prevention trials, therefore caution should be used when extrapolating the present findings to general population. To define the study end-points, we accepted the definition contained in the trials examined; however, analysis of hard end-points should have reduced potential bias. Furthermore, another potential limitation was represented by statistical power based on limited number of trials selected.

The present meta-analysis did not address as to whether vitamin E supplementation affects total mortality because total mortality was not always considered as an end-point of the trials included in the meta-analysis. This issue is of relevance as previous meta-analysis indicated that high doses of vitamin E may be associated with an increase of total mortality[4, 5]. Conversely, other metanalyses did not report this increased of total mortality[53, 54]. Another limitation of the study concerns the fact that placebo control arms of GISSI, ATBC, and PHS studies are all double counted for the overall combined estimates; this generates non-independency in the data, limited to these 3 studies.

Based on the positive results of this meta-analysis, we believe that the potential clinical benefit of vitamin E supplementation for primary or secondary prophylaxis of atherosclerosis should be further investigated in interventional trials. In this context, pharmaco-dynamic studies assessing the effect of vitamin E on markers of either clotting and platelet activation or oxidative stress should be done in patients at risk or with cardiovascular events to define the optimal dose which affects either.

In conclusion, the results of this meta-analysis are in favor of a protective role of vitamin E supplementation alone in reducing myocardial infarction. The use of a combination of antioxidants as anti-atherosclerotic therapy is ineffective and potentially harmful. Due to the wide variability of vitamin E dosage employed in interventional trials, future study should address the evaluation of the lowest vitamin E dosage which possesses anti-atherosclerotic property and effectively prevents cardiovascular events.

Acknowledgement section

Contributors' statement: LL and FV contributed to the conception and design of the study. All the authors participated in writing the manuscript, and approved the final draft. LL and LP undertook the literature search and retrieval of publications. LL, LP, ADC and LI performed statistical analysis. All authors have read and approved the submission.

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Figure Legends:

Figure 1: Studies' progression analysis.

Figure 2: Meta-analysis of myocardial infarction.

Supplementation: A= supplementation with vitamin E alone, supplementation B= supplementation with vitamin E plus other antioxidant agents.

Figure 3: Meta-analysis of fatal myocardial infarction.

Supplementation: A= supplementation with vitamin E alone, supplementation B= supplementation with vitamin E plus other antioxidant agents.

Figure 4: Meta-analysis of non-fatal myocardial infarction.

Supplementation: A= supplementation with vitamin E alone, supplementation B= supplementation with vitamin E plus other antioxidant agents.

Table 1

Characteristics of the RCT with vitamin E:

Trials	Type of supplementation	Study design	Patients included (n) ***	Age at enrolment (years)	Gender	Health Status	Type of prevention	Treatment	Follow-up (years)	Allocation Concealment
CHAOS 1996 [17](GB)	A	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*	adequate
GISSI[18] 1999 (Italy)	A/B	Open label RCT	5658	No limit	Mixed	patients surviving recent myocardial infarction (<3 months)	Secondary	Vitamin E 300 mg daily (synthetic) (=330IU daily), n-3 PUFA, or Vitamin E 300 mg daily (synthetic) plus n-3 PUFA	3.4†	adequate
Milman[19] 2008 (Israel)	A	Double blind RCT	984	≥55	Mixed	Type 2 Diabetes Mellitus and Haptoglobin 2-2 genotype	-	Vitamin E 400 IU daily (natural)	1.4	adequate
PPP[32] 2001 (Italy)	A	Open label RCT	4495	≥65	Mixed	≥1 CVD risk factor, no overt CVD event	Primary	Vitamin E 300 mg daily (synthetic)) (=330IU daily)	Mean 3.6, median 4.0	adequate
SPACE[20] 2000 (Israel)	A	Double blind RCT	196	40–75	Mixed	Haemodialysis patients with history of CVD	Secondary	Vitamin E 800 IU daily (natural)	Median	adequate

Trials	Type of supplementation	Study design	Patients included (n) ***	Age at enrolment (years)	Gender	Health Status	Type of prevention	Treatment	Follow-up (years)	Allocation Concealment
						events			1.4*	
WHS[30] 2005 (US)	A	Double blind RCT	39876	≥45	Women	No history of CVD, cancer, or other major disease	Primary	Vitamin E 600 IU every other day (natural) and aspirin (100 mg)	Mean 10.1	adequate
POPADAD[22] 2008 (Scotland)	B	Double blind RCT	638	≥40	Mixed	Diabetes Mellitus and asymptomatic peripheral arterial disease	Primary	Vitamin E 200 mg** and ascorbic acid 100 mg, aspirin, or either	Median 6.7	adequate
ATBC[23, 34] 1994 (Finland)	A/B	Double blind RCT	29133	50–69	Men	Smokers, no cancer, no other serious illnesses, no previous stroke	Primary	Vitamin E 50 mg** daily and/or 20 mg β carotene (synthetic)	Median 6.0	adequate
HATS[24] 2001 (Canada, US)	B	Double blind RCT	160	<70	Mixed	CHD, low HDL cholesterol, normal LDL	Secondary	Vitamin E 800 IU daily (natural), 1000 mg Vitamin C, 25 mg β carotene, 100 µg selenium, simvastatin, niacin	3	unclear
HOPE[25] 2000 (international)	B	Double blind RCT	9541	≥55	Mixed	High risk for CVD including previous CVD	Secondary	Vitamin E 400 IU daily (natural), ramipril	Mean 4.5	unclear

Trials	Type of supplementation	Study design	Patients included (n) ***	Age at enrolment (years)	Gender	Health Status	Type of prevention	Treatment	Follow-up (years)	Allocation Concealment
						events, vascular disease, or diabetes				
HPS[26] 2002 (UK)	B	Double blind RCT	20536	40-80	Mixed	CHD, other occlusive arterial disease, or diabetes	Secondary	Vitamin E 600 mg (synthetic) (=660 IU daily), 250 mg vitamin C, and 20 mg carotene daily	3	adequate
MVP[27] 1997 (Canada)	B	Double blind RCT	317	-	Mixed	CHD, angioplasty	Secondary	Vitamin E 350 IU, 250 mg Vitamin C, 15000 IU beta carotene, probucol, or either twice daily	0.5	adequate
PHS[28] 2008 (US)	A/B	Double blind RCT	14641	≥50	Men	Mostly healthy; 5.1% had prevalent CVD	Primary	Vitamin E 400 IU every other day (synthetic) and/or vitamin C (500 mg/day)	Mean 8.0, median 7.6	adequate
WAVE[29] 2002 (Canada, US)	B	Double blind RCT	423	-	Women	Postmenopausal women	Secondary	Vitamin E 400 IU, 500 mg Vitamin C, twice daily	Mean 2.8	adequate
WACS[21] 2007 (US)	B	Double blind RCT	8171	≥40	Women	High risk for CVD: history of CVD event or ≥3 cardiac risk factors	Secondary	Vitamin E 600 IU every other day (natural)	Mean 9.4	unclear

Trials	Type of supplementation	Study design	Patients included (n) ***	Age at enrolment (years)	Gender	Health Status	Type of prevention	Treatment	Follow-up (years)	Allocation Concealment
CLIPS[31] 2007 (international)	B	Double blind RCT	366	-	Mixed	Peripheral arterial disease	Primary	Vitamin E 600 mg**, Vitamin C 250 mg, beta carotene 25 mg, aspirin, or either	Mean 1.7	adequate

A= supplementation with vitamin E alone, supplementation B= supplementation with vitamin E plus other antioxidant agents (e.g. multivitamins[35], vitamin A[36], vitamin C[35, 37], beta carotene[38], n-3 polyunsaturated fatty acids (PUFA)[39], ramipril[40], selenium[41]).

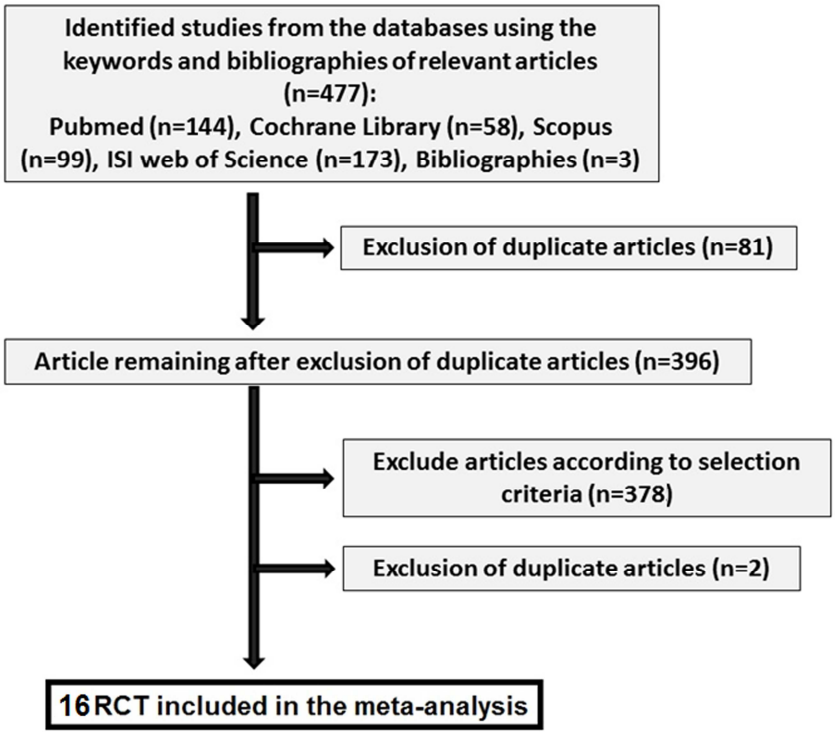
RCT=randomised controlled trial; CVD=cardiovascular disease; MI: myocardial infarction.

*Calculated as (No of days of follow-up)/365.

†Calculated as (person years)/(No of participants).

** - one IU is 0.67 milligram of alpha-tocopherol. for *natural* vitamin E (d-alpha-tocopherol); to convert milligrams of d-alpha-tocopherol to IUs multiply the number of milligrams by 1.5. For the *synthetic* form of the vitamin, called dl-alpha-tocopherol, the conversion factors is 0.45.

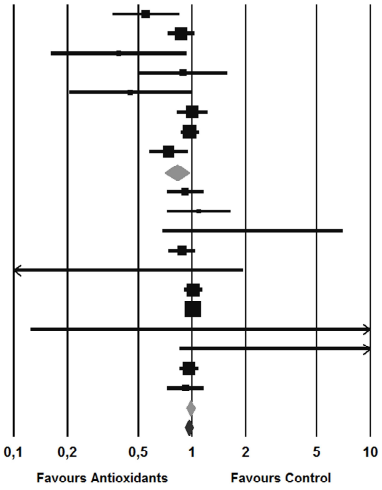
******* The number of patients is related to that included in the original study; it is not related to the number of patients reported in the study outcomes of this metanalysis, where participants who assumed the non-vitamin E agent plus placebo were not included (see "inside the table" analysis in the methods).



A

Myocardial Infarction

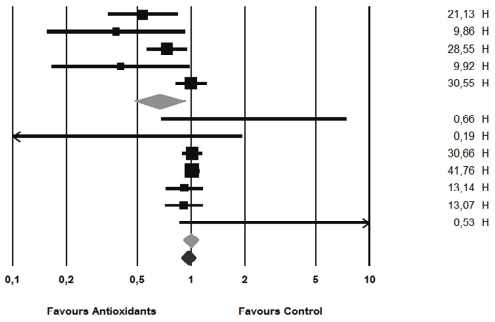
Group by Subgroups	Study name	Risk ratio	Lower limit	Upper limit	p-Value	Vitamin E	Control	Relative weight
A	CHAOS	0,554	0,361	0,850	0,007	32 / 1035	54 / 967	8,79
A	GISSI (1)	0,872	0,735	1,034	0,116	226 / 2830	259 / 2828	20,50
A	Milman	0,391	0,163	0,933	0,034	7 / 505	17 / 479	2,81
A	PPP	0,893	0,505	1,579	0,697	22 / 2231	25 / 2264	5,77
A	SPACE	0,454	0,207	0,994	0,048	8 / 97	18 / 99	3,39
A	WHS	1,005	0,825	1,224	0,959	196 / 19937	195 / 19939	18,90
A	ATBC (1)	0,976	0,869	1,096	0,682	519 / 6820	534 / 6849	23,70
A	PHS II (1)	0,742	0,580	0,949	0,017	107 / 3659	144 / 3653	16,14
A		0,825	0,707	0,962	0,014	1117 / 37114	1246 / 37078	
B	WACS	0,917	0,727	1,158	0,467	131 / 4083	143 / 4088	5,70
B	POPADAD	1,096	0,731	1,642	0,658	43 / 320	39 / 318	1,95
B	CLIPS	2,201	0,690	7,021	0,182	9 / 185	4 / 181	0,24
B	GISSI Vit. (2)	0,880	0,742	1,043	0,140	228 / 2830	259 / 2828	10,26
B	HATS	0,226	0,026	1,936	0,175	1 / 42	4 / 38	0,07
B	HOPE	1,019	0,910	1,142	0,742	532 / 4761	524 / 4780	20,75
B	HPS	1,015	0,936	1,101	0,717	1063 / 10269	1047 / 10267	35,07
B	MVP	3,038	0,126	73,454	0,494	1 / 78	0 / 79	0,03
B	WAVE	3,086	0,859	11,084	0,084	9 / 105	3 / 108	0,20
B	ATBC (2)	0,967	0,860	1,086	0,567	511 / 6781	534 / 6849	19,93
B	PHS II (2)	0,923	0,732	1,163	0,496	133 / 3656	144 / 3653	5,79
B		0,985	0,930	1,043	0,605	2661 / 33110	2701 / 33189	
Overall		0,964	0,914	1,017	0,182	3778 / 70224	3947 / 70267	



B

Myocardial Infarction (High dosage)

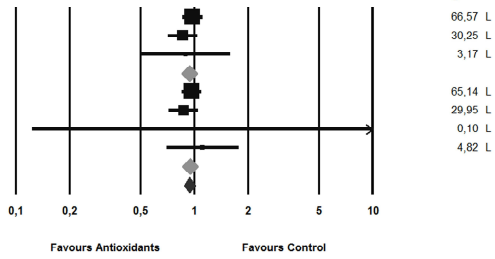
Group by Subgroups	Study name	Odds ratio	Lower limit	Upper limit	p-Value	Vitamin E	Control	Relative weight
A	CHAOS	0,539	0,345	0,843	0,007	32 / 1035	54 / 967	21,13 H
A	Milman	0,382	0,157	0,930	0,034	7 / 505	17 / 479	9,86 H
A	PHS II (1)	0,734	0,569	0,947	0,017	107 / 3659	144 / 3653	28,55 H
A	SPACE	0,404	0,167	0,981	0,045	8 / 97	18 / 99	9,92 H
A	WHS	1,005	0,824	1,227	0,959	196 / 19937	195 / 19939	30,55 H
A		0,669	0,481	0,931	0,017	350 / 25233	428 / 25137	
B	CLIPS	2,263	0,684	7,484	0,181	9 / 185	4 / 181	0,66 H
B	HATS	0,207	0,022	1,943	0,168	1 / 42	4 / 38	0,19 H
B	HOPE	1,022	0,899	1,161	0,742	532 / 4761	524 / 4780	30,66 H
B	HPS	1,017	0,929	1,113	0,717	1063 / 10269	1047 / 10267	41,76 H
B	PHS II (2)	0,920	0,723	1,170	0,496	133 / 3656	144 / 3653	13,14 H
B	WACS	0,914	0,719	1,164	0,467	131 / 4083	143 / 4088	13,07 H
B	WAVE	3,281	0,803	12,477	0,081	9 / 105	3 / 108	0,53 H
B		1,000	0,907	1,102	0,994	1878 / 23101	1869 / 23115	
Overall		0,968	0,882	1,063	0,496	2228 / 48334	2297 / 48252	



C

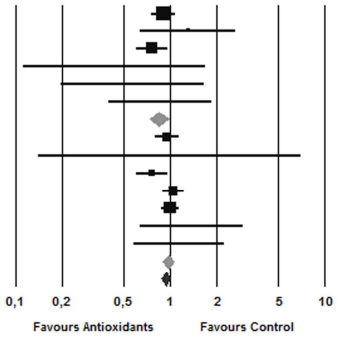
Myocardial Infarction (Low dosage)

Group by Subgroups	Study name	Odds ratio	Lower limit	Upper limit	p-Value	Vitamin E	Control	Relative weight
A	ATBC (1)	0,974	0,859	1,105	0,682	519 / 6820	534 / 6849	66,57 L
A	GISSI (1)	0,861	0,714	1,037	0,115	226 / 2830	259 / 2828	30,25 L
A	PPP	0,892	0,501	1,587	0,697	22 / 2231	25 / 2264	3,17 L
A		0,936	0,844	1,037	0,204	767 / 11881	818 / 11941	
B	ATBC (2)	0,964	0,850	1,093	0,567	511 / 6781	534 / 6849	65,14 L
B	GISSI Vit. (2)	0,869	0,722	1,047	0,140	228 / 2830	259 / 2828	29,95 L
B	MVP	3,077	0,123	76,704	0,493	1 / 78	0 / 79	0,10 L
B	POPADAD	1,111	0,698	1,767	0,658	43 / 320	39 / 318	4,82 L
B		0,942	0,851	1,043	0,250	783 / 10009	832 / 10074	
Overall		0,939	0,873	1,009	0,087	1550 / 21890	1650 / 22015	



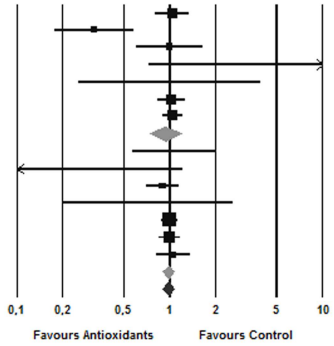
Fatal Myocardial Infarction

Group by Subgroups	Study name	Statistics for each study				Events / Total		Relative weight
		Risk ratio	Lower limit	Upper limit	p-Value	Vitamin E	Control	
A	ATBC (1)	0,895	0,746	1,073	0,230	212 / 6820	238 / 6849	56,91
A	CHAOS	1,294	0,637	2,626	0,476	18 / 1035	13 / 967	3,76
A	GISSI (1)	0,754	0,595	0,957	0,020	114 / 2830	151 / 2828	33,43
A	PPP	0,435	0,113	1,680	0,227	3 / 2231	7 / 2264	1,03
A	SPACE	0,567	0,197	1,631	0,293	5 / 97	9 / 99	1,69
A	WHS	0,857	0,397	1,853	0,695	12 / 19937	14 / 19939	3,17
A		0,843	0,735	0,967	0,015	364 / 32950	432 / 32946	
B	ATBC (2)	0,942	0,787	1,128	0,516	222 / 6781	238 / 6849	20,34
B	CLIPS	0,978	0,139	6,871	0,982	2 / 185	2 / 181	0,18
B	GISSI (2)	0,754	0,595	0,957	0,020	114 / 2830	151 / 2828	11,92
B	HOPE	1,040	0,866	1,221	0,629	287 / 4761	277 / 4760	25,29
B	HPS	0,993	0,876	1,126	0,917	464 / 10269	467 / 10267	39,54
B	POPADAD	1,355	0,632	2,905	0,435	15 / 320	11 / 318	1,19
B	WACS	1,126	0,575	2,206	0,729	18 / 4083	16 / 4088	1,53
B		0,968	0,890	1,052	0,438	1122 / 29229	1162 / 29311	
Overall		0,932	0,868	1,001	0,054	1486 / 62179	1594 / 62257	



Non Fatal Myocardial Infarction

Group by Subgroups	Study name	Risk ratio	Lower limit	Upper limit	p-Value	Vitamin E	Control	Relative weight
A	GISSI (1)	1,036	0,800	1,343	0,787	112 / 2830	108 / 2828	21,88
A	CHAOS	0,319	0,175	0,582	0,000	14 / 1035	41 / 967	10,02
A	POPADAD	0,994	0,603	1,639	0,980	28 / 320	28 / 318	12,58
A	CLIPS	3,424	0,721	16,264	0,122	7 / 185	2 / 181	2,08
A	WAVE	0,995	0,252	3,928	0,995	4 / 212	4 / 211	2,63
A	WHS	1,017	0,829	1,247	0,874	184 / 19937	181 / 19939	24,38
A	ATBC (1)	1,042	0,891	1,218	0,609	307 / 6820	296 / 6849	26,44
A		0,935	0,741	1,180	0,572	656 / 31339	660 / 31293	
B	PPP	1,071	0,564	2,036	0,834	19 / 2231	18 / 2264	1,76
B	SPACE	0,340	0,095	1,219	0,098	3 / 97	9 / 99	0,45
B	WACS	0,891	0,694	1,144	0,364	113 / 4083	127 / 4088	11,62
B	HATS	0,724	0,202	2,597	0,620	4 / 84	5 / 76	0,44
B	HPS	0,993	0,876	1,126	0,917	464 / 10269	467 / 10267	46,01
B	ATBC (2)	0,986	0,842	1,156	0,863	289 / 6781	296 / 6849	28,83
B	GISSI (2)	1,055	0,815	1,365	0,685	114 / 2830	108 / 2828	10,89
B		0,980	0,900	1,068	0,650	1006 / 26375	1030 / 26471	
Overall		0,975	0,900	1,056	0,535	1662 / 57714	1690 / 57764	



Highlights

- We examined the effect of vitamin E alone or in combination with other antioxidants on myocardial infarction.
- Vitamin E appears ineffective when associated with other antioxidants.
- When supplemented alone vitamin E reduces myocardial infarction in interventional trials.

Online Supporting Material

Supplemental Table 1:

Type of cardiovascular prevention (primary vs secondary studies) (A) and vitamin E dosage (low <400 IU vs high dosage ≥400 IU) (B).

Panel A

Factor	No of trials	Relative risk (95% CI)	p	Heterogeneity, I^2 (%)	Model
Myocardial Infarction					
Primary	6	0.96 (0.89 to 1.02)	0.196	0	Random effects
Secondary	9	0.91 (0.81 to 1.02)	0.120	56	Random effects
Fatal Myocardial Infarction					
Primary	5	0.95 (0.81 to 1.04)	0.190	0	Random effects
Secondary	6	0.94 (0.87 to 1.02)	0.159	44	Random effects
Non Fatal Myocardial Infarction					
Primary	5	1.02 (0.93 to 1.12)	0.688	0	Random effects
Secondary	7	0.88 (0.72 to 1.07)	0.198	59	Random effects

Panel B

Factor	No of trials	Relative risk (95% CI)	p	Heterogeneity, I^2 (%)	Model
Myocardial Infarction					
Low dosage (<400 IU)	11	0.90 (0.79 to 1.02)	0.099	28	Random effects
High dosage (≥400 IU)	5	0.94 (0.88 to 1.01)	0.087	3	Random effects
Fatal Myocardial Infarction					
Low dosage (<400 IU)	4	0.92 (0.83 to 1.02)	0.095	0	Random effects
High dosage (≥400 IU)	7	1.01 (0.91 to 1.12)	0.834	0	Random effects
Non Fatal Myocardial Infarction					
Low dosage (<400 IU)	4	1.02 (0.93 to 1.12)	0.639	5	Random effects
High dosage (≥400 IU)	8	0.84 (0.66 to 1.08)	0.183	7	Random effects