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RESEARCH

# Efficacy of vitamin and antioxidant supplements in prevention of cardiovascular disease: systematic review and meta-analysis of randomised controlled trials



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## Abstract

**Objective** To assess the efficacy of vitamin and antioxidant supplements in the prevention of cardiovascular diseases.

**Design** Meta-analysis of randomised controlled trials.

**Data sources and study selection** PubMed, EMBASE, the Cochrane Library, Scopus, CINAHL, and ClinicalTrials.gov searched in June and November 2012. Two authors independently reviewed and selected eligible randomised controlled trials, based on predetermined selection criteria.

**Results** Out of 2240 articles retrieved from databases and relevant bibliographies, 50 randomised controlled trials with 294 478 participants (156 663 in intervention groups and 137 815 in control groups) were included in the final analyses. In a fixed effect meta-analysis of the 50 trials, supplementation with vitamins and antioxidants was not associated with reductions in the risk of major cardiovascular events (relative risk 1.00, 95% confidence interval 0.98 to 1.02; $I^2$=42%). Overall, there was no beneficial effect of these supplements in the subgroup meta-analyses by type of prevention, type of vitamins and antioxidants, type of cardiovascular outcomes, study design, methodological quality, duration of treatment, funding source, provider of supplements, type of control, number of participants in each trial, and supplements given singly or in combination with other supplements. Among the subgroup meta-analyses by type of cardiovascular outcomes, vitamin and antioxidant supplementation was associated with a marginally increased risk of angina pectoris, while low dose vitamin $B_6$ supplementation was associated with a slightly decreased risk of major cardiovascular events. Those beneficial or harmful effects disappeared in subgroup meta-analysis of high quality randomised controlled trials within each category. Also, even though supplementation with vitamin $B_6$ was associated with a decreased risk of cardiovascular death in high quality trials, and vitamin E supplementation with a decreased risk of myocardial infarction, those beneficial effects were seen only in randomised controlled trials in which the supplements were supplied by the pharmaceutical industry.

**Conclusion** There is no evidence to support the use of vitamin and antioxidant supplements for prevention of cardiovascular diseases.

## Introduction

Cardiovascular diseases are the leading causes of deaths and disability worldwide.[1] Over the past few decades, observational epidemiological studies have reported that intake of fruit and vegetables rich in various vitamins and antioxidants reduce the risk.[2] It has been estimated that if an individual increases fruit and vegetable intake up to 600 g daily, the worldwide burden of disease could be reduced by 31% for ischaemic heart disease and 19 % for ischaemic stroke.[3] Unlike the evidence for fruit and vegetables, however, many randomised controlled trials have reported inconsistent findings regarding the efficacy of

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**Appendix 1**: Full details of 50 included trials

vitamin and antioxidant supplementation on cardiovascular diseases.[4]

Several meta-analyses have reported conflicting evidence from randomised controlled trials. In 2003, a meta-analysis of 12 trials indicated that vitamin E supplements did not provide benefit in cardiovascular death or cerebrovascular events.[5] Instead, it showed that β carotene supplementation led to a small increase in all cause mortality and cardiovascular death. In 2006, Flores-Mateo et al reported that the use of supplements containing selenium did not reduce the risk of coronary heart disease in the meta-analysis of six trials.[6] More recently, however, Lee et al found that folic acid supplementation with B vitamins had potential small benefits in the prevention of stroke,[7] and Qin et al indicated that folic acid treatment decreased the risk of cardiovascular disease by 15% in patients with end stage renal disease or advanced chronic kidney disease.[8] Even though several meta-analyses of randomised controlled trials have been published regarding the efficacy of vitamins and antioxidant supplements on cardiovascular diseases, they involved individual vitamins or antioxidants, and there was no published comprehensive meta-analysis that reviewed this topic all together in one report. To the best of our knowledge, no meta-analyses have performed subgroup analyses by important factors such as methodological quality or funding source.

We investigated the efficacy of vitamin and antioxidant supplements on cardiovascular diseases through a comprehensive meta-analysis of randomised controlled trials by various factors such as by type of prevention (primary *v* secondary), type of vitamins and antioxidants, dose of supplement, type of cardiovascular outcomes, study design, methodological quality (high *v* low), duration of treatment (<5 years *v* ≥5 years), funding source (independent organisation *v* pharmaceutical industry), provider of supplements (pharmaceutical industry *v* not pharmaceutical industry), type of control (placebo *v* no placebo), number of participants in each trial (<10 000 *v* ≥10 000), and supplements given singly or in combination with other vitamin or antioxidant supplements.

# Methods

## Literature search

We searched PubMed, Embase, the Cochrane Library, Scopus, CINAHL, and ClinicalTrials.gov in June and November 2012 using common keywords related to vitamin or antioxidant supplements and cardiovascular diseases. The keywords were as follows: "vitamin supplement," "antioxidant supplement," "vitamin A supplement," "vitamin $B_6$ supplement," "vitamin $B_{12}$ supplement," "folic acid supplement," "vitamin C supplement," "vitamin D supplement," "vitamin E supplement," "selenium supplement," "beta-carotene supplement," "lycopene supplement," or "isoflavone supplement,"; and "cardiovascular disease," "angina," "acute myocardial infarction," "transient ischemic attack," or "stroke." We also reviewed the bibliographies of relevant articles to locate additional publications. The language of publication was not restricted.

## Selection criteria

To be included randomised controlled trials had to report the efficacy of vitamin or antioxidant supplements for the prevention of cardiovascular diseases and follow participants for at least six months. If data were duplicated or shared in more than one study, we included the first published or more comprehensive study in the analysis.

## Selection of relevant studies

Based on the predetermined selection criteria, two of the authors (S-KM, WJ) independently selected all trials retrieved from the databases and bibliographies. Disagreements were resolved by discussion or in consultation with a third author (S-WO).

## Assessment of methodological quality

We assessed the methodological quality of included trials with the Jadad scale.[9] Its score ranges from 0 (very poor) to 5 (rigorous). The five point quality scale consists of points for randomisation (described as randomised, 1 point; table of random numbers or computer generated randomisation, additional 1 point), double blind (described as double blind, 1 point; use masking such as identical placebo, additional 1 point), and follow-up (state the numbers and reasons for withdrawal in each group; 1 point) in the report of each trial. All trials were classified into two groups, those with a score of ≤4 or versus 5 because the mean score for the 47 trials assessed in the current study (the full text for three trials was not available) was 4.3, and then subgroup meta-analyses were performed.

## Main and subgroup analyses

We investigated the association between vitamin or antioxidants supplementation and major cardiovascular events. Major cardiovascular events included cardiovascular death, fatal or non-fatal myocardial infarction, angina, sudden cardiac death, fatal or non-fatal stroke, and transient ischaemic attack. We also performed subgroup meta-analyses by type of prevention (primary *v* secondary: in this study, trials involving healthy populations or patients with any specific disease except for cardiovascular disease were classified as primary prevention trials, and trials involving patients with cardiovascular disease were classified as secondary prevention trials), type of supplement by quality and dose (each supplement, vitamins only, antioxidants only, or antioxidants excluding vitamins), type of outcome (cardiovascular death, angina, fatal or non-fatal myocardial infarction, stroke, or transient ischaemic attack), type of outcome in each supplement, type of study design (randomised, double blind, placebo controlled trial *v* open label, randomised controlled trial), methodological quality (high *v* low), duration of treatment (<5 years *v* ≥5 years), funding source (pharmaceutical industry *v* independent organisation), provider of supplements (pharmaceutical industry *v* not pharmaceutical industry), type of control (placebo *v* no placebo), number of participants (≥10 000 *v* <10 000), and supplements given singly or in combination with other vitamin or antioxidant supplements by quality.

## Statistical analysis

We calculated the relative risks with 95% confidence intervals by using crude 2×2 tables on the basis of intention to treat analysis, whenever possible, from the original publications. For the test of heterogeneity, we used Higgins $I^2$, which measures the percentage of total variation across trials.[10] $I^2$ was calculated as follows:

$$I^2 = 100\% \times (Q - df)/Q,$$

where Q is Cochran's heterogeneity statistic and df indicates the degrees of freedom. Negative values of $I^2$ are set to zero. $I^2$ ranges from 0% (no observed heterogeneity) to 100% (maximal heterogeneity).

To calculate pooled relative risks with 95% confidence intervals, we used both the fixed effects and random effects models. An $I^2$ value >50% was considered as substantial heterogeneity.

When there was no substantial heterogeneity, we reported the pooled estimate calculated from the fixed effects model. When there was substantial heterogeneity, we reported the pooled estimate calculated from the random effects model.

We assessed publication bias with Begg's funnel plot and Egger's test. If publication bias exists, the Begg's funnel plot is asymmetric or the Egger's test P value is <0.05. We used Stata SE version 10.0 software (StataCorp, College Station, TX) for all the statistical analyses.

## Results

By searching databases (PubMed, Embase, the Cochrane Library, Scopus, CINAHL, and ClinicalTrials.gov) and hand searching relevant bibliographies, we identified 2240 articles (fig 1⇓). After excluding 573 duplicated articles, two of authors independently reviewed and excluded 1593 articles that did not satisfy the predetermined selection criteria based on each article's title and abstract. We reviewed the full texts of the 74 remaining articles and excluded 24 articles (16 were identical trials within the same population; five were not related to the subject of this study; two were replies or comments; and one reported insufficient data). A total of 50[11-60] trials were included in the final analysis. The full details of all included trials are in appendix 1. The 50 trials included 294 478 participants with 156 663 in intervention groups and 137 815 in control groups. In the trials reporting age, the mean age of the participants ranged from 49 to 82. The year of publication of the included trials ranged between 1989 and 2012, spanning 23 years. Twelve trials were conducted in the United State, four in the United Kingdom, three in Finland, three in France, three in Italy, two in Canada, two in Israel, two in Australia, two in China, two in Germany, two in Norway, one in Sweden, one in Switzerland, one in the Netherlands, one in US/Canada, one in US/Canada/Scotland), one in Germany/the Netherlands, one in Canada/US, one in 13 countries, and one in 20 countries. The range of supplementation and follow-up periods was 6 months to 12 years. The number of participants ranged from 61 to 39 876.

Among the 50 trials, 30 were primary prevention trials (general populations, smokers and workers exposed to asbestos, patients with oesophageal dysplasia, male physicians, patients with non-melanoma skin cancer, postmenopausal women, patients undergoing chronic haemodialysis, patients with end stage renal disease, ambulatory elderly women with vitamin D insufficiency, patients with chronic renal failure, older people with femoral neck fractures, patients with diabetes mellitus, elderly women with a low serum 25-hydroxyvitamin D concentration, health professionals, people with a high fasting plasma total homocysteine concentration, or kidney transplant recipients), and 20 were secondary prevention trials (patients with cardiovascular disease, coronary heart disease, acute myocardial infarction, unstable angina, transient ischaemic attack, stroke, angiographically proved coronary atherosclerosis, vascular disease, or aortic valve stenosis).

Forty five trials were randomised, double blind, placebo controlled trials, and five were open label, randomised controlled trials. All vitamin or antioxidant supplements and placebos were administered orally either singly or in combination with other vitamin or antioxidant supplements.

The dose regimens used in each trial were as follows: vitamin A (10 000 or 25 000 IU daily), vitamin $B_6$ (3, 6, 10, 12.5, 25, 40, 48, 50, or 100 mg daily; 20 mg three times weekly), vitamin $B_{12}$ (0.4, 0.5, 1, or 2 mg daily; 6, 18, 20, 60, or 400 µg daily; 50 µg three times weekly), vitamin C (60, 120, 180, 250, 500, or 1000 mg daily), vitamin D (800 or 1000 IU daily; 200 IU twice daily; 400 IU twice daily; 300 IU daily and 100 IU daily; 100 000 IU every four months), vitamin E (60, 200, 400, 600, 800 IU daily; 400 or 600 IU alternate day; 400 IU twice daily; 30, 50, 300, 600 mg daily), β carotene (6, 15, 20, 25, 30, or 50 mg daily; 50 mg alternate day), folic acid (560 or 800 µg daily; 0.5, 0.8, 1, 1.2, 2, 2.5, 5, 15, or 40 mg daily; 5 mg three times weekly), and selenium (50, 75, 100, 122, or 122 µg daily).

Thirty nine trials used vitamin supplements only, and 22 trials used antioxidant supplements only. The additional nutritional supplements or drugs used in each trial were aspirin (325 mg daily); coenzyme Q10 (100 mg daily); calcium (93 mg daily) with or without hormone replacement therapy; application of a sun protection factor 15+ sunscreen; ramipril (angiotensin converting enzyme inhibitor; with or without aspirin (100 mg daily); zinc (20 mg daily); multivitamins and minerals; calcium carbonate (500 mg twice daily); calcium (1000 mg daily); calcium citrate (1000 mg daily); omega 3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid at a ratio of 2:1). The main outcomes used in each trial were fatal or non-fatal acute myocardial infarction, unstable angina, coronary heart disease, ischaemic heart disease, major coronary events, cardiovascular death, sudden death, transient ischaemic stroke, stroke, and cardiovascular disease.

Out of 47 trials reporting funding source, five were funded by pharmaceutical companies and 42 were funded mainly by public or governmental organisations or independent scientific foundations. Also, in 29 trials, vitamin or antioxidant supplements were provided at no cost from the pharmaceutical industry, while 18 trials paid for them or did not mention whether the pharmaceutical industry charged for them.

In the fixed effects meta-analysis of all 50 trials, use of vitamin or antioxidant supplements was not associated with reduced risks of major cardiovascular events (relative risk 1.00; 95% confidence interval 0.98 to 1.02; $I^2$=42%) (fig 2⇓). Overall, the effect sizes of the smaller randomised controlled trials tend to be less than 1.0, while the effect sizes of the larger ones tend to be null. In the 48 selected trials, the Begg's funnel plot was symmetrical, and P for bias was 0.11 in the Egger's test (two[12 22] of the 50 trials were not included because of "zero" cells in the 2×2 table) (the Begg's funnel plot is not shown in the figure).

Based on the Jadad scales, the mean score for the 47 trials assessed was 4.3, ranging from 2 to 5 (table 1⇓).

Tables 2-4⇓⇓⇓ show the efficacy of vitamin or antioxidant supplements in the prevention of the major cardiovascular events in subgroup meta-analysis by various factors. Overall, subgroup meta-analyses by type of supplement (table 2)⇓ showed that there was no significant association between vitamin or antioxidant supplements and the risk of the major cardiovascular events (figs 3-6,⇓⇓⇓⇓ and table 2⇓), while low dose vitamin $B_6$ supplementation slightly decreased the risk of major cardiovascular events (relative risk 0.92, 95% confidence interval 0.85 to 0.99; $I^2$=35%; fig 7⇓) in the fixed effects meta-analysis. Similarly, we found no significant association in the overall subgroup meta-analysis by type of outcome (cardiovascular death, fatal or nonfatal myocardial infarction, stroke, or transient ischaemic attack; table 3⇓), type of prevention (primary *v* secondary; table 2⇓), type of study design, methodological quality (high *v* low by score of 5), duration of treatment (<5 years *v* ≥5 years), funding source (independent organisation *v* pharmaceutical industry) (table 4⇓), and provider of the supplements (pharmaceutical industry *v* at cost or no mention), while vitamin $B_6$ and vitamin E supplements were associated with a reduced risk of cardiovascular death (relative

risk 0.91, 95% confidence interval 0.83 to 0.99; $I^2$=0%) and myocardial infarction (0.77, 0.65 to 0.91; $I^2$=76%), respectively, and vitamin and antioxidant supplementation marginally increased the risk of angina pectoris (1.04, 1.00 to 1.08; $I^2$=36%) (table 3⇓).

In the subgroup meta-analysis of high quality randomised controlled trials within each category of low dose vitamin $B_6$ (relative risk 0.94, 95% confidence interval 0.87 to 1.02; $I^2$=39%; fixed effects model, table 2⇓ and fig 7⇓) and angina (1.01, 0.86 to 1.18; $I^2$=57%; random effects model, table 3⇓), however, beneficial or harmful effects disappeared. Also, even though vitamin $B_6$ supplementation was associated with decreased risks of cardiovascular death in high quality trials, and vitamin E supplementation with a decreased risk of myocardial infarction, those beneficial effects were seen only in trials supplied with supplements by pharmaceutical industry (fig 8⇓ and table 3⇓).

In the subgroup meta-analysis by the number of participants in each trial, vitamin or antioxidant supplements showed a trend toward a decreased (but not significant) risk of major cardiovascular events (relative risk 0.97, 95% confidence interval 0.94 to 1.01; $I^2$=40%) in the subgroup meta-analysis of trials with <10 000 participants, while those supplements showed an increased (but not significant) risk of the major cardiovascular events (1.02, 0.99 to 1.04; $I^2$=39%) in the subgroup meta-analysis of those with ≥10 000 participants (table 4⇓).

Table 5⇓ shows the efficacy of vitamin and antioxidant supplements given singly or in combination with other vitamin or antioxidant supplements on major cardiovascular events in subgroup meta-analyses. We found no significant beneficial effect of vitamin and antioxidant supplements in most of the subgroup meta-analyses, while only vitamin E supplements had a marginally significant decreased efficacy for the major cardiovascular events in high quality trials (relative risk 0.95, 95% confidence interval 0.90 to 1.00; $I^2$=45%).

# Discussion

## Summary of main findings

In this large scale meta-analysis of randomised controlled trials, we found no evidence to support the use of vitamin or antioxidant supplements for the primary or secondary prevention of major cardiovascular events. Furthermore, these supplements were not associated with any reduced risk of the such events in the subgroup meta-analyses according to various factors such as type of vitamins and antioxidants, type of cardiovascular outcomes, study design, methodological quality, duration of treatment, funding source, provider of supplements, type of control, number of participants in each trial, and supplements given singly or in combination with other vitamins or antioxidant supplements.

## Strengths of the current meta-analysis

Our main findings are consistent with those of previous meta-analyses that investigated the association between the use of vitamin B,[7 61 62] vitamin D,[63] vitamin E,[5 64 65] β carotene,[5] folic acid,[7 8 61 62 66] or selenium[6] and cardiovascular diseases in randomised controlled trials.

Our findings, however, are inconsistent with those of previous in vivo animal studies that suggested vitamins or antioxidants inhibit the development of atherosclerosis[67-70] and in vitro laboratory studies that indicated vitamins and antioxidants reduce lipid peroxidation and free radical damage, and finally inhibit atheroslcerosis.[71-73] The findings from animal and laboratory studies are associated with the oxidative modification hypothesis of atherosclerosis. This hypothesis, which claims that the oxidation of low density lipoprotein cholesterol initiates atherosclerosis, could explain these associations.[70] It suggests that accumulated low density lipoprotein in the subendothelial space of arteries is oxidised to minimally modified low density lipoprotein by vascular cells, which then induces accumulation of monocytes and macrophages, which stimulate further peroxdiation of low density lipoprotein.[74] This reaction makes oxidised low density lipoprotein more negatively charged and completely oxidised.[75] The uptake of completely oxidised low density lipoprotein leads to massive uptake of cholesterol by the macrophages.[70] It also stimulates the binding of monocytes to the endothelium, promotes the release of lipids and lysosomal enzymes, and thus enhances the progression of atherosclerosis.[70 76]

Our meta-analysis indicates that there is a discrepancy in findings between in vivo animal or in vitro laboratory studies and randomised controlled trials with regard to the association between vitamin or antioxidants (natural forms in fruit and vegetables or synthetic forms) and cardiovascular disease. Several theories could explain this discrepancy. Firstly, preclinical studies such as animal studies and in vitro laboratory studies might not represent the biological processes in the human body.[73] Thus, even though vitamins or antioxidant substances show benefits against a certain disease in preclinical studies, they might show no benefit or could be harmful under clinical circumstances. Secondly, the beneficial effects of vitamin or antioxidant supplements might be related to the timing of their administration. For example, the beneficial effects vitamin C occur in the early stages of atherosclerosis,[73] and once the atherosclerotic plaque has developed it has no beneficial effect.[77] In the trials we included in our analysis, the mean age of participants ranged from 49 to 82, the ages at which atherosclerotic plaques or changes might be already formed.[73]

We found a similar discrepancy in findings between case-control studies and randomised controlled trials. This could be explained by methodological biases of case-control studies. Case-control studies use retrospective assessment of each participant's information on fruit and vegetable consumption and are thus susceptible to two potential biases: recall and selection.

Even though cohort studies are less biased than case-control studies, some important methodological issues might explain the differences in findings between cohort studies and randomised controlled trials. The diet assessment tools such as the food frequency questionnaire might not precisely assess an individual's long term diet or might not provide sufficient information on fruit and vegetable consumption. Also, and more importantly, the use of vitamin or antioxidant supplements in randomised controlled trials should not be seen as equivalent to the intake of fruit and vegetables in cohort studies, which contain other various micronutrients as well as specific nutritional substances. Beneficial effects of vitamin or antioxidant supplements on cardiovascular disease might be obtained from the combination of various nutrients, not from one or several specific nutrients.

## Strengths and weaknesses in relation to other meta-analyses

Our findings are similar to those of the previous meta-analysis of randomised controlled trials on the association between vitamin or antioxidant supplementation and other outcomes such as mortality and cancer. In 2007, Bjelakovic et al reported that vitamin A, vitamin E, or β carotene supplements were

associated with increased mortality in a meta-analysis of 47 low bias (high quality) trials with 180 938 participants, while vitamin C and selenium were not associated with mortality.[78] Regarding the negative effect of antioxidant supplements on mortality, they suggested that the elimination of free radicals in the human body through antioxidant supplementation interferes with essential defensive mechanisms such as apoptosis, phagocytosis, and detoxification and might lead to an increased mortality.[78] Their updated meta-analysis including the recently published trials had similar findings on this issue and suggested that antioxidant supplements should be considered as medicinal products and should undergo sufficient evaluation before they are marketed.[79] In 2010, Myung et al reported that antioxidant supplements had no primary or secondary preventive effect on cancer and even increased the risk of bladder cancer in a meta-analysis of 22 randomised controlled trials.[80]

Because of these discrepancies in results between preclinical studies and clinical trials, the findings from preclinical studies on the effects or actions of vitamin or antioxidant substances should not be directly applied to humans.

In the meantime, when we performed subgroup meta-analyses by quality (high *v* low), dose (low *v* high), and supplements given singly or in combination with other supplements, we found no overall association between vitamin or antioxidant supplements and the risk of major cardiovascular events, while vitamin and antioxidant supplementation were associated with a marginally increased risk of angina pectoris, and low dose vitamin $B_6$ supplementation with a slightly decreased risk of major cardiovascular events. In the subgroup meta-analysis of high quality randomised controlled trials within each category, however, beneficial or harmful effects disappeared. We cannot therefore conclude that vitamin and antioxidant supplements are harmful for angina pectoris or that vitamin $B_6$ supplements are beneficial for major cardiovascular events. Also, even though vitamin $B_6$ supplementation was associated with a decreased risk of cardiovascular mortality in high quality trials, and vitamin E supplementation was associated with a decreased risk of myocardial infarction, those beneficial effects were shown only in trials with supplements provided by the pharmaceutical industry. So we cannot completely exclude the possibility that this might have influenced the respective trial design, results, or interpretations.

We also found that there was a trend toward an increased (not significant) risk of major cardiovascular events for the supplementation group in subgroup meta-analysis of trials with ≥10 000 participants, while there was a trend toward a decreased (not significant) risk in subgroup meta-analysis of trials with <10 000 participants. Given that a larger sample size is more accurate than a smaller size, we cannot exclude that vitamin or antioxidant supplementation might be associated with an increase in the risk of cardiovascular disease. Further large scale trials are needed to confirm this.

## Weaknesses of the current meta-analysis

There are several limitations in the current study. Firstly, we investigated the association only between synthetic vitamin and antioxidant supplements and cardiovascular disease. Thus, our findings could not be directly applied to fruit and vegetables rich in natural vitamins or antioxidants or natural vitamins derived or extracted from plants. Secondly, we were unable to evaluate whether vitamin and antioxidant supplementation would be beneficial against cardiovascular disease for populations who are deficient in vitamins or antioxidants at baseline. Further randomised controlled trials in those populations are needed. Thirdly, we used the Jadad scale to assess the methodological quality of the trials, which has been criticised because it is subject to the generic problems of scales, has a strong emphasis on reporting rather than conduct, and does not cover concealment of allocation, one of the important biases in randomised controlled trials.[81] As an alternative, the Cochrane Risk of Bias (RoB) tool has been used to evaluate internal validity of randomised controlled trials since 2008. Hartling et al, however, reported that the inter-rater agreement varied substantially across domains in the Cochrane tool, and it took considerably longer to complete than the Jadad scale.[82] Further validated tools for the assessment of quality are needed. Finally, we assessed the methodological quality of the trials based only on the data presented in each article. Thus, we might not have assessed the actual performance or biases of each trial.

## Meaning of the findings

In summary, we found no evidence to support the use of vitamin or antioxidant supplements in the prevention of cardiovascular disease. Also, recent meta-analyses have shown that vitamin or antioxidant supplements are associated with increased mortality and have no preventive effect on cancer or were even associated with increases in some types of cancer. Most countries permit the pharmaceutical or food industry to sell these supplements under the name of functional food or medical food, and many people take vitamin or antioxidant supplements in the belief that they improve their health. Based on recent meta-analyses of randomised controlled trials, including the current study, however, governments and regulating agencies for food and drugs should consider vitamin and antioxidant supplements as medicinal products and strictly evaluate their efficacy and safety before marketing.

## Unanswered questions and future research

Further randomised controlled trials are required to determine whether vitamin and antioxidant supplementation would be beneficial against cardiovascular disease for people who are deficient in vitamins or antioxidants at baseline. Regarding the assessment of methodological quality of each trial, further validated tools that could assess the actual performance or biases of each trial should be developed.

Contributors: BC and S-KM were responsible for the initial plan, study design, conducting the study, data interpretation, and manuscript drafting. S-KM was responsible for statistical analysis. S-KM, WJ, and S-WO were responsible for data collection, data extraction, and data interpretation. SMP, B-KK, and B-J P were responsible for data interpretation and manuscript drafting. BC and S-KM are guarantors.

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Data sharing: No additional data available.

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**What is already known on this topic**

Over the past few decades, observational epidemiological studies have reported that intake of fruit and vegetables rich in various vitamins and antioxidants is associated with a reduced risk of cardiovascular disease

Unlike the evidence for the benefits of fruit and vegetables, however, randomised controlled trials have had inconsistent results regarding benefits of vitamin or antioxidant supplements

Even though several meta-analyses of randomised controlled trials have been published, those involved individual vitamin or antioxidant supplements, and there has been no published comprehensive meta-analysis that reviewed this topic all at once in one report

**What this study adds**

This large scale meta-analysis of randomised controlled trials suggests that there is no evidence to support the use of vitamin or antioxidant supplements for the primary or secondary prevention of major cardiovascular events

Governments and regulating agencies for food and drug should consider vitamin and antioxidant supplements as medicinal products and strictly evaluate their efficacy and safety before marketing

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# Tables

**Table 1| Methodological quality, based on Jadad scale, of 47* included trials on efficacy of vitamin and antioxidant supplements in prevention of cardiovascular diseases**

| | Randomisation | Description of randomisation methods | Double blind | Used identical placebo | Follow-up reporting | Total score |
|---|---|---|---|---|---|---|
| Steiner, 1995[13] | 1 | 0 | 1 | 1 | 1 | 4 |
| Omenn, 1996 (CARET)[14] | 1 | 1 | 1 | 1 | 1 | 5 |
| Stephens, 1996 (CHAOS)[15] | 1 | 1 | 1 | 1 | 1 | 5 |
| Mark, 1996 (LNIT)[16] | 1 | 1 | 1 | 1 | 0 | 4 |
| Hennekens, 1996 (PHS)[17] | 1 | 0 | 1 | 1 | 1 | 4 |
| Greenberg, 1996 (SCP)[18] | 1 | 1 | 1 | 1 | 1 | 5 |
| Rapola, 1997 (ATBC)[19] | 1 | 1 | 1 | 1 | 1 | 5 |
| Virtamo, 1998 (ATBC)[20] | 1 | 1 | 1 | 1 | 1 | 5 |
| GISSI, 1999[21] | 1 | 1 | 0 | 0 | 1 | 3 |
| Komulainen, 1999 (KOS)[22] | 1 | 0 | 1 | 1 | 1 | 4 |
| Green, 1999 (NSCP)[23] | 1 | 0 | 0 | 1 | 1 | 3 |
| Yusuf, 2000 (HOPE)[24] | 1 | 0 | 1 | 1 | 0 | 3 |
| Boaz, 2000 (SPACE)[25] | 1 | 1 | 1 | 1 | 0 | 4 |
| Brown, 2001 (HATS)[26] | 1 | 0 | 1 | 1 | 1 | 4 |
| De Gaetano, 2001 (PPP)[27] | 1 | 1 | 0 | 0 | 1 | 3 |
| You, 2001[28] | 1 | 0 | 1 | 1 | 1 | 4 |
| HPS, 2002[30] | 1 | 1 | 0 | 1 | 1 | 4 |
| Schnyder, 2002 (SHS)[31] | 1 | 0 | 1 | 1 | 1 | 4 |
| Waters, 2002 (WAVE)[32] | 1 | 1 | 1 | 1 | 1 | 5 |
| Liem, 2003 (Goes)[33] | 1 | 1 | 0 | 0 | 1 | 3 |
| Righetti, 2003[34] | 1 | 1 | 0 | 0 | 1 | 3 |
| Trivedi, 2003[35] | 1 | 0 | 1 | 1 | 1 | 4 |
| Lange, 2004[36] | 1 | 0 | 1 | 1 | 1 | 4 |
| Hercberg, 2004 (SU.VI.MAX)[37] | 1 | 1 | 1 | 1 | 1 | 5 |
| Toole, 2004 (VISP)[38] | 1 | 1 | 1 | 1 | 1 | 5 |
| Wrone, 2004[39] | 1 | 1 | 1 | 1 | 1 | 5 |
| Brazier, 2005[40] | 1 | 1 | 1 | 1 | 1 | 5 |
| Lee, 2005 (WHS)[41] | 1 | 1 | 1 | 1 | 1 | 5 |
| Zoungas, 2006 (ASFAST)[42] | 1 | 0 | 1 | 1 | 1 | 4 |
| Lonn, 2006 (HOPE-2)[43] | 1 | 1 | 1 | 1 | 1 | 5 |
| Bønaa, 2006 (NORVIT)[44] | 1 | 1 | 1 | 1 | 1 | 5 |
| Stranges, 2006 (NPC)[45] | 1 | 1 | 1 | 1 | 0 | 4 |
| Jamison, 2007 (HOST)[46] | 1 | 1 | 1 | 1 | 1 | 5 |
| Hsia, 2007 (WHI)[47] | 1 | 0 | 1 | 1 | 0 | 3 |
| Berggren, 2008[48] | 1 | 0 | 0 | 0 | 1 | 2 |
| Milman, 2008 (ICARE)[49] | 1 | 1 | 1 | 1 | 1 | 5 |
| Prince, 2008[50] | 1 | 1 | 1 | 1 | 1 | 5 |
| Albert, 2008 (WAFACS)[51] | 1 | 0 | 1 | 1 | 1 | 4 |
| Ebbing, 2008 (WENBIT)[52] | 1 | 1 | 1 | 1 | 1 | 5 |
| Hodis, 2009 (BVAIT)[53] | 1 | 1 | 1 | 1 | 1 | 5 |
| House, 2010 (DIVINe)[54] | 1 | 1 | 1 | 1 | 1 | 5 |
| Heinz, 2010[55] | 1 | 0 | 1 | 1 | 1 | 4 |
| Armitage, 2010 (SEARCH)[56] | 1 | 1 | 1 | 1 | 1 | 5 |
| Galan, 2010 (SU.FOL.OM3)[57] | 1 | 1 | 1 | 1 | 1 | 5 |

**Table 1 (continued)**

| | Randomisation | Description of randomisation methods | Double blind | Used identical placebo | Follow-up reporting | Total score |
|---|---|---|---|---|---|---|
| VITATOPS 2010[58] | 1 | 1 | 1 | 1 | 1 | 5 |
| Bostom, 2011 (FAVORIT)[59] | 1 | 1 | 1 | 1 | 1 | 5 |
| Sesso, 2012 (PHS2)[60] | 1 | 1 | 1 | 1 | 1 | 5 |

*We were unable to retrieve full text from three trials: Korpela et al, 1989,[11] Kuklinski et al, 1994,[12] and Rafiee et al, 2002.[29]

**Table 2| Efficacy of vitamin and antioxidant supplements in the prevention of the major cardiovascular events in subgroup meta-analysis by type of prevention and type of supplement**

| Factor | No of trials | Relative risk (95% CI) | Heterogeneity $I^2$ (%) | Model |
|---|---|---|---|---|
| All | 50 | 1.00 (0.98 to 1.02) | 42 | Fixed effects |
| Prevention: | | | | |
| Primary | 30 | 1.01 (0.98 to 1.03) | 42 | Fixed effects |
| Secondary | 20 | 1.00 (0.97 to 1.03) | 44 | Fixed effects |
| Type of supplement: | | | | |
| Vitamins only | 39 | 0.99 (0.97 to 1.01) | 44 | Fixed effects |
| Low quality trials | 17 | 0.99 (0.96 to 1.02) | 32 | Fixed effects |
| High quality trials | 22 | 0.99 (0.94 to 1.05) | 53 | Random effects |
| Antioxidants only | 22 | 0.98 (0.96 to 1.02) | 41 | Fixed effects |
| Low quality trials | 11 | 0.99 (0.96 to 1.03) | 25 | Fixed effects |
| High quality trial | 9 | 0.97 (0.91 to 1.02) | 49 | Fixed effects |
| Vitamin A | 2 | 0.98 (0.45 to 2.16) | 87 | Random effects |
| Low dose (10 000 IU/day) | 1 | 0.63 (0.37 to 1.07) | NA | NA |
| High dose (25 000 IU/day) | 1 | 1.41 (1.15 to 1.73)* | NA | NA |
| Vitamin $B_6$ | 16 | 0.96 (0.92 to 1.01) | 33 | Fixed effects |
| Low dose (3-25 mg/day) | 8 | 0.92 (0.85 to 0.99)* | 35 | Fixed effects |
| Low quality trials | 3 | 0.76 (0.61 to 0.94)* | 0 | Fixed effects |
| High quality trials | 5 | 0.94 (0.87 to 1.02) | 39 | Fixed effects |
| High dose (40-100 mg/day) | 8 | 0.99 (0.94 to 1.05) | 22 | Fixed effects |
| Vitamin $B_{12}$ | 17 | 0.99 (0.95 to 1.02) | 37 | Fixed effects |
| Low dose (6 µg-0.5 mg/day) | 11 | 0.96 (0.90 to 1.02) | 34 | Fixed effects |
| High dose (1-2 mg/day) | 6 | 1.00 (0.96 to 1.05) | 43 | Fixed effects |
| Folic acid | 21 | 0.99 (0.95 to 1.02) | 35 | Fixed effects |
| Low dose (500 µg-5 mg/day) | 17 | 0.99 (0.96 to 1.03) | 39 | Fixed effects |
| High dose (10-40 mg/day) | 4 | 0.89 (0.78 to 1.03) | 0 | Fixed effects |
| Vitamin C† | 7 | 0.99 (0.94 to 1.04) | 16 | Fixed effects |
| Low dose (120-250 mg/day) | 3 | 0.99 (0.94 to 1.04) | 31 | Fixed effects |
| High dose (500-1000 mg/day) | 4 | 0.98 (0.94 to 1.12) | 28 | Fixed effects |
| Vitamin D | 7 | 1.02 (0.98 to 1.07) | 23 | Fixed effects |
| Low dose (120-250 mg/day) | 2 | 1.05 (0.99 to 1.12) | 0 | Fixed effects |
| High dose (500-1000 mg/day) | 5 | 0.94 (0.86 to 1.03) | 0 | Fixed effects |
| Vitamin E† | 17 | 0.97 (0.94 to 1.01) | 44 | Fixed effects |
| Low dose (60 IU-250 mg/day) | 13 | 0.96 (0.92 to 1.01) | 35 | Fixed effects |
| High dose (500-600 mg/day) | 4 | 0.84 (0.52 to 1.35) | 69 | Random effects |
| β carotene | 11 | 1.04 (0.96 to 1.12) | 55 | Random effects |
| Low dose (6-25 mg/day) | 6 | 0.99 (0.95 to 1.03) | 7 | Fixed effects |
| High dose (30-50 mg/day) | 5 | 1.14 (0.96 to 1.35) | 69 | Random effects |
| Selenium | 7 | 0.91 (0.77 to 1.06) | 47 | Fixed effects |
| Low dose (50-100 µg/day) | 5 | 0.85 (0.70 to 1.04) | 44 | Fixed effects |
| High dose (122-200 µg /day) | 2 | 0.57 (0.10 to 3.16) | 67 | Fixed effects |

NA=not applicable.

*P≤0.05.

†For subgroup meta-analysis of vitamin C and vitamin E, we used data from 2008 PHS2 article[83] because data were not available in 2012 PHS article.

**Table 3| Efficacy of vitamin and antioxidant supplements in prevention of major cardiovascular events in subgroup meta-analysis by outcome**

| | No of trials | Relative risk (95% CI) | Heterogeneity $I^2$ (%) | Model |
|---|---|---|---|---|
| Cardiovascular death | 32 | 1.01 (0.97 to 1.05) | 41 | Fixed effects |
| Vitamin A | 2 | 0.98 (0.45 to 2.16) | 87 | Random effects |
| Vitamin $B_6$ | 8 | 0.91 (0.83 to 0.99)* | 0 | Fixed effects |
| Low quality trials | 4 | 0.93 (0.75 to 1.14) | 12 | Fixed effects |
| High quality trials | 4 | 0.90 (0.82 to 0.99)* | 0 | Fixed effects |
| Not supplied by pharmaceutical industry | 2 | 0.96 (0.84 to 1.10) | 0 | Fixed effects |
| Supplied by pharmaceutical industry | 2 | 0.85 (0.75 to 0.97)* | 0 | Fixed effects |
| Not supplied by pharmaceutical industry | 3 | 0.96 (0.83 to 1.10) | 0 | Fixed effects |
| Supplied by pharmaceutical industry | 5 | 0.88 (0.79 to 0.98)* | 0 | Fixed effects |
| Vitamin $B_{12}$ | 9 | 0.96 (0.90 to 1.03) | 27 | Fixed effects |
| Folic acid | 11 | 0.96 (0.89 to 1.03) | 11 | Fixed effects |
| Vitamin C† | 6 | 1.03 (0.95 to 1.12) | 27 | Fixed effects |
| Vitamin D | 3 | 0.90 (0.76 to 1.07) | 27 | Fixed effects |
| Vitamin E† | 15 | 0.98 (0.92 to 1.04) | 37 | Fixed effects |
| β carotene | 10 | 1.10 (0.96 to 1.27) | 61 | Random effects |
| Selenium | 15 | 0.98 (0.92 to 1.04) | 37 | Fixed effects |
| Vitamin | 2 | 0.98 (0.45 to 2.16) | 87 | Random effects |
| Angina | 10 | 1.04 (1.00 to 1.08)* | 36 | Fixed effects |
| Low quality trials | 6 | 1.05 (1.00 to 1.09)* | 25 | Fixed effects |
| High quality trials | 4 | 1.01 (0.86 to 1.18) | 57 | Random effects |
| Vitamin $B_6$ | 4 | 0.93 (0.72 to 1.20) | 77 | Random effects |
| Vitamin $B_{12}$ | 4 | 0.93 (0.72 to 1.20) | 77 | Random effects |
| Folic acid | 4 | 0.93 (0.72 to 1.20) | 77 | Random effects |
| Vitamin C† | 2 | 0.94 (0.85 to 1.03) | 0 | Fixed effects |
| Vitamin D | 1 | 1.07 (0.93 to 1.23) | NA | NA |
| Vitamin E† | 3 | 1.15 (0.99 to 1.33) | 0 | Fixed effects |
| Myocardial infarction | 34 | 1.00 (0.96 to 1.03) | 0 | Fixed effects |
| Vitamin $B_6$ | 13 | 0.99 (0.91 to 1.07) | 11 | Fixed effects |
| Vitamin $B_{12}$ | 14 | 0.99 (0.93 to 1.06) | 4 | Fixed effects |
| Folic acid | 15 | 0.99 (0.93 to 1.06) | 0 | Fixed effects |
| Vitamin C† | 4 | 0.96 (0.87 to 1.07) | 0 | Fixed effects |
| Vitamin D | 2 | 1.06 (0.92 to 1.21) | 0 | Fixed effects |
| Vitamin E† | 12 | 0.77 (0.65 to 0.91)* | 76 | Random effects |
| Low quality trials | 5 | 0.76 (0.57 to 1.01) | 81 | Random effects |
| High quality trials | 7 | 0.75 (0.58 to 0.97)* | 75 | Random effects |
| Not supplied by pharmaceutical industry | 4 | 0.79 (0.53 to 1.17) | 62 | Random effects |
| Supplied by pharmaceutical industry | 3 | 0.67 (0.42 to 1.07)* | 86 | Random effects |
| Primary prevention | 7 | 0.72 (0.54 to 0.95)* | 76 | Random effects |
| Not supplied by pharmaceutical industry | 3 | 0.79 (0.42 to 1.50) | 55 | Random effects |
| Supplied by pharmaceutical industry | 4 | 0.63 (0.42 to 0.97)* | 82 | Random effects |
| Secondary prevention | 5 | 0.79 (0.61 to 1.02) | 80 | Random effects |
| Not supplied by pharmaceutical industry | 4 | 0.79 (0.53 to 1.17) | 62 | Random effects |
| Supplied by pharmaceutical industry | 8 | 0.73 (0.59 to 0.92)* | 82 | Random effects |
| β carotene | 4 | 0.95 (0.80 to 1.14) | 52 | Random effects |
| Selenium | 3 | 0.87 (0.59 to 1.28) | 0 | Fixed effects |
| Fatal myocardial infarction | 9 | 1.02 (0.92 to 1.12) | 43 | Fixed effects |
| Vitamin $B_6$ | 1 | 1.00 (0.75 to 1.33) | NA | NA |
| Vitamin $B_{12}$ | 1 | 1.00 (0.75 to 1.33) | NA | NA |

**Table 3 (continued)**

| | No of trials | Relative risk (95% CI) | Heterogeneity $I^2$ (%) | Model |
|---|---|---|---|---|
| Folic acid | 1 | 1.00 (0.75 to 1.33) | NA | NA |
| Vitamin E† | 3 | 0.57 (0.32 to 1.03) | 0 | Fixed effects |
| β carotene | 1 | 1.05 (0.95 to 1.17) | NA | NA |
| Selenium | 1 | 1.12 (0.43 to 2.87) | NA | NA |
| Non-fatal myocardial infarction | 13 | 0.83 (0.66 to 1.04) | 89 | Random effects |
| Vitamin $B_6$ | 3 | 1.08 (0.90 to 1.30) | 22 | Fixed effects |
| Vitamin $B_{12}$ | 4 | 1.03 (0.93 to 1.14) | 1 | Fixed effects |
| Folic acid | 4 | 1.03 (0.93 to 1.14) | 1 | Fixed effects |
| Vitamin C† | 4 | 0.85 (0.70 to 1.04) | 0 | Random effects |
| Vitamin E† | 9 | 0.57 (0.32 to 1.03) | 0 | Fixed effects |
| β carotene | 4 | 0.95 (0.80 to 1.14) | 52 | Random effects |
| Selenium | 3 | 0.82 (0.53 to 1.27) | 0 | Fixed effects |
| Stroke | 32 | 0.97 (0.93 to 1.02) | 0 | Fixed effects |
| Vitamin $B_6$ | 12 | 0.93 (0.85 to 1.01) | 13 | Fixed effects |
| Vitamin $B_{12}$ | 5 | 0.91 (0.80 to 1.03) | 8 | Fixed effects |
| Folic acid | 7 | 0.90 (0.79 to 1.01) | 19 | Fixed effects |
| Vitamin C† | 4 | 0.98 (0.88 to 1.09) | 0 | Fixed effects |
| Vitamin D | 5 | 1.00 (0.88 to 1.13) | 6 | Fixed effects |
| Vitamin E† | 12 | 1.00 (0.93 to 1.09) | 20 | Fixed effects |
| β carotene | 2 | 0.98 (0.89 to 1.07) | 0 | Fixed effects |
| Selenium | 1 | 1.09 (0.68 to 1.72) | NA | NA |
| Transient ischaemic attack | 5 | 1.12 (0.97 to 1.30) | 0 | Fixed effects |
| Vitamin B6 | 2 | 1.12 (0.88 to 1.42) | 0 | Fixed effects |
| Vitamin $B_{12}$ | 2 | 1.12 (0.88 to 1.42) | 0 | Fixed effects |
| Folic acid | 2 | 1.12 (0.88 to 1.42) | 0 | Fixed effects |
| Vitamin D | 1 | 1.12 (0.96 to 1.42) | NA | NA |
| Vitamin E† | 2 | 0.93 (0.59 to 1.47) | 0 | Fixed effects |

NA=not applicable.

*P≤0.05.

†For subgroup meta-analysis of vitamin C and vitamin E, we used data from 2008 PHS2 article[83] because data were not available in 2012 PHS article.

Table 4| **Efficacy of vitamin and antioxidant supplements in prevention of major cardiovascular events in subgroup meta-analysis by various factors**

| Factor | No of trials | Relative risk (95% CI) | Heterogeneity, $I^2$ (%) | Model |
|---|---|---|---|---|
| Study design: | | | | |
| RDBPCT | 45 | 1.00 (0.98 to 1.02) | 46 | Fixed effects |
| OLRCT | 5 | 0.98 (0.89 to 1.07) | 0 | Fixed effects |
| Methodological quality: | | | | |
| High quality (Jadad score 5) | 24 | 0.99 (0.96 to 1.03) | 45 | Fixed effects |
| Low quality (Jadad score ≤4) | 23 | 1.01 (0.98 to 1.03) | 32 | Fixed effects |
| Duration of treatment (years): | | | | |
| <5 | 34 | 0.97 (0.90 to 1.04) | 52 | Random effects |
| ≥5 | 16 | 1.01 (0.98 to 1.03) | 0 | Fixed effects |
| Funding source: | | | | |
| Pharmaceutical industry | 5 | 1.01 (0.96 to 1.07) | 0 | Fixed effects |
| Independent organisation | 42 | 1.00 (0.98 to 1.02) | 42 | Fixed effects |
| Supply source for supplements: | | | | |
| Pharmaceutical industry | 29 | 0.99 (0.97 to 1.02) | 33 | Fixed effects |
| Not pharmaceutical industry | 18 | 1.01 (0.98 to 1.05) | 47 | Fixed effects |
| Type of control: | | | | |
| Placebo | 44 | 1.00 (0.98 to 1.02) | 46 | Fixed effects |
| No placebo | 6 | 0.97 (0.89 to 1.06) | 0 | Fixed effects |
| No of participants in each trial: | | | | |
| <10 000 | 40 | 0.97 (0.94 to 1.01) | 40 | Fixed effects |
| ≥10 000 | 10 | 1.02 (0.99 to 1.04) | 39 | Fixed effects |

RDBPCT=randomised, double blind, placebo-controlled trial; OLRCT=open label, randomised controlled trial.

**Table 5| Efficacy of vitamin and antioxidant supplements given singly or combined with other vitamin or antioxidant supplements in prevention of major cardiovascular events in subgroup meta-analysis**

| Factor | No of trials | Relative risk (95% CI) | Heterogeneity, $I^2$ (%) | Model |
|---|---|---|---|---|
| All | 50 | 1.00 (0.98 to 1.02) | 42 | Fixed effects |
| Vitamin A: | | | | |
| Given singly | NA | — | — | — |
| Combined with others | 2 | 0.98 (0.45 to 2.16) | 87 | Random effects |
| Vitamin $B_6$: | | | | |
| Given singly | NA | — | — | — |
| Combined with others | 16 | 0.96 (0.92 to 1.01) | 33 | Fixed effects |
| Low quality trials | 5 | 0.94 (0.73 to 1.21) | 66 | Random effects |
| High quality trials | 11 | 0.96 (0.91 to 1.01) | 1 | Fixed effects |
| Vitamin $B_{12}$: | | | | |
| Given singly | NA | — | — | — |
| Combined with others | 17 | 0.99 (0.95 to 1.02) | 37 | Fixed effects |
| Low quality trials | 5 | 0.94 (0.73 to 1.21) | 66 | Random effects |
| High quality trials | 12 | 0.98 (0.95 to 1.02) | 18 | Fixed effects |
| Folic acid: | | | | |
| Given singly | 4 | 1.02 (0.84 to 1.23) | 47 | Fixed effects |
| Combined with others | 17 | 0.99 (0.95 to 1.02) | 37 | Fixed effects |
| Given singly or combined | 21 | 0.99 (0.95 to 1.02) | 35 | Fixed effects |
| Low quality trials | 8 | 0.99 (0.90 to 1.08) | 49 | Fixed effects |
| High quality trials | 12 | 0.98 (0.95 to 1.02) | 18 | Fixed effects |
| Vitamin C*: | | | | |
| Given singly | NA | — | — | — |
| Combined with others | 7 | 0.99 (0.94 to 1.06) | 16 | Fixed effects |
| Low quality trials | 4 | 0.99 (0.94 to 1.04) | 44 | Fixed effects |
| High quality trials | 3 | 0.99 (0.88 to 1.11) | 0 | Fixed effects |
| Vitamin D | | | | |
| Given singly | 2 | 0.95 (0.86 to 1.05) | 11 | Fixed effects |
| Combined with others | 5 | 1.04 (0.99 to 1.10) | 0 | Fixed effects |
| Given singly or combined | 7 | 1.02 (0.98 to 1.07) | 23 | Fixed effects |
| Low quality trials | 5 | 1.02 (0.98 to 1.08) | 47 | Fixed effects |
| High quality trials | 2 | 1.01 (0.45 to 2.27) | 0 | Fixed effects |
| Vitamin E*: | | | | |
| Given singly | 10 | 0.93 (0.85 to 1.01) | 57 | Random effects |
| Combined with others | 7 | 0.99 (0.94 to 1.04) | 15 | Fixed effects |
| Given singly or combined | 17 | 0.97 (0.94 to 1.01) | 44 | Fixed effects |
| Low quality trials | 9 | 0.99 (0.95 to 1.03) | 43 | Fixed effects |
| High quality trials | 8 | 0.95 (0.90 to 1.00)† | 45 | Fixed effects |
| β carotene: | | | | |
| Given singly | 5 | 1.02 (0.96 to 1.08) | 31 | Fixed effects |
| Combined with others | 6 | 1.00 (0.81 to 1.23) | 70 | Random effects |
| Given singly or combined | 11 | 1.04 (0.96 to 1.12) | 55 | Random effects |
| Low quality trials | 6 | 0.99 (0.95 to 1.03) | 30 | Fixed effects |
| High quality trials | 5 | 1.13 (0.98 to 1.29) | 64 | Random effects |
| Selenium: | | | | |
| Given singly | 3 | 0.34 (0.06 to 2.05) | 70 | Random effects |
| Combined with others | 4 | 0.88 (0.72 to 1.08) | 26 | Fixed effects |
| Given singly or combined | 7 | 0.91 (0.77 to 1.06) | 47 | Fixed effects |
| Low quality trials | 4 | 0.91 (0.73 to 1.12) | 43 | Fixed effects |

**Table 5 (continued)**

| Factor | No of trials | Relative risk (95% CI) | Heterogeneity, $I^2$ (%) | Model |
|---|---|---|---|---|
| High quality trials | 1 | 0.98 (0.77 to 1.24) | NA | NA |

NA=not applicable.

*For subgroup meta-analysis of vitamin C and vitamin E, we used data from 2008 PHS2 article[83] because data were not available in 2012 PHS article.

†P≤0.05.

# Figures

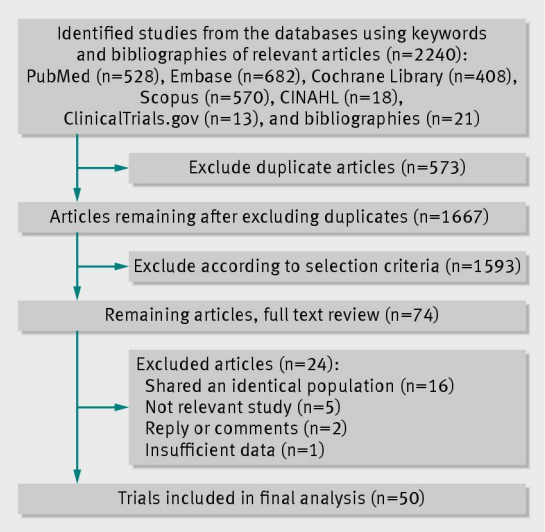


**Fig 1** Flow diagram for identification of relevant clinical trials examining effect of vitamins and supplements in prevention of cardiovascular disease

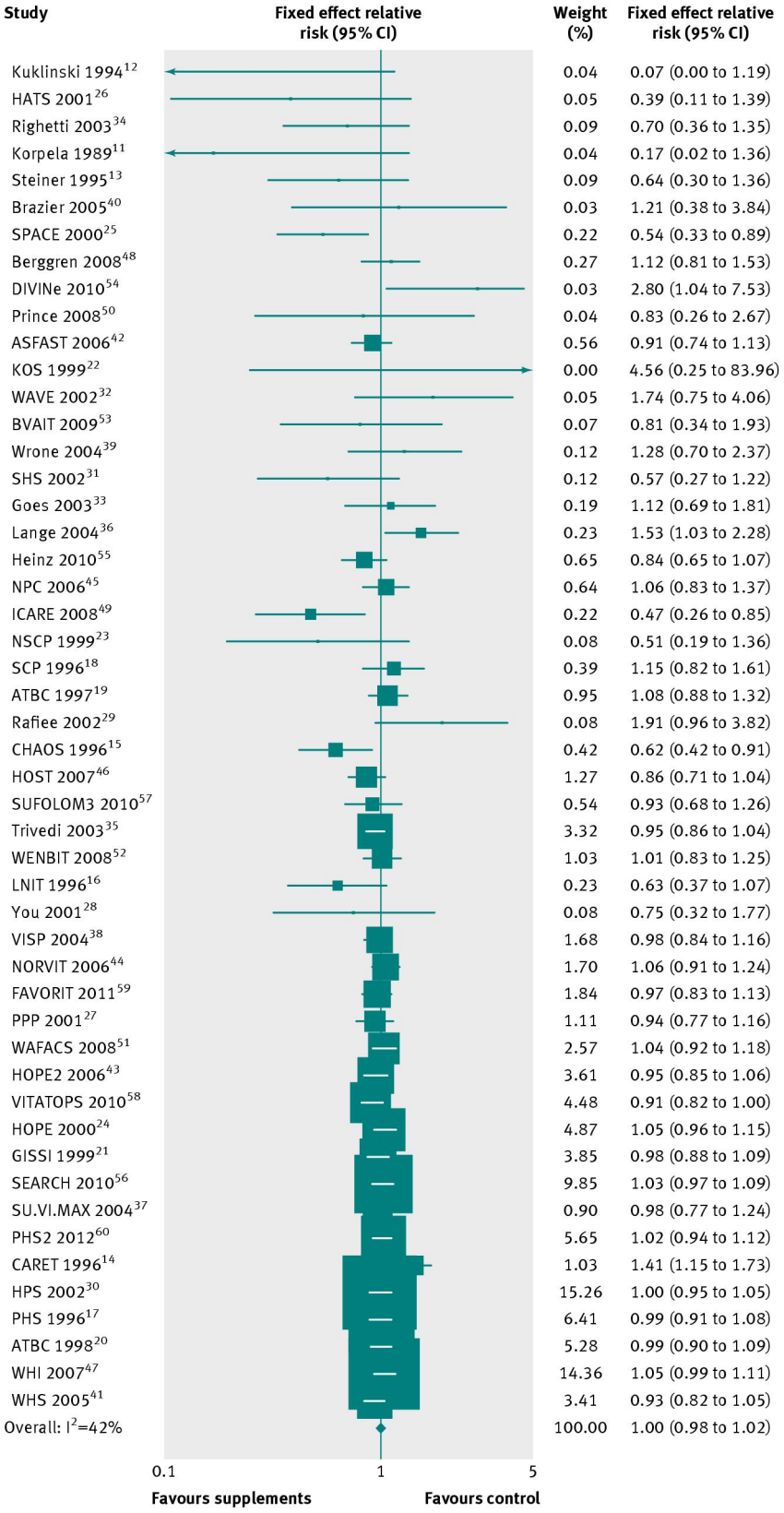


**Fig 2** Efficacy of vitamin and antioxidant supplements in prevention of major cardiovascular events in meta-analysis of 50 randomised controlled trials sorted in ascending order of number of participants

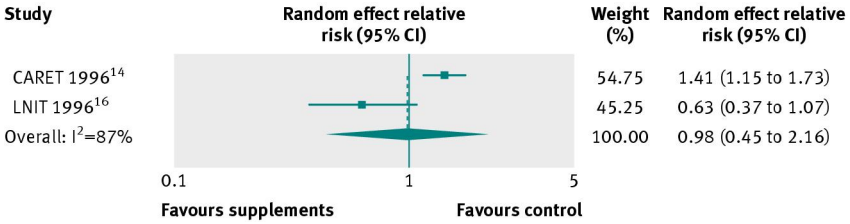


**Fig 3** Efficacy of vitamin A supplements in prevention of major cardiovascular events in subgroup meta-analysis of randomised controlled trials

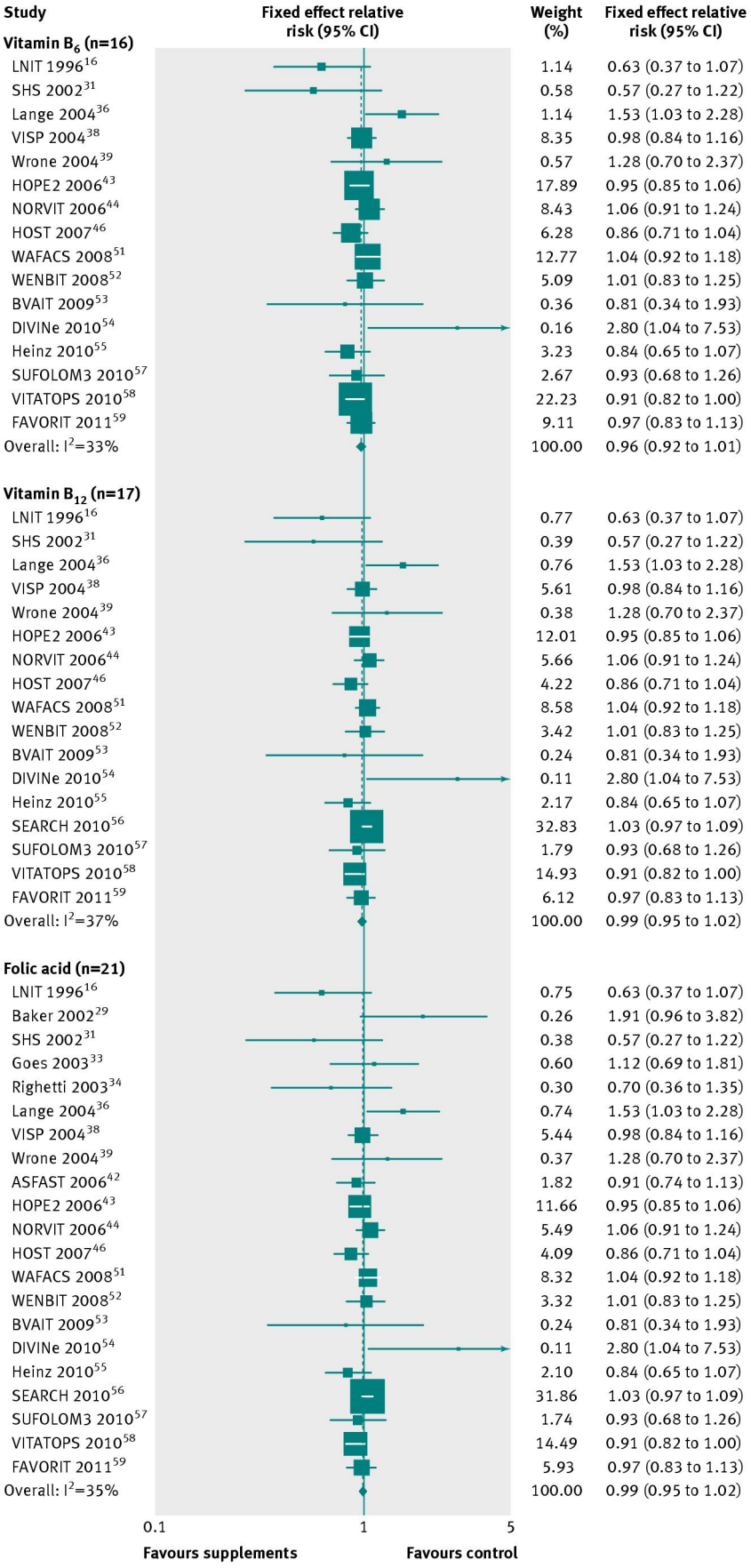


**Fig 4** Efficacy of vitamins $B_6$ and $B_{12}$ and folic acid supplements in prevention of major cardiovascular events in subgroup meta-analysis of randomised controlled trials

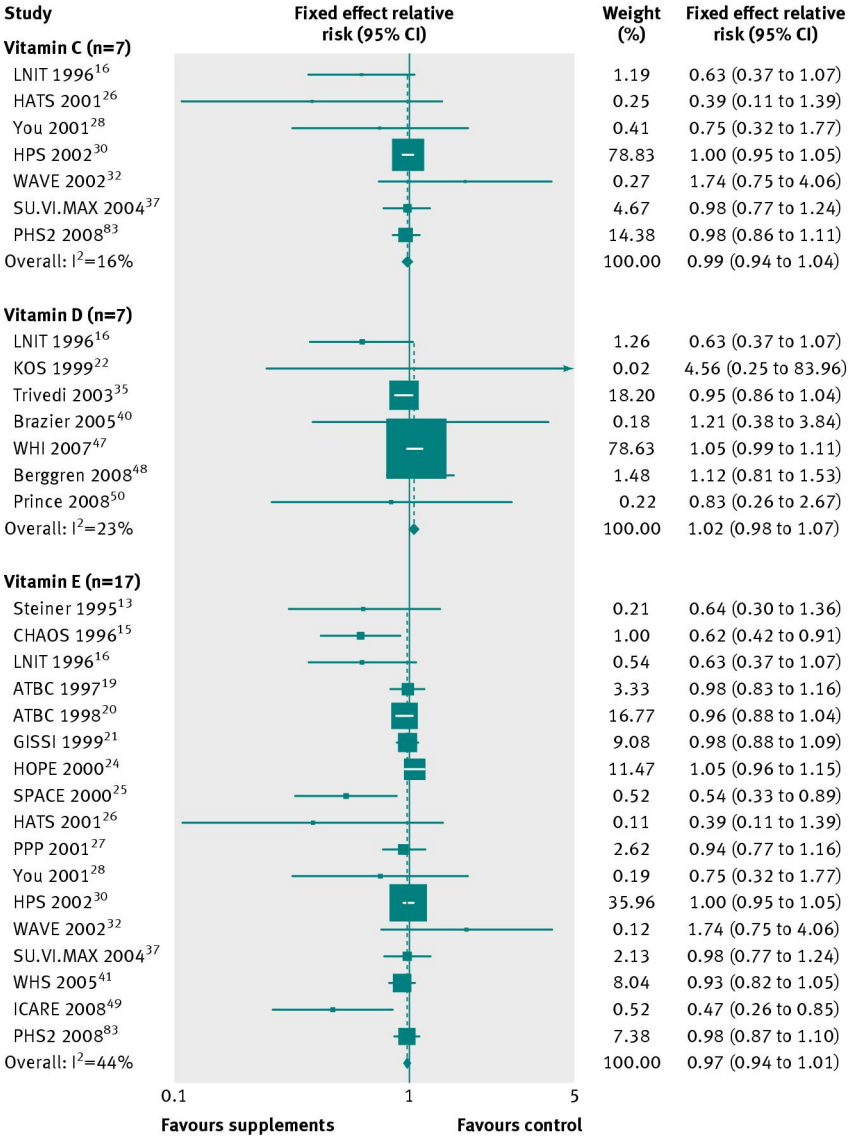


**Fig 5** Efficacy of vitamins C, D, and E supplements in prevention of major cardiovascular events in subgroup meta-analysis of randomised controlled trials. For subgroup meta-analysis of vitamin C and vitamin E, we used data from 2008 PHS2 article[83] because data were not available in 2012 PHS article

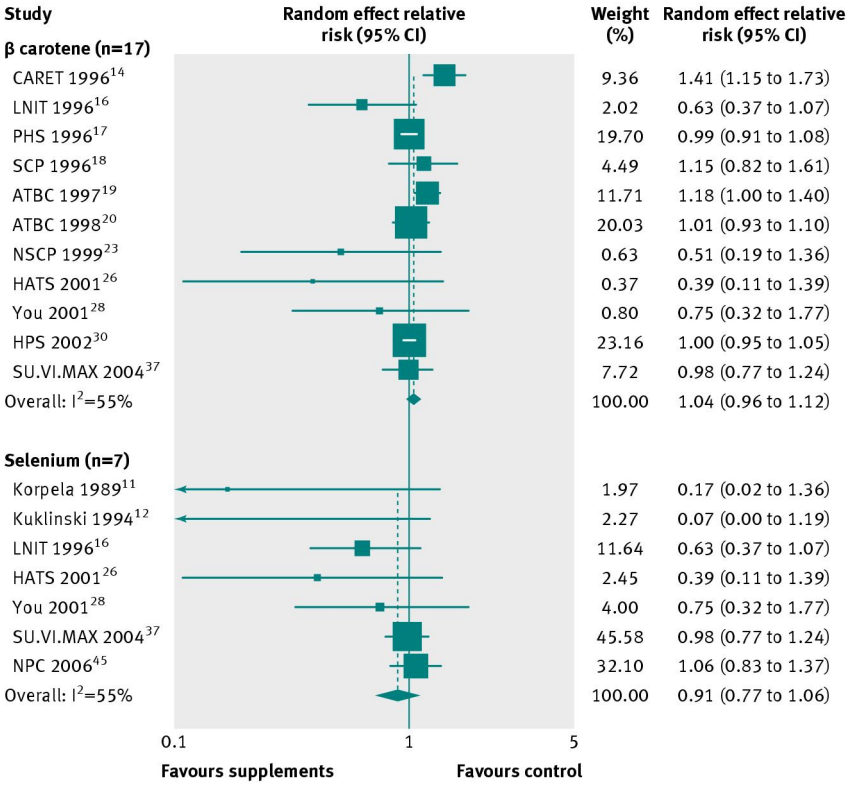


**Fig 6** Efficacy of β carotene and selenium supplements in prevention of major cardiovascular events in subgroup meta-analysis of randomised controlled trials

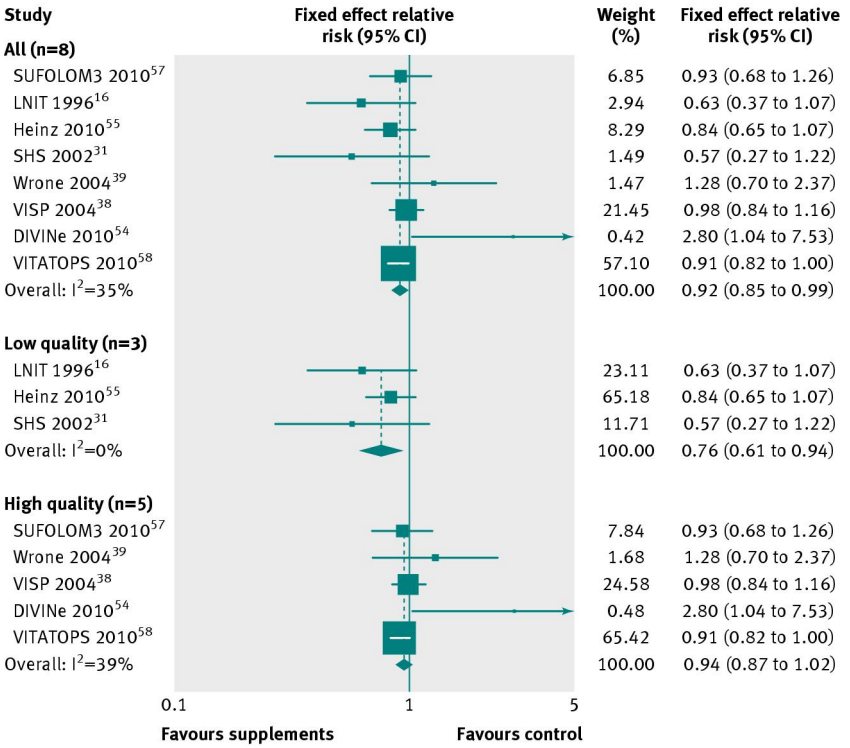


**Fig 7** Efficacy of low dose vitamin $B_6$ supplements in prevention of major cardiovascular events in subgroup meta-analysis of randomised controlled trials by study quality according to Jadad scale

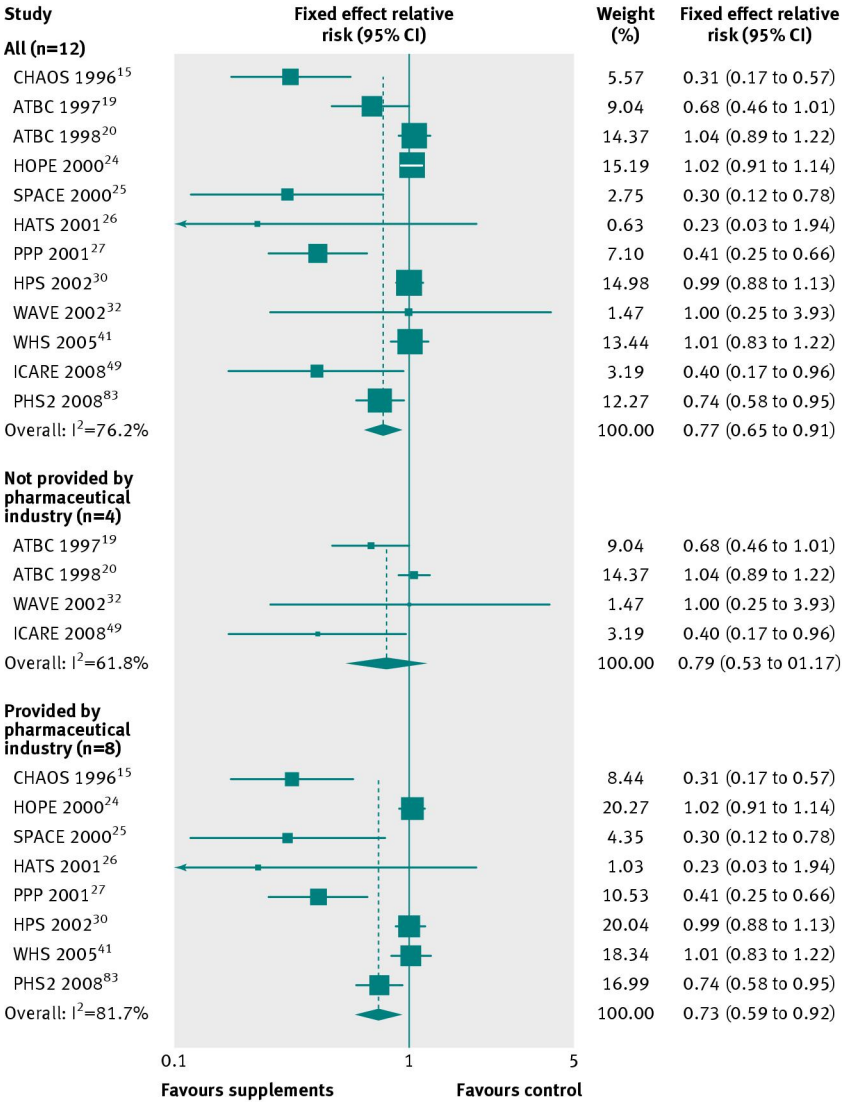


**Fig 8** Efficacy of vitamin E supplements in prevention of myocardial infarction in subgroup meta-analysis of randomised controlled trials according to provider of supplements (pharmaceutical industry or other). For subgroup meta-analysis of vitamin E, we used data from 2008 PHS2 article[83] because data were not available in 2012 PHS article