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ORIGINAL ARTICLE

Vitamin E Supplementation and Mortality in Healthy People: A Meta-Analysis of Randomised Controlled Trials

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Abstract
Purpose To evaluate the effect of oral vitamin E supplementation on all-cause mortality in apparently healthy people.
Methods A systematic review and meta-analysis was conducted on randomised controlled trials (RCTs) with ≥6 months of follow up investigating the effect of vitamin E supplementation on healthy adults in developed countries. Electronic databases (MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials) and reference lists of trial reports were searched for RCTs published between 1966 and June 2012. Three investigators assessed eligibility of identified trials. Disagreements were resolved by consensus. Two investigators independently extracted data according to the criteria.
Results There were 18 RCTs identified with 142,219 apparently healthy participants (71,116 in vitamin E intervention groups and 71,103 in control groups) that were included in the final analysis. Fixed effect and random effects analysis of the 18 trials revealed that supplementation with vitamin E was not associated with all-cause mortality (relative risk 1.01, 95 % confidence interval 0.97 – 1.05, p=0.65). Subgroup analyses by type of vitamin E (natural or synthetic), dose or duration of exposure, study design or quality, and pre-specified mortality outcome showed no association with all-cause mortality.
Conclusions The evidence from pooled analysis of 18 randomised controlled trials undertaken in apparently healthy people shows no effect of vitamin E supplementation at a dose of 23–800 IU/day on all-cause mortality.

Keywords Vitamin E · Supplements · Clinical trials · Mortality

Introduction

Dietary supplementation with the antioxidant Vitamin E has been encouraged in the past for the prevention and treatment of cardiovascular disease (CVD) and other diseases. This was based on evidence from in vitro studies that suggested a role in the prevention of atherosclerosis [1], and from large observational studies which reported that lower rates of heart disease were associated with higher dietary intake of vitamin E [2, 3].

Despite this, most randomised controlled trials (RCTs) have not shown any benefit of vitamin E supplementation for CVD and cancer prevention. Meta analyses of RCTs indicate that vitamin E supplementation is not beneficial in the prevention of CVD [4–6], cancer [7–9], Alzheimer's disease or mild cognitive dementia [10]. Furthermore, a number of meta-analyses indicated that supplementary vitamin E increases the risk of haemorrhagic stroke [11] and all-cause mortality [12–15].

Notwithstanding the lack of evidence for health benefits of supplementation, vitamin E is taken by substantial numbers of people for primary prevention. Dietary supplements have long been an important source of vitamin E intake in the USA. Results from the 1999–2001 and 2000–2002 US National Health and Nutrition Examination

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Surveys (NHANES) showed that 64 % of the mean daily intake of vitamin E (alpha-tocopherol) amongst adults >19 years was obtained from supplements [16], and that supplemental vitamin E was the 6th highest contributor to total dietary antioxidant capacity [17]. Despite a significant decline in vitamin E supplement sales in the USA between 2004 and 2005 following publicity about studies reporting negative effects of supplementation [18], the USA NHANES results (2007–2010) showed that 3.7 % of adults continued to use vitamin E, with the most frequently cited reason being to improve overall health [19].

There is little information available on the extent of specific vitamin supplement use in Australia, although surveys indicate that at least half of adults use complementary and alternative medicines [20–23]. Amongst the participants in the 2007 National Prescribing Service (NPS) Complementary Medicines Survey [24] and the 2010 24 h National Census of Medicines [25], 53.8 % and 46.3 % had used vitamin supplements, respectively. Approximately one-quarter of participants in the NPS survey had taken oral vitamin E supplements [24]. Amongst 1,200 Australians over 65 years, 7.5 % reported taking vitamin E supplements [26]. In the 2011–2012 Australian National Health Survey 48.8 % of people with heart and circulatory conditions claimed to have taken dietary supplements, including vitamins, in the preceding two weeks [27].

Given the high numbers of people who take vitamin E supplements with an expectation of improvement to overall health, it is important to establish if supplementation is associated with an increased risk of mortality as has been reported in previous meta-analyses [12–15]. The results from these meta-analyses may have been confounded by the inclusion of trials investigating vitamin E supplementation in combination with other antioxidants, minerals or dietary supplements, such as β-carotene which has itself been associated with an increased risk of lung and gastric cancer amongst smokers and asbestos workers [28]. Some included trials were undertaken in developing countries where poor nutritional status along with other oxidative stresses may pre-dispose the population to vitamin E deficiency [29]. Furthermore, many of the meta-analyses included trials with participants selected on the basis of having serious comorbidities and hence were not representative of the general population [12–15]. Therefore, to overcome limitations in previously published meta-analyses we conducted a meta-analysis of RCTs undertaken in very highly or highly developed countries that investigated vitamin E monotherapy amongst apparently healthy adults.

Methods

We undertook a systematic review and meta-analysis in accordance with the PRISMA Statement [30].

Literature Search

We searched MEDLINE and EMBASE (from 1966 to May 2010) and the Cochrane Central Register of Controlled Clinical Trials. Keywords and MESH terms for vitamin E ("vitamin E" or "alpha-tocopherol") were combined with filters designed to identify randomised clinical trials. The search was limited to humans, and English language publications. The search was repeated in July 2012 for the period of June 2010 until May 2012.

Selection Criteria

To be included, studies had to meet pre-specified selection criteria as follows.

1. Be a randomised, placebo-controlled trial with -
   - an intervention period of ≥6 months;
   - no intervention co-supplements, i.e. other antioxidants or medications, concurrently with vitamin E unless balanced by a corresponding control arm that also included the additional antioxidant, supplement or medication.
2. Investigate the effect of any dose of synthetic (dl-alpha-tocopherol) or natural (d-alpha-tocopherol) oral vitamin E supplementation;
3. Include adult men and/or non-pregnant women;
4. Trial participants must be in good general health. On this basis, we included the following:
   - Trials in which participants were recruited from the general population;
   - Trials in which participants had non-systemic medical conditions, such as knee osteoarthritis;
   - Trials in which otherwise healthy participants had risk factors for CVD, such as smoking, hypercholesterolaemia or atherosclerosis;
   - Trials in which participants had chronic conditions, such as diabetes mellitus without serious comorbidities or complications.
5. Be undertaken in highly or very highly developed countries, defined according to the United Nations Human Development Index [31];
6. The number of deaths was available for intervention and control groups, and mortality was either a pre-specified primary or secondary outcome, or the methods indicated complete follow-up of participants or full ascertainment of deaths.

Exclusion Criteria

The following types of trials were excluded:

- Trials that selected patients on the basis of having a serious disease that may result in lower life expectancy, such as cancer, recent myocardial infarction, chronic infectious disease, Alzheimer's disease or end stage renal disease;
- Trials undertaken in developing countries, due to the higher likelihood of participants having underlying nutritional deficiencies;
- Trials where no deaths were reported.

Study Selection

Three authors (AC, LP and MB) screened the titles and abstracts and excluded papers that did not meet all of the selection criteria. If the abstract did not include sufficient information the full paper was obtained and evaluated. Two authors (AC and MB) evaluated the remaining studies as full text papers.

Assessment of Trial Quality

Two authors (AC and MB) appraised the methodological quality of all included studies using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials [32]. Any disagreement was resolved by discussion. Studies were classified as low quality if more than one of the following criteria was assessed to be unclear or indicative of high risk of bias (allocation sequence generation, allocation concealment, blinding, complete outcome data reporting, selective outcome reporting, and other biases).

Data Extraction

Two unblinded authors (AC and MB) independently extracted data, including authors of study, year of publication, trial design, country of origin, participant health status and risk factors, sex, inclusion criteria, natural or synthetic form of vitamin E, dose of vitamin E and treatment regimen, duration of follow-up, number of participants and number of deaths in each of the treatment groups. Disagreements were resolved by consensus. We contacted the authors to obtain further information if it was not reported in the full text article (for instance, if the results indicated that there were deaths, but either the number or treatment group was not specified).

Main and Subgroup Analyses

We investigated the association between oral supplementation of vitamin E and all-cause mortality.

Participants randomised to vitamin E were compared to participants not randomised to vitamin E. For parallel group trials, participants randomised to vitamin E only were compared with participants randomised to the corresponding placebo. For factorial trials, all participants randomised to vitamin E were compared to all participants not randomised to vitamin E on the condition that any other active interventions were balanced.

Subgroup analyses determined *a priori* were performed for form of vitamin E supplement administered (synthetic or natural), dose of vitamin E and duration of exposure to vitamin E. *Post hoc* sub group analyses included study design (parallel group or factorial) and whether mortality was a prespecified outcome of the trial.

Statistical Analysis

Both fixed effect and random effects models were used to calculate pooled relative risks with 95 % confidence intervals and p values. In trials where no deaths occurred in one arm (5 trials) the software program added 0.5 to each of the four cell counts to enable calculation of the relative risk. Heterogeneity was investigated using scatter plot analysis and the Cochran Q test. Publication bias was assessed using funnel plots and Begg and Mazumdar or Egger's test. All analyses were performed using Comprehensive Meta-Analysis version 2 (Biostat, Englewood NJ) [33].

Results

Figure 1 illustrates the process of identifying trials that fulfilled the selection criteria. The search identified 14,759 references of possible interest. Duplicate references and irrelevant references were excluded through screening of the titles and abstracts. Following evaluation of the abstracts, 1,150 references remained that described the results of RCTs of oral vitamin E supplementation in adults. We then excluded 1,039 articles describing trials which did not meet the inclusion criteria. This included 20 articles that were excluded because there was no follow up of deaths, mortality was not reported, or no deaths occurred. The 8 trials in which no deaths occurred included a total of 390 participants with 184 randomised to vitamin E and 206 to control groups. The final 111 articles described trials that met the inclusion criteria and the full text of these articles was reviewed; 18 of these articles reported mortality data and were included in the analysis.

Study Characteristics

Table 1 summarises the characteristics of the 18 trials included in the analysis. Eight trials had a parallel group

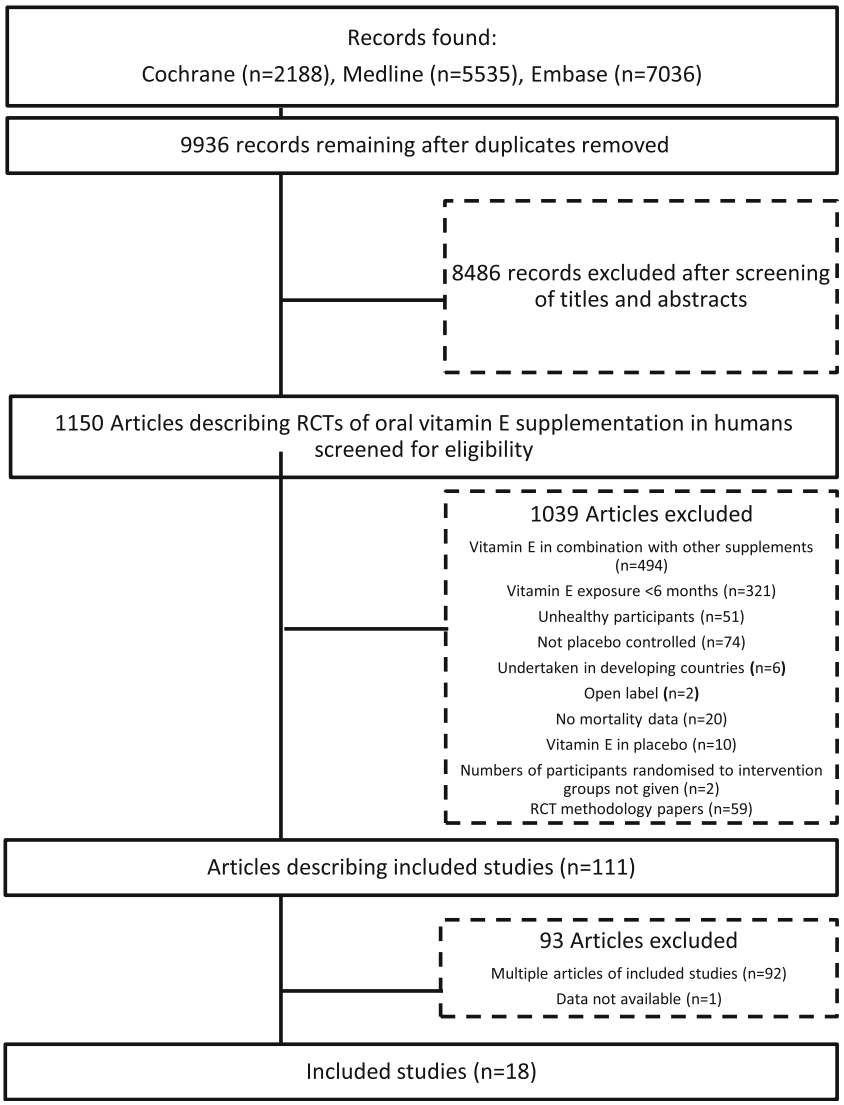

Fig. 1 Flow chart for identification of selected trials

(PG) design with vitamin E monotherapy being the only intervention. Ten trials had a factorial design (FAC). In 1 factorial trial the co-intervention was pole-striding exercise and in the other 9 factorial trials the co-intervention was another supplement or medication. There were a total of 142,219 participants in the trials, with 71,116 randomised to vitamin E and 71,103 randomised to control groups. Amongst the participants randomised to vitamin E and control groups there were a reported 5,348 and 5,310 deaths, respectively.

The period of supplementation and follow up ranged from 6 months to 10.1 years. All vitamin E supplements were administered orally. Synthetic vitamin E was used in 6 trials and natural vitamin E was used in 10 trials. In 2 trials the type of vitamin E used was not specified [34, 35]. The dose of vitamin E administered ranged from 23 IU/day to 800 IU/day. In 8 trials the intervention group was given vitamin E monotherapy. Half of the trials were undertaken in North America, with 7 from the USA and 2 from Canada. Four trials were carried out in Europe, 3 in Australia, 1 in New Zealand and 1 in Israel.

Five trials were conducted in men and two in women, and the remaining trials included both sexes. Among the 18 trials, 6 included participants in good general health, and without current serious illness. Ten trials were conducted in participants with no current serious illness but with varying levels of risk for CVD including metabolic syndrome (1 trial), hypercholesterolaemia (1 trial), coronary artery disease (1 trial), smokers (3 trials), increased CVD risk (2 trials), type II diabetes (1 trial), and peripheral vascular disease (1 trial). The remaining trials included participants with knee osteoarthritis (1 trial) and non-alcoholic steatohepatitis (1 trial). The age of participants ranged from 45 to 76 years. Twelve trials were assessed to be of high quality and 6 trials were of medium or low quality.

Table 1 Design and characteristics of the randomised controlled trials included in the meta-analysis

Trial name, author, year	Country	Study Design	Participant details				Vitamin E details			Additional Supplements or therapies	Mortality outcome	Study Quality
			Total no.	Mean Age (y) at enrolment	Male (%)	Health Status	Dose (IU/day)	Maximum exposure (y)	Type			
Hoffman et al. 1999 [36]	Canada	PG	39	70 (Placebo) 66 (Vitamin E)	100	Veterans with existing CAD and no acute CVD events 3 months prior or significant medical conditions	400 [a]	0.5	Natural	None	Pre-specified trial outcome (sudden death).	Low
Collins et al. 2003 [34]	USA	FAC	52	67	98	PAD, with no comorbid conditions	400	0.5	Not specified	Pole-striding exercise	Not pre-specified	High
Wluka et al. 2002 [37]	Australia	PG	136	64	45	Knee OA with no history of previous stroke or poorly controlled hypertension, major comorbidities such as cancer or life threatening illnesses	500	2.0	Natural	None	Not pre-specified	Low
Manning et al. 2013 [35]	New Zealand	FAC	151	57 (Placebo & vitamin E groups) 54 (ALA + vitamin E) 55 (ALA)	63	Metabolic syndrome with no known type 2 diabetes, significant underlying illness or chronic infection, no cigarette smoking	100	1.0	Not specified	Lipoic acid	Not pre-specified	High
PIVENS, Sanyal et al. 2010 [38]	USA	PG	167	46	40	Non-alcoholic steatohepatitis, without diabetes	800	1.85	Natural	None	Not pre-specified	Low
deWaart et al. 2001 [39]	Netherlands	PG	218	60	100	Smokers, without diabetes or other illness interfering with participation	400	2.0	Synthetic	None	Complete ascertainment of deaths	Medium
VEAPS, Hodis et al. 2002 [40]	USA	PG	353	56	45	Healthy, low-risk with no signs or symptoms of CVD	400	3.0	Synthetic	None	Pre-specified trial outcome. Reported for all participants	High
MAVET, Magliano et al. 2006 [41]	Australia	PG	409	64	45	Smokers, with no life-threatening illness, previous carotid artery surgery or existing carotid stenosis warranting surgery, MI or stroke within the prior 6 months or uncontrolled hypertension	500	4.0	Natural	None	Complete ascertainment of deaths	High
ASAP, Salonen et al. 2000 [42]	Finland	FAC	520	45–69 [b]	49	Hypercholesterolaemia with no type I diabetes, uncontrolled hypertension, any condition limiting mobility or severe disease shortening life expectancy.	272	3.0	Natural	Vitamin C	Complete ascertainment of deaths. Checked death registry, confirmed by email.	Low
Graat et al. 2002 [43]	Netherlands	FAC	652	73	50	Non-institutionalised, no history of cancer, liver disease or fat malabsorption in the 5 years before randomisation	200[a]	1.25	Synthetic	Multivitamin-mineral	Not pre-specified	High

Table 1 (continued)

Trial name, author, year	Country	Study Design	Participant details				Vitamin E details			Additional Supplements or therapies	Mortality outcome	Study Quality
			Total no.	Mean Age (y) at enrolment	Male (%)	Health Status	Dose (IU/day)	Maximum exposure (y)	Type			
VECAT, McNeil et al. 2004 [44]	Australia	PG	1193	66	44	Good general health	500	4.0	Natural	None	Pre-specified trial outcome. Death=major adverse event; contributing cause of death ascertained from death certificate	High
Milman et al. 2008 [45]	Israel	PG	1434	69 (Placebo) 70 (Vitamin E)	48	Type II diabetics without uncontrolled hypertension, MI or stroke within 1 month of enrolment	400	2.0	Natural	None	Pre-specified secondary outcome	High
WACS, Cook et al. 2007 [46]	USA	FAC	8171	61	0	High risk for CVD (history of CVD event or ≥3 CVD risk factors), no history of cancer or serious non CVD illness	600 [c]	10.1	Natural	Vitamin C, beta-carotene	Pre-specified trial outcome	High
HOPE, Lonn et al. [47]	Canada	FAC	9541	66	Mixed	High risk for CVD (history of CAD or PAD, prior stroke, diabetes mellitus plus ≥1 other CVD risk factor). Excluded: Individuals with heart failure, uncontrolled hypertension or overt nephropathy, or who had prior MI or stroke within 4 weeks of study beginning	400	7.0	Natural	Ramipril	Pre-specified trial outcome	High
PHSII, Gaziano et al. 2009 [48]	USA	FAC	14641	64	100	Apparently healthy with no history of cirrhosis or active liver disease, or serious illness. Individuals with a history of cancer or MI or stroke were eligible to enrol.	400	10.0	Synthetic	Vitamin C	Pre-specified trial outcome. Total mortality confirmed by endpoints committee or by obtaining death certificate	High
ATBC, Virtamo et al. 2003 [49]	Finland	FAC	29133	57	100	Smokers, with no cancer, other serious illness, or previous stroke	50 [a]	6.0	Synthetic	Beta-carotene	Pre-specified trial outcome	Medium
SELECT, Lippman et al. 2008 [50]	USA	FAC	35553	63 (Control groups) 62 (Vitamin E) [d]	100	Healthy, with no prior prostate cancer diagnosis, >4 ng/ml serum PSA, digital rectal examination suspicious for cancer, history of haemorrhagic stroke or abnormal blood pressure.	400	7.33	Synthetic	Selenium	All men followed to death or loss to follow-up. Death index searches were conducted for all men who had a last contact 18 months before the search (July 2008)	High

Table 1 (continued)

Trial name, author, year	Country	Study Design	Participant details				Vitamin E details			Additional Supplements or therapies	Mortality outcome	Study Quality
			Total no.	Mean Age (y) at enrolment	Male (%)	Health Status	Dose (IU/day)	Maximum exposure (y)	Type			
WHS, Lee et al. 2005 [51]	USA	FAC	39876	55	0	Healthy with no history of cancer, CHD, cerebrovascular disease, or other major chronic illness	600 [c]	10.9	Natural	Aspirin	Pre-specified trial outcome. Pre-specified outcome and confirmed by death certificate or endpoint committee	High

ALA antioxidant alpha-lipoic acid; *CVD* cardiovascular disease; *CAD* coronary artery disease; *PAD* peripheral artery disease; *OA* osteoarthritis; *CHD* coronary heart disease; *MI* myocardial infarction; *PSA* prostate specific antigen; *ASAP* antioxidant supplementation in atherosclerosis prevention; *SELECT* selenium and vitamin E cancer prevention trial; *PIVENS* pioglitazone or vitamin E for NASH study; *VEAPS* vitamin E atherosclerosis prevention study; *WACS* women's antioxidant cardiovascular study; *VECAT* vitamin E, cataract, and age-related maculopathy study; *MAVET* the melbourne atherosclerosis vitamin E trial; *WHS* women's health study; *HOPE* heart outcomes prevention evaluation; *PHSII* physician's health study II; *ATBC* alpha-tocopherol, beta-carotene cancer prevention study; *PG* parallel group trial; *FAC* factorial trial

[a] mg/day

[b] Range of participant age (mean not specified)

[c] 600 IU administered on alternate days

[d] Median of participant ages for intervention groups (mean not specified)

The Effect of Vitamin E on All-Cause Mortality

Amongst individual trials the effect of supplemental vitamin E on mortality varied from RR 0.32 to RR 3.09. In both fixed effect and random effects meta-analysis including all of the 18 trials (Fig. 2), there was no significant effect of supplementation with Vitamin E on the risk of all-cause mortality (RR 1.008; 95 % CI 0.97 to 1.05; p=0.65). For the combined 18 trials, statistical testing showed no evidence of heterogeneity (Chi^2 p=0. 857, I^2=0.000). Overall, the effect sizes of the studies with more than 8,000 participants were close to 1.0. There was no significant publication bias amongst the studies as indicated by the Begg and Mazumdar rank correlation test (two tailed, p=0.82 with continuity correction) and Egger's regression test (two tailed, p=0.92).

Sensitivity analyses were performed after removing any studies in which participants had risk factors for CVD (10 studies). There was a small shift towards the null effect, and the result was not significant (RR 1.005; 95 % CI 0.95 to 1.06; p=0.87). When these studies were removed individually, the largest impact on effect size occurred when the study by Virtamo [49], carried out in men who smoke, was excluded (RR 1.004; 95 % CI 0.96 to 1.05; p=0.87).

For further sensitivity analysis we performed a meta-analysis removing each of the 18 studies, one at a time. The largest impact on the effect size occurred when the SELECT trial [50] was removed (RR 1.02; 95 % CI 0.98 to 1.06; p=0.35), however the result was still not significant.

Subgroup analyses were conducted by vitamin E form (synthetic or natural), dose and duration of exposure, trial design, trial quality and whether mortality was a pre-specified outcome. Table 2 shows that risk of mortality did not change with the form and dose of vitamin E supplement used and the duration of exposure. Similarly, the study design and trial quality showed no association with risk of mortality.

Discussion

Summary of Main Findings

This meta-analysis of randomised controlled trials of oral vitamin E supplementation does not support an association between oral vitamin E and an increased risk of all-cause mortality in apparently healthy adults. Furthermore, there is no evidence for a relationship between the form (natural or synthetic), dose or duration of exposure of vitamin E and risk of all-cause mortality.

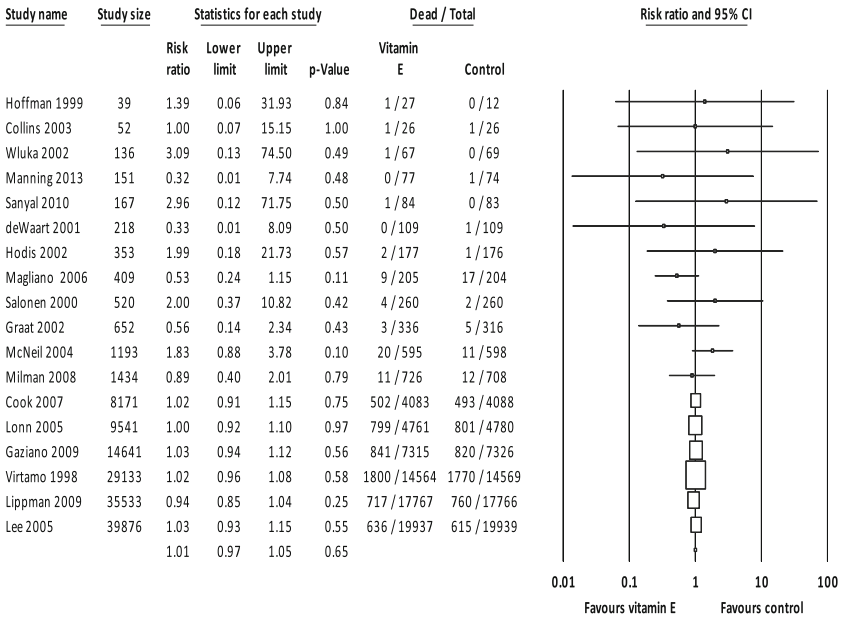

Fig 2 Effect of vitamin E supplementation on the risk of all-cause mortality. The symbols are proportional to the study weight and the horizontal lines represent the 95 % confidence intervals

Comparison with Findings from Other Meta-Analyses

Since 2005 several meta-analyses examining the association between all-cause mortality and vitamin E supplementation have been published. Three meta-analyses reported a small but significant increase in the risk of mortality amongst patients taking vitamin E [12–15, 29]. Two meta-analyses reported no effect of vitamin E supplementation on all-cause mortality [52, 53]

The principal differences between the current study and previous meta-analyses are:

1. We included only trials of vitamin E supplementation in apparently healthy patients. Although participants in 11 of the included trials had an elevated risk of CVD, the pooled RR did not change significantly in a sensitivity analysis where these trials were excluded. Apart from Fortmann and colleague's meta-analysis which included only 5 trials

Table 2 Subgroup analysis for the effect of vitamin E supplementation on the risk of all-cause mortality

Subgroup	Number of trials	Relative risk (RR)	95 % CI	P value	Heterogeneity	
					Chi ^{2} P value	(I^2)
Vitamin E type [a, b]						
Synthetic	6	1.00	0.96 to 1.05	0.88	0.65	0.00
Natural	10	1.02	0.96 to 1.08	0.57	0.63	0.00
Vitamin E dose (IU/day) [a]						
<400	7	1.02	0.97 to 1.07	0.41	0.93	0.00
≥400	11	0.99	0.94 to 1.05	0.82	0.57	0.00
Duration of exposure [a]						
<3 years	8	0.85	0.46 to 1.58	0.61	0.94	0.00
≥3 years	10	1.01	0.97 to 1.05	0.63	0.50	0.00
Mortality is a pre-specified trial outcome						
Yes	9	1.01	0.97 to 1.05	0.60	0.74	0.00
No	9	0.71	0.40 to 1.26	0.24	0.82	0.00
Study design						
Parallel group	8	1.04	0.68 to 1.58	0.87	0.91	0.00
Factorial	10	1.01	0.97 to 1.05	0.66	0.43	0.00
Study quality [a]						
High	12	1.00	0.96 to 1.05	0.90	0.64	0.00
Medium/Low	6	1.02	0.96 to 1.08	0.55	0.85	0.00

[a] Specified in advance

[b] Vitamin E type not available for Manning et al. 2012 [35] and Collins et al. 2003 [34]

that were all primary prevention trials [52], all previous meta-analyses included some trials for which participants were selected on the basis of having conditions such as amyotrophic lateral sclerosis (ALS) [13], hepatitis [13], cirrhosis [13, 53], Alzheimer's disease [12, 13], Parkinson's disease [13–15], or were dialysis patients with CVD (SPACE trial) [12,13,54]. While the Bjelakovic meta-analyses were specifically planned to investigate antioxidant supplementation in health and disease [13–15], the suitability of combining results from these heterogeneous populations has been questioned [55];

2. Our meta-analysis included only trials undertaken in highly or very highly developed countries as opposed to earlier meta-analyses which included large trials undertaken in developing countries such as China [12–15, 53];
3. Our analysis only included parallel group trials in which participants were randomised to vitamin E monotherapy or placebo. We did not include parallel group trials where participants took vitamin E in combination with other supplements as in earlier meta-analyses [12–15]. We included factorial trials in which vitamin E was given with other supplements, but only if the additional supplements were balanced across the vitamin E and control groups;
4. We included trials with at least 1 death in any arm in contrast to a previous meta-analysis which excluded trials with fewer than 10 deaths [12];
5. Our analysis includes 3 studies that were not included in any other meta analyses [35, 36, 38], contributing a further 357 participants;
6. We excluded trials in which there was no placebo, or if the control group received any vitamin E. This contrasts with other meta-analyses [13–15]. Some other meta-analyses [53] also included open-label phases of trials such as the ASAP trial [42]. We included data only from the blinded phases of RCTs.

Our conclusion that there is no association between oral vitamin E supplementation and an increased risk of all-cause mortality is in agreement with the conclusions reached by Fortmann et al. [52] and Abner et al. [53]. This is despite a low level of overlap between the trials included in the Abner meta-analysis and the current meta-analysis (4 of the 11 trials included in Abner's vitamin E alone meta-analysis were included in our analysis). All trials included in the Fortmann meta-analysis were included in our meta-analysis, although our analysis included an additional 13 trials and 22,516 participants.

The conclusion drawn by Miller 2005 [12], Bjelakovic (2007, 2012 and 2013) [13–15] and Gee 2011 [29]- that vitamin E supplementation significantly increases the risk of all-cause mortality is not supported by our meta-analysis. We note that the majority of these meta-analyses pooled results from trials of vitamin E monotherapy versus placebo with results from trials of vitamin E taken in combination with other supplements versus placebo.

Implications

In large observational studies an inverse association between cardiovascular disease and intake of dietary vitamin E suggested a preventive or therapeutic role for vitamin E mediated through its anti-oxidant properties. [56, 57] The role of oxidation in cardiovascular disease remains strongly supported by contemporary evidence, although the precise mechanism(s) by which lipid oxidation triggers atherogenesis is still uncertain. [58] Explanations for negative clinical trial results mostly focus on trial parameters such as duration, dose and form of supplement, or inappropriate selection of participants with respect to nutritional and health status. [58, 59] Our result adds to the evidence that supplemental vitamin E has no discernible clinical impact amongst individuals who are not nutrient deficient.

Strengths of the Current Study

Our analysis has numerous strengths. It included only randomised controlled trials and included a large number of participants. It was determined *a priori* to only include trials undertaken in countries where populations were unlikely to be nutrient and/or vitamin deficient, and in apparently healthy participants without current serious disease. We assessed the methodological quality of the included trials and excluded trials that investigated vitamin E in combination with other antioxidants or in the form of multivitamins. The large studies with more than 1,000 participants in each group, and which therefore contributed the greatest weight to the meta-analysis, were of high quality. In addition, separate pooled analyses were performed for trials that used synthetic or natural vitamin E.

Limitations of the Current Study

The trials included in this analysis examined varying dosages of synthetic or natural vitamin E and adherence to supplements may not have been optimal. It is also possible that trial participants may have taken other unreported supplements.

This analysis is subject to the usual limitations that are associated with meta-analysis including selection bias. The meta-analysis did not take account of the 8 trials (including a total of 390 participants) in which no events (mortality) occurred in either arm. Similarly, 5 trials (including a total of 518 participants which did not report mortality and gave no reasons for participant losses to follow-up were not included. However, the small study sizes of these trials (range 64–236 participants) means that they would have little impact on the

pooled result. Finally, study quality was assessed on the basis of information reported in the published papers which may not reflect how the trial was actually conducted.

Conclusion

There is no evidence of an effect (either positive or negative) of vitamin E supplementation on all-cause mortality in apparently healthy people as determined by pooled analysis of 18 randomised controlled trials including a total of 71,116 and 71,103 people randomised to vitamin E and control groups, respectively. The results provide no support for recommending vitamin e supplementation to healthy adults.

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Conflict of Interest AC, MB and LP declare that they have no conflict of interest. JM has received honoraria for service on advisory boards for Pfizer, Bayer and Janssen-Cilag.

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