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의학박사 학위논문

Efficacy of Vitamin and Antioxidant Supplements in the Prevention of Cardiovascular Disease

- A Meta-Analysis of Randomized Controlled Trials

비타민 및 항산화보충제의 심혈관질환 예방에 대한 효능

– 무작위배정비교임상시험의 메타분석 –

2013 년 2 월

서울대학교 대학원

의학과 가정의학전공

명 승 권

A thesis of the Degree of Doctor of Philosophy

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February 2013

Department of Medicine
Seoul National University College of Medicine
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Efficacy of Vitamin and Antioxidant Supplements in the Prevention of Cardiovascular Disease

- A Meta-Analysis of Randomized Controlled Trials -

by

Seung-Kwon Myung

A thesis submitted to the Department of Medicine
in partial fulfillment of the requirement for the Degree of
Doctor of Philosophy in Medical Science (Family Medicine)
at Seoul National University College of Medicine

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비타민 및 항산화보충제의 심혈관질환 예방에 대한 효능

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이 논문을 의학박사 학위논문으로 제출함

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2012년 12월

위 원 장 (인)

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위 원 (인)

위 원 (인)

학위논문 원문제공 서비스에 대한 동의서

본인의 학위논문에 대하여 서울대학교가 아래와 같이 학위논문 제공하는 것에 동의합니다.

1. 동의사항

① 본인의 논문을 보존이나 인터넷 등을 통한 온라인 서비스 목적으로 복제할 경우 저작물의 내용을 변경하지 않는 범위 내에서의 복제를 허용합니다.

② 본인의 논문을 디지털화하여 인터넷 등 정보통신망을 통한 논문의 일부 또는 전부의 복제.배포 및 전송 시 무료로 제공하는 것에 동의합니다.

2. 개인(저작자)의 의무

본 논문의 저작권을 타인에게 양도하거나 또는 출판을 허락하는 등 동의 내용을 변경하고자 할 때는 소속대학(원)에 공개의 유보 또는 해지를 즉시 통보하겠습니다.

3. 서울대학교의 의무

① 서울대학교는 본 논문을 외부에 제공할 경우 저작권 보호장치(DRM)를 사용하여야 합니다.

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논문 제목: Efficacy of Vitamin and Antioxidant Supplements in the Prevention of Cardiovascular Disease: A Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Introduction Randomized controlled trials have reported inconsistent findings regarding the efficacy of vitamin and antioxidant supplements in the prevention of cardiovascular diseases. The current study aimed to investigate the efficacy of vitamin and antioxidant supplements in the prevention of cardiovascular diseases by using a meta-analysis of randomized controlled trials.

Methods We searched PubMed, EMBASE, the Cochrane Library, Scopus, CINAHL, and ClinicalTrials.gov in June and additionally November 2012. Two of the authors independently reviewed and selected eligible randomized controlled trials, based on pre-determined selection criteria. A meta-analysis of randomized controlled trials was performed.

Results Out of 2,240 articles retrieved from databases and relevant bibliographies, a total of 50 RCTs, which involved 294,478 participants (156,663 intervention and 137,815 control groups), were included in the final analyses. In a fixed-effect meta-analysis of 50 RCTs, supplementation with vitamins and antioxidants did not reduce the risk of major cardiovascular events (relative risk [RR], 1.00; 95% confidence interval [CI], 0.98-1.02; I^2 = 41.6%). Overall, no beneficial effect of those supplements was observed 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, supply source for supplement, 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 marginally increased the risk of angina pectoris, while low-dose vitamin B6 supplementation slightly decreased the risk of major cardiovascular events. However, in the subgroup meta-analysis of high-quality RCTs within each category, those beneficial or harmful effects disappeared. Also, even though vitamin B6 supplementation decreased the risk of cardiovascular death in high-quality trials, and vitamin E supplementation decreased the risk of myocardial infarction, those beneficial effects were only shown in RCTs supplied with supplements by pharmaceutical industry.

Conclusion Our meta-analysis found that there is no evidence to support the use of vitamin and antioxidant supplements in the prevention of cardiovascular diseases.

Keywords: Vitamin supplements, antioxidant supplements, cardiovascular disease, Meta-analysis, Randomized Controlled Trials

Student number: 2011-30549

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LIST OF ABBREVIATIONS

CVD, cardiovascular disease; RCT, randomized controlled trial; n.a., not available; RDBPCT, randomized, double-blind, placebo-controlled trial; OLRCT, open-label, randomized, controlled trial; AMI, acute myocardial infarction; TIA, transient ischemic attack; CV, cardiovascular; MI, myocardial infarction; HRT, hormone replacement therapy; DM, diabetes mellitus; HDL, high-density lipoprotein; CHD, coronary heart disease; CAD, coronary artery disease; CRF, chronic renal failure; EPA, eicosapentanoic acid; DHA, docosahexaenoic acid, CARET, the Beta-Carotene and Retinol Efficacy Trial; CHAOS, the Cambridge Heart Antioxidant Study; LNIT, the Linxian Nutrition Intervention Trial; PHS, the Physicians' Health Study; SCP, the Skin Cancer Prevention Study; ATBC, the Alpha-tocopherol Beta-carotene Cancer Prevention Study; GISSI, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-Prevenzione trial; KOS, the Kuopio Osteoporosis Study; NSCP, the Nambour Skin Cancer Prevention trial; HOPE, the Heart Outcomes Prevention Evaluation Study; SPACE, Secondary Prevention with Antioxidants of Cardiovascular disease in Endstage renal disease; HATS, the HDL-Atherosclerosis Treatment Study; PPP, the Primary Prevention Project; HPS, the Heart Protection Study; SU.VI.MAX, the Supplemenatation en Vitamines et Mineraux Antioxydants; WHS, the Women's Health Study; ASFAST, the Atherosclerosis and Folic Acid Supplementation Trial; HOPE-2, The Heart Outcomes Prevention Evaluation 2 study; NORVIT, the Norwegian Vitamin Trial; NPC, the Nutritional Prevention of Cancer trial; WHI, the Women's Health Initiative; ICARE, the Israel Cardiovascular Events Reduction with Vitamin E trial; WAFACS, the Women's Antioxidant and Folic Acid Cardiovascular Study; WENBIT, the Western Norway B Vitamin Intervention Trial; BVAIT, the B-Vitamin

Atherosclerosis Intervention Trial; DIVINe, the Diabetic Intervention with Vitamins to Improve Nephropathy; SEARCH, the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine study; SU.FOL.OM3, the Supplémentation en Folates et Omega-3; VITATOPS, the Vitamins to Prevent Stroke trial; VISP, the Vitamin Intervention for Stroke Prevention randomized controlled trial; FAVORIT, the Folic Acid for Vascular Outcome Reduction in Transplantation trial

INTRODUCTION

Cardiovascular diseases (CVDs) are well known as 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 reduced the risk of CVD.[2] Also, 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 ischemic heart disease (IHD) and 19 % for ischemic stroke, respectively.[3] However, unlike fruit and vegetables, many randomized controlled trials (RCTs) have reported inconsistent findings regarding the efficacy of vitamin and antioxidant supplementation on CVDs.[4]

Regarding the conflicting evidence from RCTs, several meta-analyses have been reported. In 2003, a meta-analysis of 12 RCTs indicated that vitamin E supplements did not provide benefit in cardiovascular death or cerebrovascular accident.[5] Instead, it showed beta-carotene supplementation led to a small increase in all-cause mortality and cardiovascular death. Also, in 2006, Flores-Mateo et al reported the use of supplements containing selenium did not reduce the risk of coronary heart disease (CHD) in the meta-analysis of 6 RCTs.[6] On the other hand, recently, Lee et al found that folic acid supplementation with B vitamins among had potential small benefits in the prevention of stroke,[7] and Qin et al indicated that folic acid treatment decreased the risk of CVD by 15% in patients with end-stage renal disease (ESRD) or advanced chronic kidney disease (ACKD).[8] Even though several

meta-analyses of RCTs have been published regarding the efficacy of vitamins and antioxidant supplements on CVDs, those involved individual vitamin or antioxidant supplement, respectively, and there was no published comprehensive meta-analysis that reviewed this topic all at once in one report. More importantly, to the best of our knowledge, there was no meta-analysis that had performed subgroup analyses by important factors such as methodological quality or funding source, so far.

In the current study, we investigated the efficacy of vitamin and antioxidant supplements on CVDs via a comprehensive meta-analysis of RCTs by various factors such as by type of prevention (primary vs. secondary), type of vitamins and antioxidants, dose of supplement, type of cardiovascular outcomes, study design, methodological quality (high vs. low), duration of treatment (<5 years vs. ≥5 years), funding source (independent organization vs. pharmaceutical industry), supply source for supplement (pharmaceutical industry vs. not pharmaceutical industry), type of control (placebo vs. no placebo), number of participants in each trial (<10,000 vs. ≥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 2012 and additionally in November 2012, using common keywords related to vitamin or antioxidant supplements and CVDs. The keywords were as follows: "vitamin supplement," "antioxidant supplement," 'vitamin A supplement," "vitamin B6 supplement," "vitamin B12 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.' Also, we reviewed the bibliographies of relevant articles to locate additional publications. The language of publication was not restricted.

Selection criteria

We included randomized controlled trials that met all of the following criteria: reported the efficacy of vitamin or antioxidant supplements for the prevention of CVDs; followed participants for at least 6 months. If data were duplicated or shared in more than one study, the first published or more comprehensive study was included in the analysis.

Selection of relevant trials

Based on the pre-determined selection criteria, two of the authors (Myung SK, Ju W) independently selected all trials retrieved from the databases and bibliographies. Disagreements between evaluators were resolved by discussion or in consultation with a third author (Oh SW).

Assessment of methodological quality

The methodological quality of included trials were assessed based on the Jadad scale,[9] which is the most widely used assessment tool. Its score ranges from zero (very poor) to five-point (rigorous). The 5-point quality scale consists of points for randomization (described as randomized, 1 point; table of random numbers or computer-generated randomization, 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 lower vs. 5 because the mean score for the 47 trials assessed in the current study (the full texts for three trials were 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 CV death, fatal or non-fatal myocardial infarction (MI), angina, sudden cardiac death, fatal or non-fatal stroke, and transient ischemic

attack (TIA). Also, subgroup meta-analyses were performed by various factors as follows: type of prevention (primary vs. secondary: in this study, trials involving the healthy populations or patients with any specific disease except for CVD were classified as those on primary prevention, and trials involving patients with CVD were classified as those on secondary prevention.), type of supplement by methodological quality and dose (each supplement, vitamins only, antioxidants only, or antioxidants excluding vitamins), type of outcome (CV death, angina, fatal or nonfatal MI, stroke, or TIA), type of outcome in each supplement, type of study design (randomized, double-blind, placebo-controlled trial [RDBPCT] vs. open-label, randomized controlled trial [OLRCT]), methodological quality (high vs. low), duration of treatment (less than 5 years vs. 5 years or longer), funding source (pharmaceutical industry vs. independent organization), supply source for supplement (pharmaceutical industry vs. not pharmaceutical industry), type of control (placebo vs. no placebo), and number of participants (≥10,000 vs. <10,000), and supplements given singly or in combination with other vitamin or antioxidant supplements by quality.

Statistical analysis

We calculated the RRs with 95% CIs by using crude 2×2 tables on the basis of an intention-to-treat analysis, whenever possible, from the original publications. For the test of heterogeneity, we utilized 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 RRs with 95% CIs, both the fixed-effects and random-effects models were used. An I^2 value >50% was considered as substantial heterogeneity. When substantial heterogeneity was not observed, the pooled estimate calculated based on the fixed-effects model was reported. When substantial heterogeneity was observed, the pooled estimate calculated based on the random-effects model was reported.

Publication bias was assessed by using Begg's funnel plot and Egger's test. If publication bias exists, the Begg's funnel plot is asymmetric or the *P* value is less than ·05 by the Egger's test. We used Stata SE version 10·0 software package (StataCorp, College Station, TX) for all the statistical analyses.

RESULTS

Selection of trials

Figure 1 shows a flow diagram of how we identified relevant clinical trials. By searching six databases, i.e. PubMed, EMBASE, the Cochrane Library, Scopus, CINAHL, and hand-searching relevant bibliographies, a total of 2,240 articles were identified.

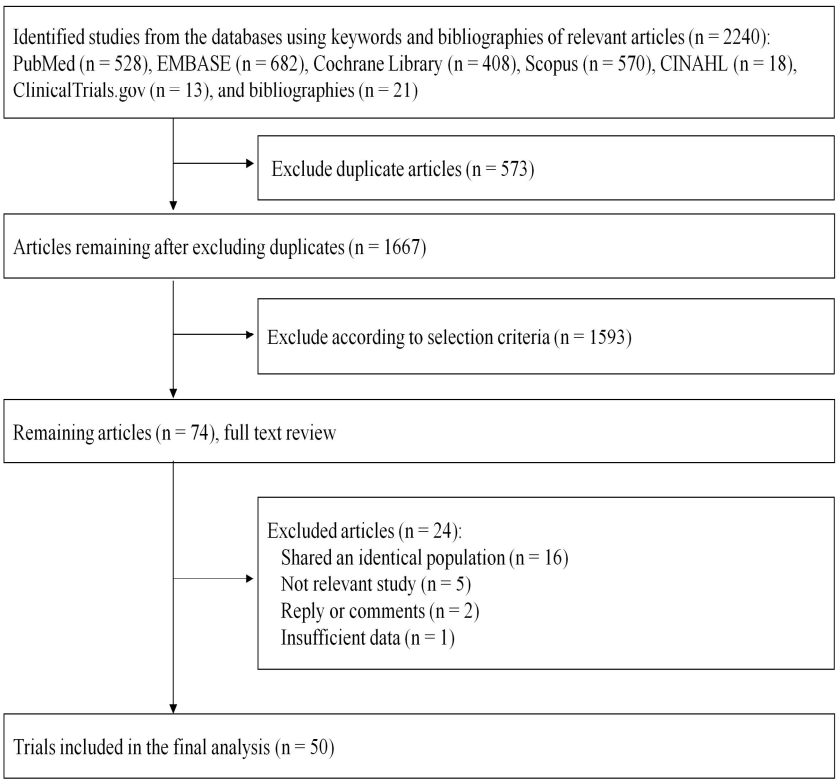


Figure 1. Flow Diagram for Identification of Relevant Clinical Trials.

After excluding 573 duplicated articles, two of authors independently reviewed and excluded additional 1,593 articles that did not satisfy the pre-determined selection criteria based on each article's title and abstract. We reviewed the full texts of the remaining 74 articles and excluded 24 articles because of the following reasons: an identical trial with the same population (n = 16); a trial not related to the subject of this study (n = 5); reply or comments (n = 2); and a trial reporting insufficient data (n = 1). A total of 50[11-60] trials were included in the final analysis.

General characteristics of trials

Table 1 (next page) shows the general characteristics of the 50 trials included in the final analysis. All the 50 trials involved a total of 294,478 participants with 156,663 intervention and 137,815 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. The countries where the studies were conducted were as follows: US (n = 12), UK (n = 4), Finland (n = 3), France (n = 3), Italy (n = 3), Canada (n = 2), Israel (n = 2), Australia (n = 2), China (n = 2), Germany (n = 2), Norway (n = 2), Sweden (n = 1), Switzerland (n = 1), the Netherlands (n = 1), US/Canada (n = 1), US/Canada/Scotland (n = 1), Germany/the Netherlands (n = 1), Canada/US (n = 1), 13 countries (n = 1), and 20 countries (n = 1). 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 esophageal dysplasia, male physicians, patients with nonmelanoma skin cancer, postmenopausal women, chronic hemodialysis patients, patients with end-stage renal disease, ambulatory elderly women with vitamin D insufficiency, patients with chronic

Table 1. Characteristics of Trials Included in the Final Meta-Analysis (n = 50)

	Source (Project Name)	Country Location	Design (Type of Prevention)	Participants (Average Age, y; Women, %)	Duration of Supplementation, y (Follow-up Period, y)	Intervention vs. Control	Main Outcome Measures Used in the Present Meta-analysis	No. of participants for major CV events /No. of participants	
								Supplement group	Conrol group
1	Korpela et al, 1989	n.a.	RDBPCT (Secondary)	81 patients with AMI	6 (6)	Selenium-rich yeast (122 μg/d) vs. placebo	Cardiac death and non-fatal reinfarct	1/40	6/41
2	Kuklinski et al, 1994	Germany	RDBPCT (Secondary)	61 patients with AMI	1(1)	Sodium selenite (100 μg/d) + coenzyme Q10 (100 mg/d) vs. placebo	Cardiac death	0/32	6/29
3	Steiner et al, 1995	U.S.	RDBPCT (Secondary)	100 patients with TIA (71; 58)	2 (2)	Vitamin E (400 IU/d) + aspirin (325 mg/d) vs. aspirin (325 mg/d)	Stroke, recurrent TIA, hemorrhagic events, and other CV events	9/52	13/48

	Source (Project Name)	Country Location	Design (Type of Prevention)	Participants (Average Age, y; Women, %)	Duration of Supplementation, y (Follow-up Period, y)	Intervention vs. Control	Main Outcome Measures Used in the Present Meta-analysis	No. of participants for major CV events /No. of participants	
								Supplement group	Conrol group
4	Omenn et al, 1996 (CARET)	U.S.	RDBPCT (Primary)	18,314 smokers (current and former) and workers exposed to asbestos (57;44)	4 (4)	Beta-carotene (30 mg/d) + vitamin A (25,000 IU/d) vs. placebo	CV death	226/9,420	151/8,894
5	Stephens et al, 1996 (CHAOS)	U.K.	RDBPCT (Secondary)	2,002 patients with angiographically proven coronary atherosclerosis (62; 16)	1.5 (1.5)	Vitamin E (400 or 800 IU/d) vs. placebo	Major CV events	41/1,035	62/967
6	Mark et al, 1996 (LNIT)	China	RDBPCT (Primary)	3,318 patients with esophageal dysplasia (54; 56)	6 (6)	Multiple vitamin/mineral supplements* daily vs. placebo	Cerebrovascular death	22/1,657	35/1,661

	Source (Project Name)	Country Location	Design (Type of Prevention)	Participants (Average Age, y; Women, %)	Duration of Supplementation, y (Follow-up Period, y)	Intervention vs. Control	Main Outcome Measures Used in the Present Meta-analysis	No. of participants for major CV events /No. of participants	
								Supplement group	Conrol group
7	Hennekens et al, 1996 (PHS)	U.S.	RDBPCT (Primary)	22,071 U.S. male physicians (40-84; 0)	12 (12)	Beta-carotene (50 mg/alternate day) vs. placebo	All important CV events	967/11,036	972/11,035
8	Greenberg et al, 1996 (SCP)	U.S.	RDBPCT (Primary)	1,720 patients with nonmelanoma skin cancer (basal cell or squamous cell skin cancer) (63; 31)	4.3 (8.2)	Beta-carotene (50 mg/d) vs. placebo	CV death	68/861	59/859
9	Rapola et al, 1997 (ATBC)	Finland	RDBPCT (Secondary)	1,862 men with a history of myocardial infarction (60; 0)	5.3 (5.3)	Beta-carotene (20 mg/d) or vitamin E (50 mg/d) vs. placebo	All coronary events	330/1,424	94/438

	Source (Project Name)	Country Location	Design (Type of Prevention)	Participants (Average Age, y; Women, %)	Duration of Supplementation, y (Follow-up Period, y)	Intervention vs. Control	Main Outcome Measures Used in the Present Meta-analysis	No. of participants for major CV events /No. of participants	
								Supplement group	Conrol group
10	Virtamo et al, 1998 (ATBC)	Finland	RDBPCT (Primary)	27,171 male smokers with no history of myocardial infarction (57; 0)	6.1 (6.1)	Beta-carotene (20 mg/d) or vitamin E (50 mg/d) vs. placebo	Primary major coronary events	1,577/20,422	534/6,849
11	Marchioli et al, 1999 (GISSI)	Italy	OLRCT (Secondary)	11,324 patients surviving recent (<3 months) myocardial infarction (59; 15)	3.5 (3.5)	Vitamin E (300 mg/d) vs. none	CV death, non-fatal MI, and non-fatal stroke	571/5,666	584/5,668

	Source (Project Name)	Country Location	Design (Type of Prevention)	Participants (Average Age, y; Women, %)	Duration of Supplementation, y (Follow-up Period, y)	Intervention vs. Control	Main Outcome Measures Used in the Present Meta-analysis	No. of participants for major CV events /No. of participants	
								Supplement group	Conrol group
12	Komulainen et al, 1999 (KOS)	Finland	RDBPCT (Primary)	323 postmenopausal women (53; 100)	5 (5)	Vitamin D_3 (300 and 100 IU/d during the fifth year) + calcium (93 mg/d) with or without HRT vs. calcium (93 mg/d)	MI	4/228	0/115
13	Green et al, 1999 (NSCP)	Australia	RDBPCT (Primary)	1,621 residents (49; 56)	4.5 (4.5)	Beta-carotene (30 mg/d) with or without daily application of a sun protection factor 15-plus sunscreen vs. placebo	CVD	6/801	12/820

	Source (Project Name)	Country Location	Design (Type of Prevention)	Participants (Average Age, y; Women, %)	Duration of Supplementation, y (Follow-up Period, y)	Intervention vs. Control	Main Outcome Measures Used in the Present Meta-analysis	No. of participants for major CV events /No. of participants	
								Supplement group	Conrol group
14	Yusuf et al, 2000 (HOPE)	Canada	RDBPCT (Secondary)	9,541 patients with a history CVD or DM at high risk for CV events (66; 27)	4.5 (4.5)	Vitamin E (400 IU/d) with or without ramipril vs. placebo	MI, stroke, and death from CV causes	772/4,761	739/4,780
15	Boaz et al, 2000 (SPACE)	Israel	RDBPCT (Secondary)	196 hemodialysis patients with pre-existing cardiovascular disease (65; 31)	1.4 (1.4)	Vitamin E (800 IU/d) vs. placebo	Total CVD endpoints including sudden death	18/97	34/99

	Source (Project Name)	Country Location	Design (Type of Prevention)	Participants (Average Age, y; Women, %)	Duration of Supplementation, y (Follow-up Period, y)	Intervention vs. Control	Main Outcome Measures Used in the Present Meta-analysis	No. of participants for major CV events /No. of participants	
								Supplement group	Conrol group
16	Brown et al, 2001 (HATS)	Canada and U.S.	RDBPCT (Secondary)	160 patients with coronary disease and low HDL cholesterol levels (53; 13)	3 (3)	Vitamin C (1000 mg/d) + vitamin E (800 IU/d) + natural beta-carotene (25 mg/d) + selenium (100 μg/d) vs. placebo	CV death or nonfatal infarct	3/42	7/38

	Source (Project Name)	Country Location	Design (Type of Prevention)	Participants (Average Age, y; Women, %)	Duration of Supplementation, y (Follow-up Period, y)	Intervention vs. Control	Main Outcome Measures Used in the Present Meta-analysis	No. of participants for major CV events /No. of participants	
								Supplement group	Conrol group
17	Roncaglioni et al, 2001 (PPP)	Italy	OLRCT (Secondary)	4,495 patients with hypertension, hypercholesterolemia, DM, obesity, family history of premature myocardial infarction, or elderly individuals (64; 58)	3.6 (3.6)	Vitamin E (300 mg/d) with or without aspirin (100 mg/d) vs. control	Total CV events or CVD	158/2,231	170/2,264

	Source (Project Name)	Country Location	Design (Type of Prevention)	Participants (Average Age, y; Women, %)	Duration of Supplementation, y (Follow-up Period, y)	Intervention vs. Control	Main Outcome Measures Used in the Present Meta-analysis	No. of participants for major CV events /No. of participants	
								Supplement group	Conrol group
18	You et al, 2001	China	RDBPCT (Primary)	3,411 residents (35-69; n.a.)	3.3 (3.3)	Vitamin C (500 mg/d) + vitamin E (200 IU/d) + beta-carotene (15 mg/d) + selenium (75 μg/d) vs. placebo	CV death	9/1,706	12/1,705
19	Baker et al, 2002	n.a.	RDBPCT (Secondary)	1,882 patients with CHD (n.a.)	1.7 (n.a.)	Folic acid (5 mg/d) vs. placebo	CHD	23/942	12/940
20	Collins et al, 2002 (HPS)	U.K.	RDBPCT (Secondary)	20,536 patients with coronary disease, other occlusive disease, or DM (40-80; 25)	5 (5)	Vitamin C (250 mg/d) + vitamin E (600 mg/d) + beta-carotene (20 mg/d) vs. placebo	Any major vascular event	2306/10,269	2312/10,267

	Source (Project Name)	Country Location	Design (Type of Prevention)	Participants (Average Age, y; Women, %)	Duration of Supplementation, y (Follow-up Period, y)	Intervention vs. Control	Main Outcome Measures Used in the Present Meta-analysis	No. of participants for major CV events /No. of participants	
								Supplement group	Conrol group
21	Schnyder et al, 2002 (SHS)	Switzerland	RDBPCT (Secondary)	553 patients with established coronary atherosclerosis after percutaneous coronary intervention (63; 20)	0.5 (0.9)	Folic acid (1 mg/d) + vitamin B6 (10 mg/d) + vitamin B_{12} (400 μg/d) vs. placebo	Nonfatal MI and cardiac death	10/272	18/281
22	Waters et al, 2002 (WAVE)	U.S. and Canada	RDBPCT (Secondary)	423 postmenopausal women with coronary stenosis (65; 100)	2.8 (2.8)	Vitamin C (500 mg twice/d) + vitamin E (400 IU twice/d) vs. placebo	CV death or nonfatal MI	14/212	8/211
23	Liem et al, 2003 (Goes)	The Netherlands	OLRCT (Secondary)	593 patients with stable CAD (65; 22)	2 (2)	Folic acid (0.5 mg/d) vs. control	CV death and or any CV events	32/300	28/293

	Source (Project Name)	Country Location	Design (Type of Prevention)	Participants (Average Age, y; Women, %)	Duration of Supplementation, y (Follow-up Period, y)	Intervention vs. Control	Main Outcome Measures Used in the Present Meta-analysis	No. of participants for major CV events /No. of participants	
								Supplement group	Conrol group
24	Righetti et al, 2003	Italy	OLRCT (Primary)	81 chronic hemodialysis patients (64; 44)	1 (1)	Folic acid (5 mg or 15 mg/d) vs. control	New CV events	13/51	11/30
25	Trivedi et al, 2003	U.K.	RDBPCT (Primary)	2,686 men and women living in the general community (75; 24)	5 (5)	Vitamin D3 (100,000 IU/4 m) vs. placebo	CVD	477/1,345	503/1,341
26	Lange et al, 2004	Germany and the Netherlands	RDBPCT (Secondary)	636 patients who had undergone successful coronary stenting (61; 73)	0.5 (0.5)	Folic acid (1.2 mg/d) + vitamin B6 (48 mg/d) + vitamin B12 (60 μg/d) vs. placebo	Major adverse coronary events	53/316	35/320

	Source (Project Name)	Country Location	Design (Type of Prevention)	Participants (Average Age, y; Women, %)	Duration of Supplementation, y (Follow-up Period, y)	Intervention vs. Control	Main Outcome Measures Used in the Present Meta-analysis	No. of participants for major CV events /No. of participants	
								Supplement group	Conrol group
27	Hercberg et al, 2004 (SU.VI. MAX)	France	RDBPCT (Primary)	12,741 adults (35-60; 61)	7.5 (7.5)	Vitamin C (120 mg/d) + vitamin E (30 mg/d) + beta-carotene (6 mg/d) + selenium (100 μg/d) + zinc (20 mg/d) vs. placebo	Ischemic CVD	134/6,364	137/6,377
28	Toole et al, 2004 (VISP)	U.S., Canada, and Scotland	RDBPCT (Secondary)	3,680 patients with nondisabling ischemic stroke (66; 38)	2 (2)	High dose: folic acid (2.5 mg/d) + vitamin B6 (25 mg/d) + vitamin B_{12} (0.4 mg/d) vs. low dose: folic acid (20 μg/d) + vitamin B6 (200 μg/d) + vitamin B_{12} (6 μg/d)	Ischemic stroke or CHD	249/1,827	257/1,853

	Source (Project Name)	Country Location	Design (Type of Prevention)	Participants (Average Age, y; Women, %)	Duration of Supplementation, y (Follow-up Period, y)	Intervention vs. Control	Main Outcome Measures Used in the Present Meta-analysis	No. of participants for major CV events /No. of participants	
								Supplement group	Conrol group
29	Wrone et al, 2004	U.S.	RDBPCT (Primary)	510 patients with ESRD (60; 50)	2 (2)	Folic acid (5 mg/d) or folic acid (15 mg/d) vs. folic acid (1 mg/d) with multivitamins** in all arms	MI, cerebrovascular accident, and TIA	34/342	13/168
30	Brazier et al, 2005	France	RDBPCT (Primary)	192 ambulatory elderly women with vitamin D insufficiency (75; 100)	1 (1)	Vitamin D3 (400 IU twice/d) + calcium carbonate (500 mg twice/d) vs. placebo	CV events	6/95	5/96
31	Lee et al, 2005 (WHS)	U.S.	RDBPCT (Primary)	39,876 healthy women (55; 100)	10.1 (10.1)	Vitamin E (600 IU/alternate day) vs. placebo	Major CV events	482/19,937	517/19,939

	Source (Project Name)	Country Location	Design (Type of Prevention)	Participants (Average Age, y; Women, %)	Duration of Supplementation, y (Follow-up Period, y)	Intervention vs. Control	Main Outcome Measures Used in the Present Meta-analysis	No. of participants for major CV events /No. of participants	
								Supplement group	Conrol group
32	Zoungas et al, 2006 (ASFAST)	Australia and New Zealand	RDBPCT (Primary)	315 patients with CRF (57; 32)	3.6 (3.6)	Folic acid (15 mg/d) vs. placebo	All CV events or death from CV cause	77/156	86/159
33	Lonn et al, 2006 (HOPE-2)	13 countries including Canada, U.S., Brazil, western Europe, Slovakia, etc.	RDBPCT (Secondary)	5,522 patients who had vascular disease or diabetes (69; 28)	5 (5)	Folic acid (2.5 mg/d) + vitamin B_6 (50 mg/d) + vitamin B_{12} (1 mg/d) vs. placebo	Composite of death from CV causes, myocardial infarction, or stroke	519/2,,758	547/2764

	Source (Project Name)	Country Location	Design (Type of Prevention)	Participants (Average Age, y; Women, %)	Duration of Supplementation, y (Follow-up Period, y)	Intervention vs. Control	Main Outcome Measures Used in the Present Meta-analysis	No. of participants for major CV events /No. of participants	
								Supplement group	Conrol group
34	Bonaa et al, 2006 (NORVIT)	Norway	RDBPCT (Secondary)	3,749 patients who had had an acute MI (63; 26)	3 (3)	Folic acid (0.8 mg/d) + vitamin B_6 (40 mg/d) + vitamin B_{12} (0.4 mg/d) / folic acid (0.8 mg/d) + vitamin B_{12} (0.4 mg/d)/ vitamin B_6 (40 mg/d) vs. placebo	Nonfatal or fatal MI (including sudden death attributed to coronary heart disease) and nonfatal or fatal stroke	544/2,806	172/943
35	Stranges et al, 2006 (NPC)	U.S.	RDBPCT (Primary)	1,004 nonmelanoma skin cancer patients without CVD	7.6 (7.6)	Selenium (200 μg/d) vs. placebo	All CVD	103/504	96/500

	Source (Project Name)	Country Location	Design (Type of Prevention)	Participants (Average Age, y; Women, %)	Duration of Supplementation, y (Follow-up Period, y)	Intervention vs. Control	Main Outcome Measures Used in the Present Meta-analysis	No. of participants for major CV events /No. of participants	
								Supplement group	Conrol group
36	Jamison et al, 2007 (HOST)	U.S.	RDBPCT (Primary)	2,056 patients with advanced chronic kidney disease or ESRD (66; 2)	3.2 (3.2)	Folic acid (40 mg/d) + vitamin B_6 (100 mg/d) + vitamin B_{12} (2 mg/d) + vs. placebo	MI and stroke	166/1,032	191/1,024
37	Hsia et al, 2007 (WHI)	U.S.	RDBPCT (Primary)	36,282 postmenopausal women (62; 100)	7 (7)	Vitamin D3 (200 IU twice/d) + calcium carbonate (500 mg twice/d) vs. placebo	CV events	2,281/18,176	2,172/18,106
38	Berggren et al, 2008	Sweden	OLRCT (Primary)	199 older people with femoral neck fractures (82; 74)	1 (1)	Vitamin D (800 IU/d) + calcium (1000 mg/d) vs. control	CVD	47/102	40/97

	Source (Project Name)	Country Location	Design (Type of Prevention)	Participants (Average Age, y; Women, %)	Duration of Supplementation, y (Follow-up Period, y)	Intervention vs. Control	Main Outcome Measures Used in the Present Meta-analysis	No. of participants for major CV events /No. of participants	
								Supplement group	Conrol group
39	Millman et al, 2008 (ICARE)	Israel	RDBPCT (Primary)	1,434 patients with DM (69; 52)	1.5 (1.5)	Vitamin E (400 IU/d) vs. placebo	MI, stroke, and CV death	16/102	40/97
40	Prince et al, 2008	Australia	RDBPCT (Primary)	302 elderly women with a low serum 25-hydroxy vitamin D concentration (77; 100)	1 (1)	Vitamin D2 (1,000 IU/d) + calcium citrate (1,000 mg/d) vs. placebo + calcium citrate (1,000 mg/d)	Ischemic heart disease and stroke	5/151	6/151

	Source (Project Name)	Country Location	Design (Type of Prevention)	Participants (Average Age, y; Women, %)	Duration of Supplementation, y (Follow-up Period, y)	Intervention vs. Control	Main Outcome Measures Used in the Present Meta-analysis	No. of participants for major CV events /No. of participants	
								Supplement group	Conrol group
41	Albert et al, 2008 (WAFACS)	U.S.	RDBPCT (Secondary)	5,442 women who were US health professionals with either a history of CVD or 3 or more coronary risk factors (63; 100)	7.3 (7.3)	Folic acid (2.5 mg/d) + vitamin B_6 (50 mg/d) + vitamin B_{12} (1 mg/d) vs. placebo	Combined major CVD	406/2,721	390/2,721

	Source (Project Name)	Country Location	Design (Type of Prevention)	Participants (Average Age, y; Women, %)	Duration of Supplementation, y (Follow-up Period, y)	Intervention vs. Control	Main Outcome Measures Used in the Present Meta-analysis	No. of participants for major CV events /No. of participants	
								Supplement group	Conrol group
42	Ebbing et al, 2008 (WENBIT)	Norway	RDBPCT (Secondary)	3,096 patients with coronary artery disease or aortic valve stenosis (62; 79)	3.2 (3.2)	Folic acid (0.8 mg/d) + vitamin B_6 (40 mg/d) + vitamin B_{12} (0.4 mg/d)/ folic acid (0.8 mg/d) + vitamin B_{12} (0.4 mg/d)/ vitamin B_6 (40 mg/d) vs. placebo	AMI, unstable angina, and stroke	313/2,311	104/779
43	Hodis et al, 2009 (BVAIT)	U.S.	RDBPCT (Primary)	506 people with a high fasting plasma total homocysteine level (61; 39)	3.1 (3.1)	Folic acid (5 mg/d) + vitamin B_6 (50 mg/d) + vitamin B_{12} (0.4 mg/d) vs. placebo	CV events	9/254	11/252

	Source (Project Name)	Country Location	Design (Type of Prevention)	Participants (Average Age, y; Women, %)	Duration of Supplementation, y (Follow-up Period, y)	Intervention vs. Control	Main Outcome Measures Used in the Present Meta-analysis	No. of participants for major CV events /No. of participants	
								Supplement group	Conrol group
44	House et al, 2010 (DIVINe)	Canada	RDBPCT (Primary)	238 patients with type 1 or 2 diabetes and a clinical diagnosis of diabetic nephropathy (60; 11)	2.7 (2.7)	Folic acid (2.5 mg/d) + vitamin B_6 (25 mg/d) + vitamin B_{12} (1 mg/d) vs. placebo	MI and stroke	14/119	5/119

	Source (Project Name)	Country Location	Design (Type of Prevention)	Participants (Average Age, y; Women, %)	Duration of Supplementation, y (Follow-up Period, y)	Intervention vs. Control	Main Outcome Measures Used in the Present Meta-analysis	No. of participants for major CV events /No. of participants	
								Supplement group	Conrol group
45	Heinz et al, 2010	Germany	RDBPCT (Primary)	650 patients with ESRD (61; 42)	2 (2)	Folic acid (5 mg three times/w) + vitamin B_6 (20 mg three times/w) + vitamin B_{12} (50 μg three times/w) vs. folic acid (0.2 mg three times/w) + vitamin B_6 (1 mg three times/w) + vitamin B_{12} (4 μg three times/w)	CV events	83/327	98/323
46	Armitage et al, 2010 (SEARCH)	U.K.	RDBPCT (Secondary)	12,064 survivors of myocardial infarction (64; 17)	6.7 (6.7)	Folic acid (2 mg/d) + vitamin B_{12} (1 mg/d) vs. placebo	Major coronary events and stroke	1,537/6,033	1,493/6,031

	Source (Project Name)	Country Location	Design (Type of Prevention)	Participants (Average Age, y; Women, %)	Duration of Supplementation, y (Follow-up Period, y)	Intervention vs. Control	Main Outcome Measures Used in the Present Meta-analysis	No. of participants for major CV events /No. of participants	
								Supplement group	Conrol group
47	Galan et al, 2010 (SU.FOL. OM3)	France	RDBPCT (Secondary)	2,501 patients with a history of MI, unstable angina, or ischaemic stroke (61; 20)	4.7 (4.7)	Folic acid (560 µg/d) + vitamin B_6 (3 mg/d) + vitamin B_{12} (20 µg/d) ± omega-3 fatty acids (EPA and DHA at a ratio of 2:1) vs. placebo	Major CV events (non-fatal MI, stroke, or CV death)	75/1,242	82/1,259

	Source (Project Name)	Country Location	Design (Type of Prevention)	Participants (Average Age, y; Women, %)	Duration of Supplementation, y (Follow-up Period, y)	Intervention vs. Control	Main Outcome Measures Used in the Present Meta-analysis	No. of participants for major CV events /No. of participants	
								Supplement group	Conrol group
48	Graeme et al, 2010 (VITATOPS)	20 countries from four continents including Australia, U.K., New Zealand, etc.)	RDBPCT (Secondary)	8,164 patients with recent TIA or stroke (63; 36)	3.4 (3.4)	Folic acid (2 mg/d) + vitamin B_6 (25 mg/d) + vitamin B_{12} (0.5 mg/d) vs. placebo	Stroke, MI, or vascular death	616/4,089	678/4,075

	Source (Project Name)	Country Location	Design (Type of Prevention)	Participants (Average Age, y; Women, %)	Duration of Supplementation, y (Follow-up Period, y)	Intervention vs. Control	Main Outcome Measures Used in the Present Meta-analysis	No. of participants for major CV events /No. of participants	
								Supplement group	Conrol group
49	Bostom et al, 2011 (FAVORIT)	U.S.	RDBPCT (Primary)	4,110 stable kidney transplant recipients (52; 37)	4 (4)	Folic acid (5.0 mg/d) + vitamin B_6 (50 mg/d) + vitamin B_{12} (1 mg/d) vs. vitamin B_6 (1.4 mg/d) + vitamin B_{12} (2.0 μg/d) with multivitamins in both arms	Any primary CVD outcome	269/2,056	278/2,054
50	Sesso et al, 2012 (PHS2)	U.S.	RDBPCT (Primary)	14,641 U.S. male physicians (64; 0)	11.2 (11.2)	Multivitamin vs. placebo	Major CV events	876/7,317	856/7,324

* Vitamins A/B_1/B_2/ B_6/ B_{12} /C/D/E, folic acid, beta-carotene, biotin, pantothenic acid, calcium, phosphorus, iodine, iron, magnesium, copper, manganese, potassium, chloride, molybdenum, selenium, and zinc.
** Vitamins B_1/B_3/B_6/ B_{12} /C, pantothenic acid, and biotin.
n.a., not available; RDBPCT, randomized, double-blind, placebo-controlled trial; OLRCT, open-label, randomized, controlled trial; AMI, acute myocardial

infarction; TIA, transient ischemic attack; CV, cardiovascular; MI, myocardial infarction; HRT, hormone replacement therapy; DM, diabetes mellitus; HDL, high-density lipoprotein; CHD, coronary heart disease; CAD, coronary artery disease; CRF, chronic renal failure; EPA, eicosapentanoic acid; DHA, docosahexaenoic acid

CARET, the Beta-Carotene and Retinol Efficacy Trial; CHAOS, the Cambridge Heart Antioxidant Study; LNIT, the Linxian Nutrition Intervention Trial; PHS, the Physicians' Health Study; SCP, the Skin Cancer Prevention Study; ATBC, the Alpha-tocopherol Beta-carotene Cancer Prevention Study; GISSI, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-Prevenzione trial; KOS, the Kuopio Osteoporosis Study; NSCP, the Nambour Skin Cancer Prevention trial; HOPE, the Heart Outcomes Prevention Evaluation Study; SPACE, Secondary Prevention with Antioxidants of Cardiovascular disease in Endstage renal disease; HATS, the HDL-Atherosclerosis Treatment Study; PPP, the Primary Prevention Project; HPS, the Heart Protection Study; SU.VI.MAX, the Supplemenatation en Vitamines et Mineraux Antioxydants; WHS, the Women's Health Study; ASFAST, the Atherosclerosis and Folic Acid Supplementation Trial; HOPE-2, The Heart Outcomes Prevention Evaluation 2 study; NORVIT, the Norwegian Vitamin Trial; NPC, the Nutritional Prevention of Cancer trial; WHI, the Women's Health Initiative; ICARE, the Israel Cardiovascular Events Reduction with Vitamin E trial; WAFACS, the Women's Antioxidant and Folic Acid Cardiovascular Study; WENBIT, the Western Norway B Vitamin Intervention Trial; BVAIT, the B-Vitamin Atherosclerosis Intervention Trial; DIVINe, the Diabetic Intervention with Vitamins to Improve Nephropathy; SEARCH, the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine study; SU.FOL.OM3, the Supplémentation en Folates et Omega-3; VITATOPS, the Vitamins to Prevent Stroke trial; VISP, the Vitamin Intervention for Stroke Prevention randomized controlled trial; FAVORIT, the Folic Acid for Vascular Outcome Reduction in Transplantation trial.

renal failure, older people with femoral neck fractures, patients with DM, elderly women with a low serum 25-hydroxy vitamin D concentration, health professionals, people with a high fasting plasma total homocysteine, or kidney transplant recipients), and 20 were secondary prevention trials (patients with CVD, CHD, AMI, unstable angina, TIA, stroke, angiographically proven coronary atherosclerosis, vascular disease, or aortic valve stenosis).

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

The dosage regimens used in each trial were as follows: vitamin A (10,000 or 25,000 IU daily), vitamin B6 (3, 6, 10, 12.5, 25, 40, 48, 50, or 100 mg daily; 20 mg three times weekly), vitamin B12 (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 1,000 mg daily), vitamin D (800 or 1,000 IU daily; 200 IU twice daily; 400 IU twice daily; 300 IU daily and 100 IU daily; 100,000 IU every 4 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), beta-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 antioxidant supplements only. The additional 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; with or without application of a sun protection factor 15-plus sunscreen; with or without 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 (1,000 mg daily); calcium citrate (1,000 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 nonfatal AMI, unstable angina, CHD, IHD, major coronary events, CV death, sudden death, TIA, stroke, and CVD.

Out of 47 trials reporting its funding source in each article, five trials were funded by pharmaceutical companies, while 42 trials were funded by mainly public or governmental organizations or independent scientific foundations. Also, in twenty-nine trials, vitamin or antioxidant supplements were provided at no cost from pharmaceutical companies, while 18 trials paid for them or did not mention whether pharmaceutical companies provided them without charge.

Efficacy of vitamin or antioxidant supplements on cardiovascular disease in all 50trials

In the fixed-effects meta-analysis of all 50 trials, the use of vitamin or antioxidant supplements did not reduce the risk of major cardiovascular events (RR, 1.00; 95% CI, 0.98-1.02; $I^2 = 41.5\%$) **(Figure 2)**.

Figure 2 shows the forest plot sorted in ascending order by the number of participants. Overall, the effect sizes of the smaller RCTs tend to be less than 1.0, while the effect sizes of the larger ones tend to be null.

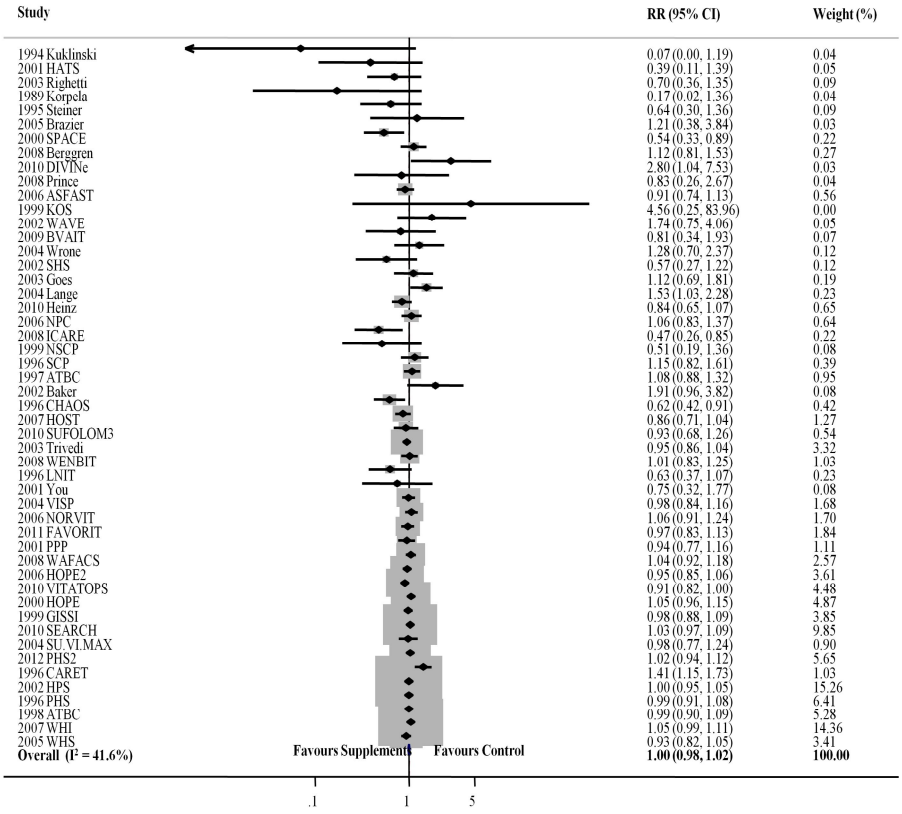
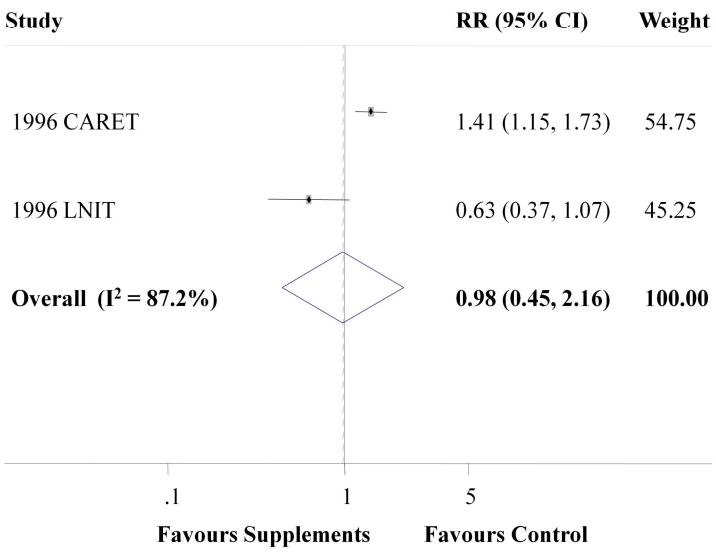
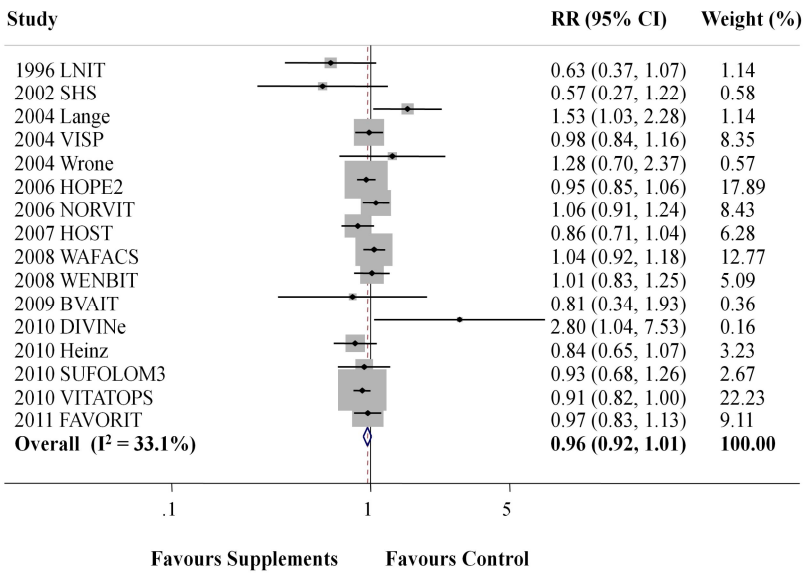


Figure 2. Efficacy of vitamin and antioxidant supplements in the prevention of the major cardiovascular events in a meta-analysis of randomized controlled trials sorted in ascending order by the number of participants (n = 50). RR, Relative risk; CI, Confidence interval.

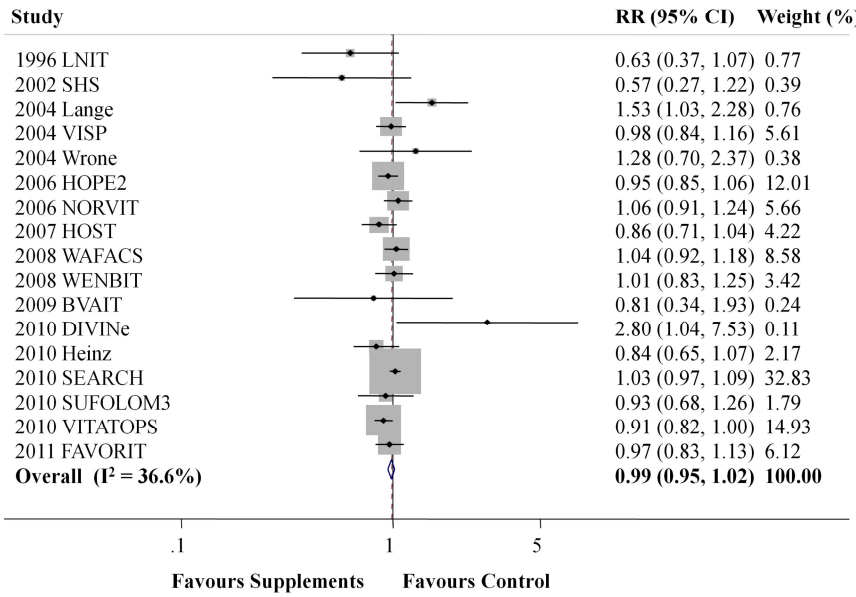
Vitamin A (n = 2: RE)



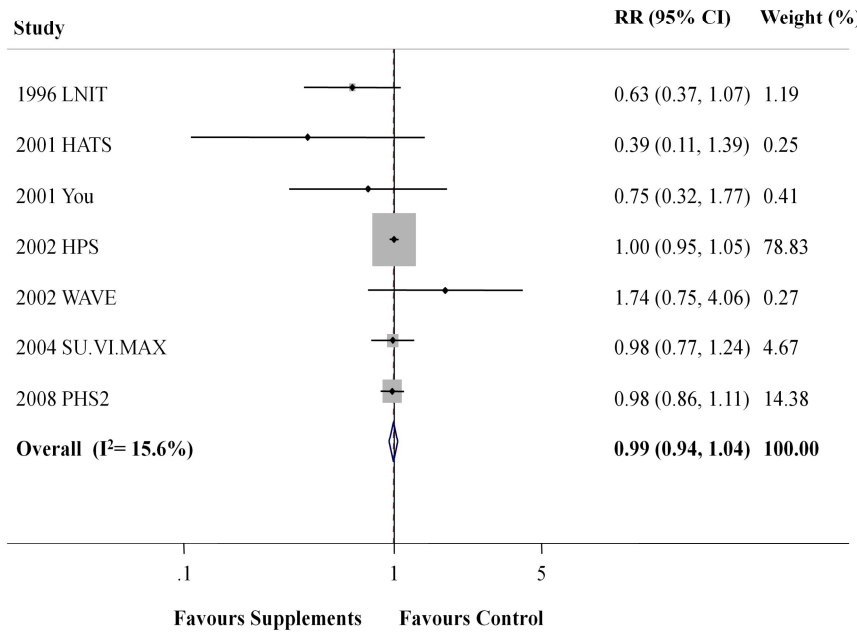
Vitamin B6 (n = 16: FE)



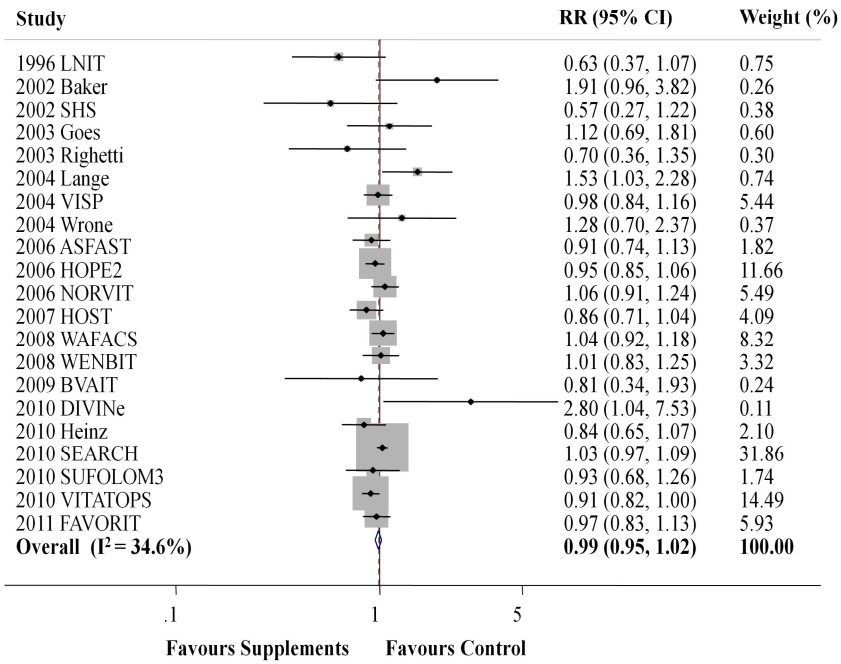
Vitamin B12 (n = 17: FE)



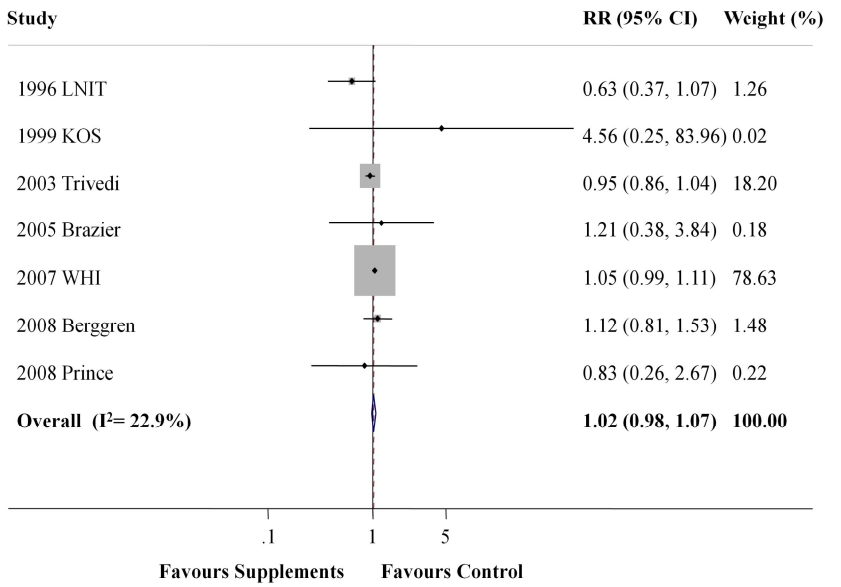
Vitamin C (n = 7: FE)



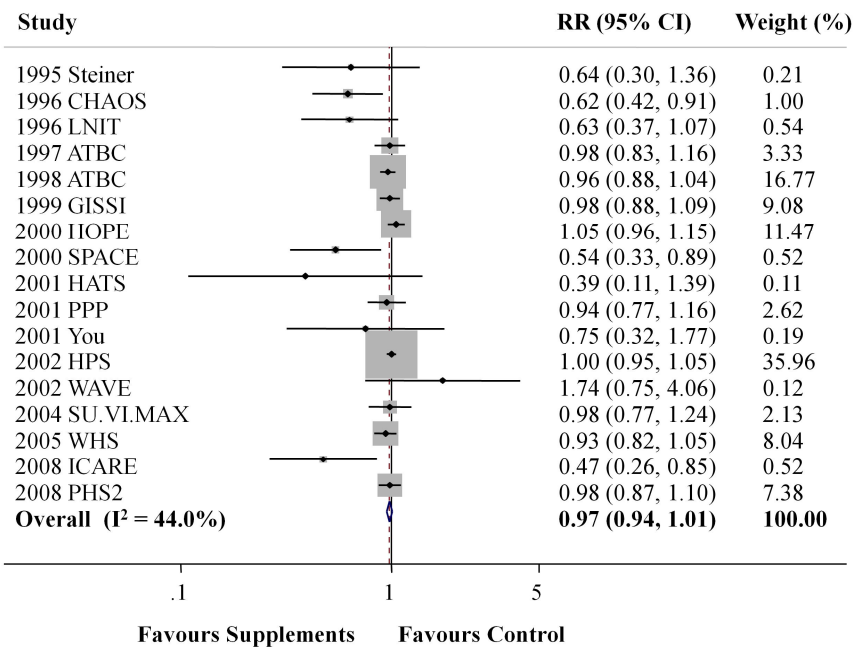
Folic acid (n = 21: FE)



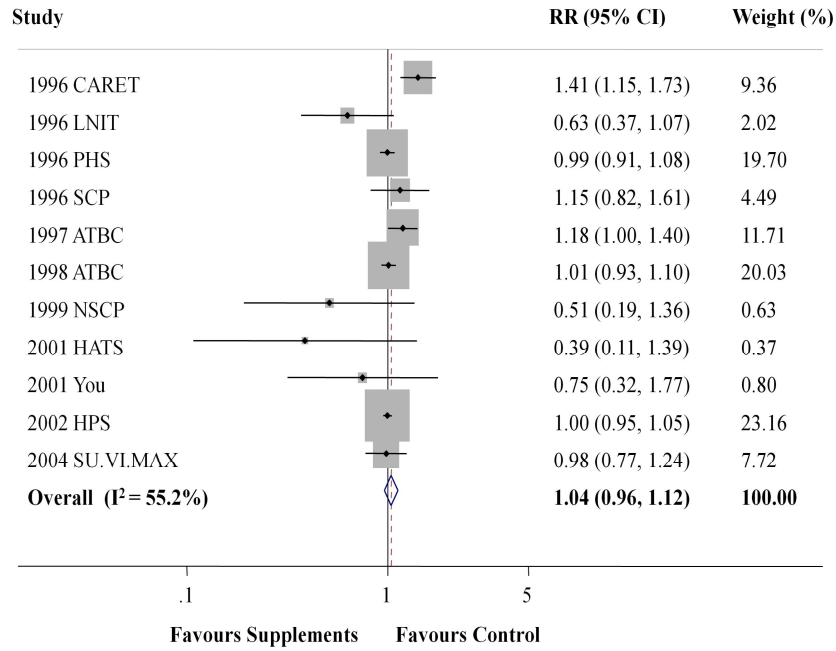
Vitamin D (n = 7: FE)



Vitamin E (n = 17: FE)



Beta-carotene (n = 17: RE)



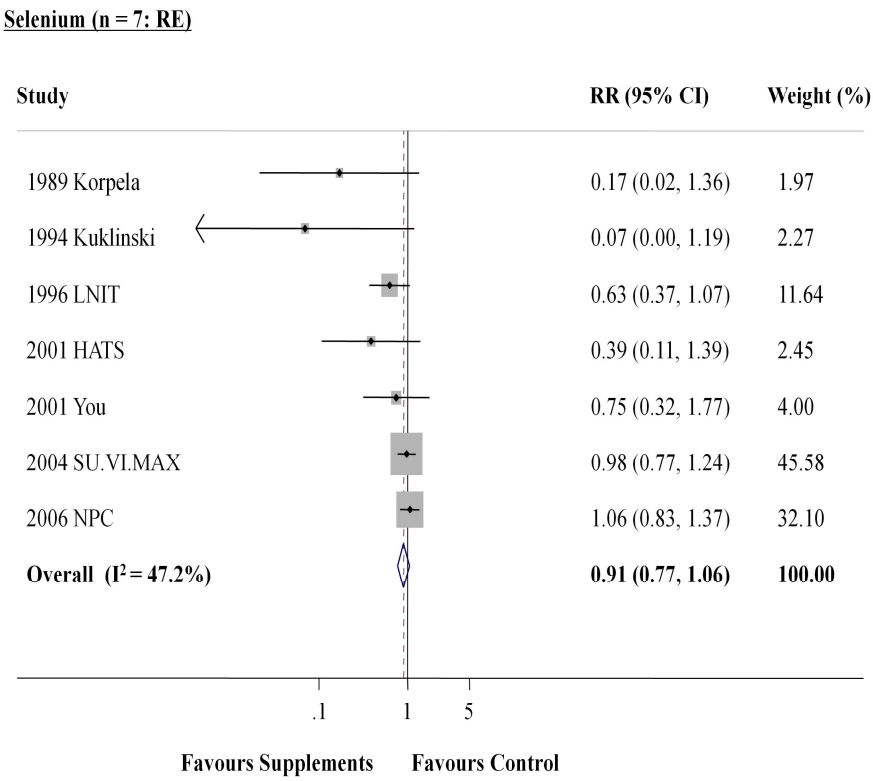
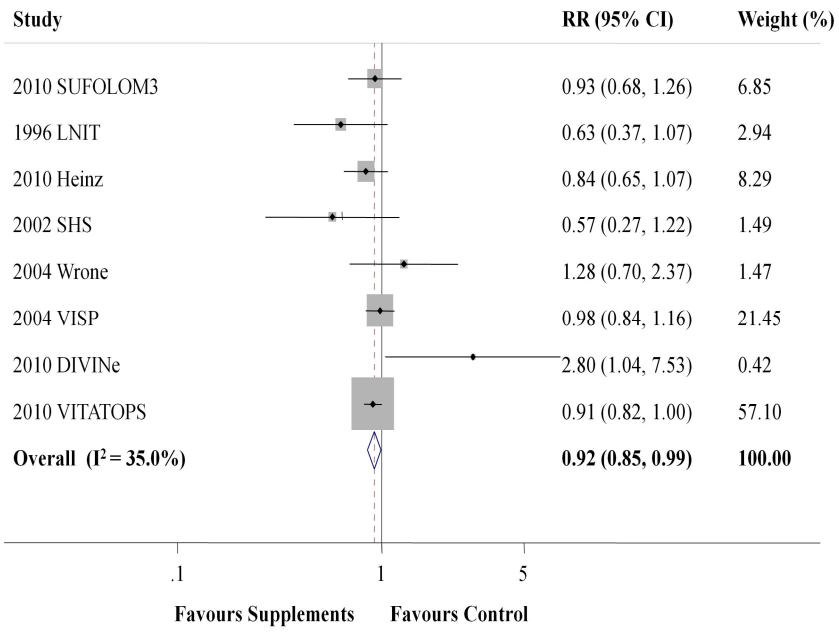
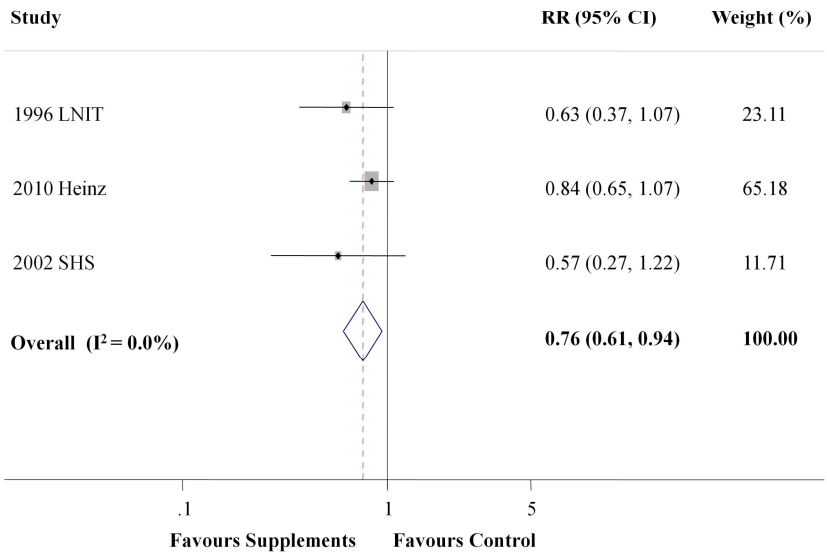


Figure 3. Efficacy of vitamin and antioxidant supplements in the prevention of the major cardiovascular events in subgroup meta-analysis of randomized controlled trials by type of supplements. RR, Relative risk; CI, Confidence interval; FE, Fixed-effect model; RE, Random-effect model. For the subgroup meta-analysis of vitamin C and vitamin E, the data of the PHS2 article[83] published in 2008 were used because data are not available in the 2012 PHS article.

All (n = 8)



Low-quality (n = 3)



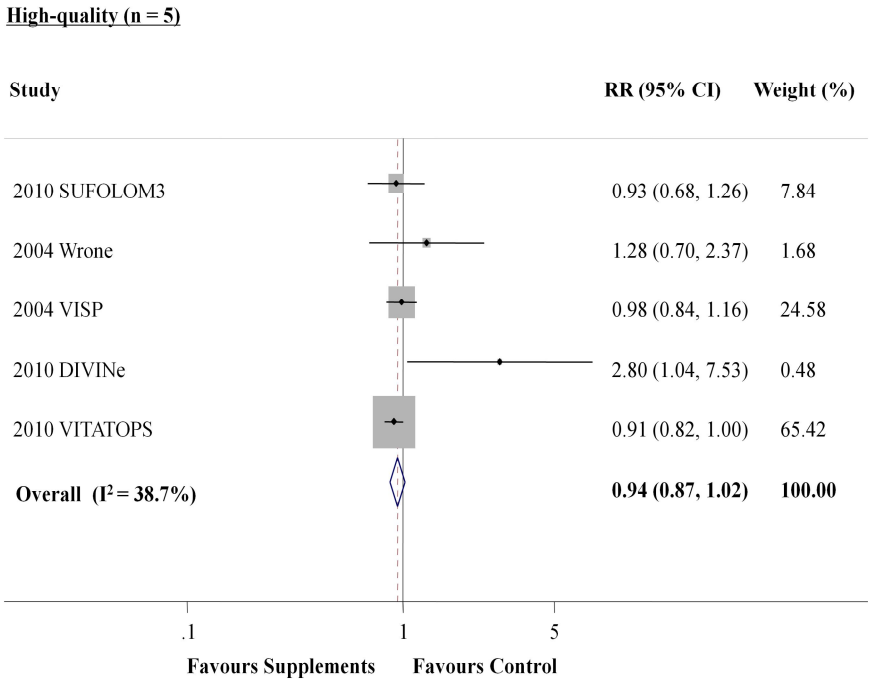
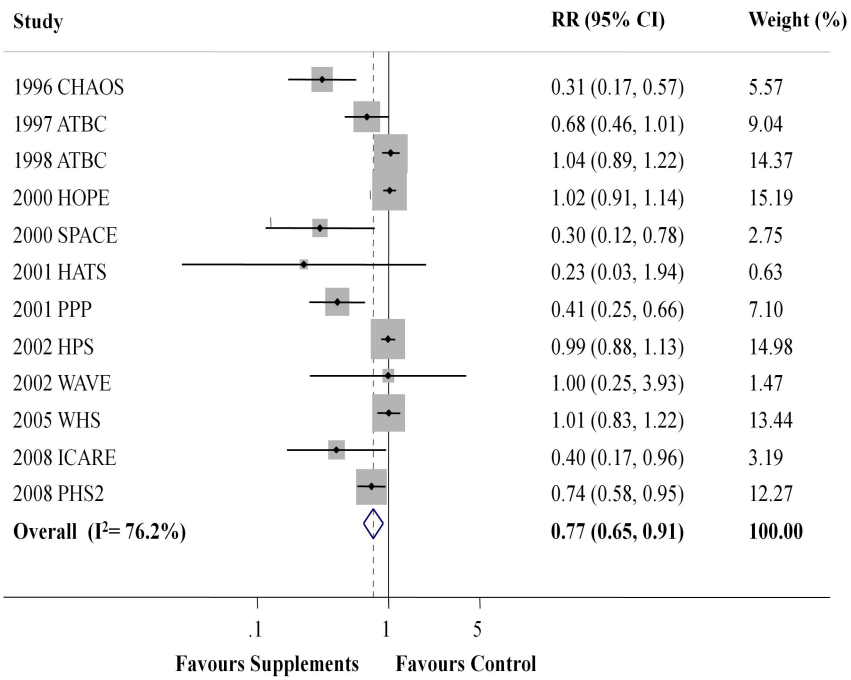
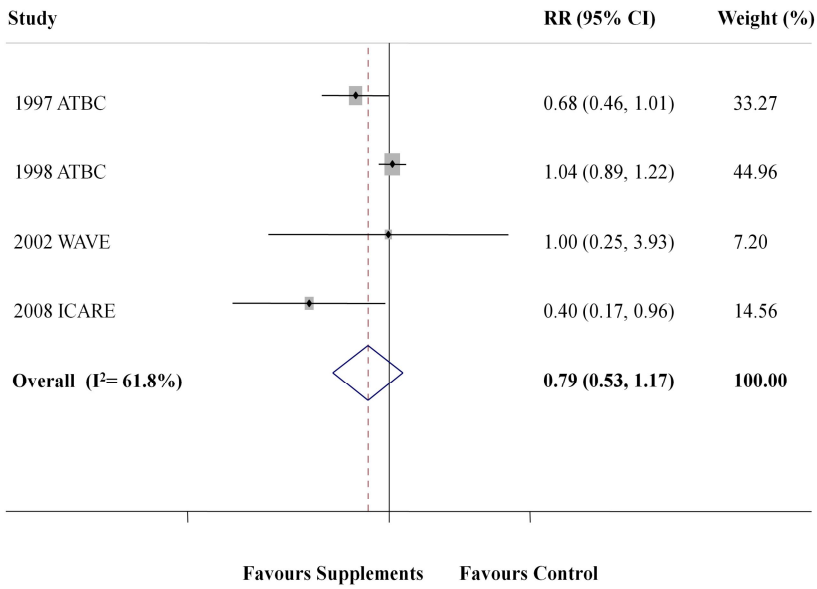


Figure 4. Efficacy of low-dose vitamin B6 supplements in the prevention of the major cardiovascular events in subgroup meta-analysis of randomized controlled trials by study quality. RR, Relative risk; CI, Confidence interval; FE, Fixed-effect model; RE, Random-effect model.

All (n = 12)



Trials not supplied (n = 4)



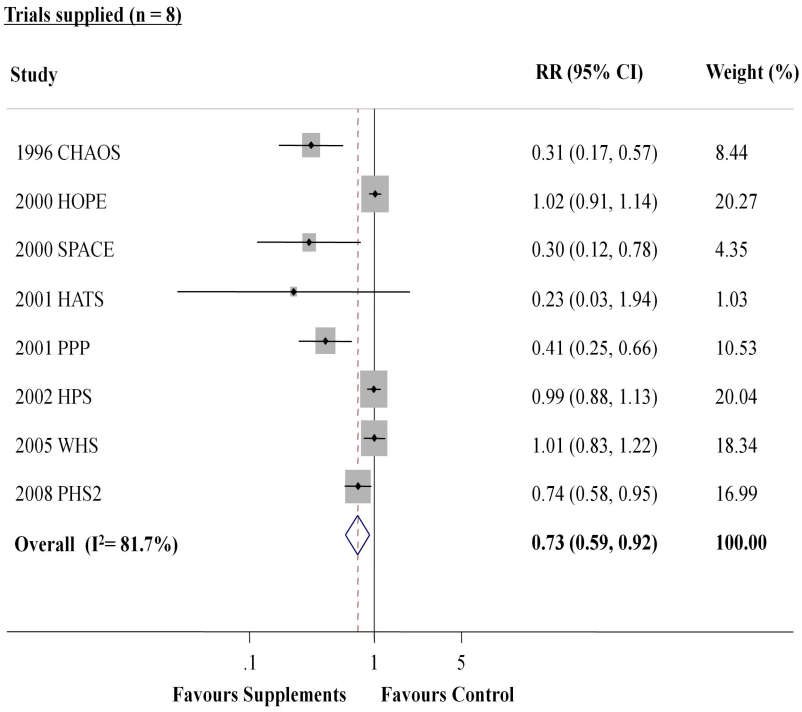


Figure 5. Efficacy of vitamin E supplements in the prevention of myocardial infarction in subgroup meta-analysis of randomized controlled trials by supply with supplements from pharmaceutical industry. RR, Relative risk; CI, Confidence interval; FE, Fixed-effect model; RE, Random-effect model.

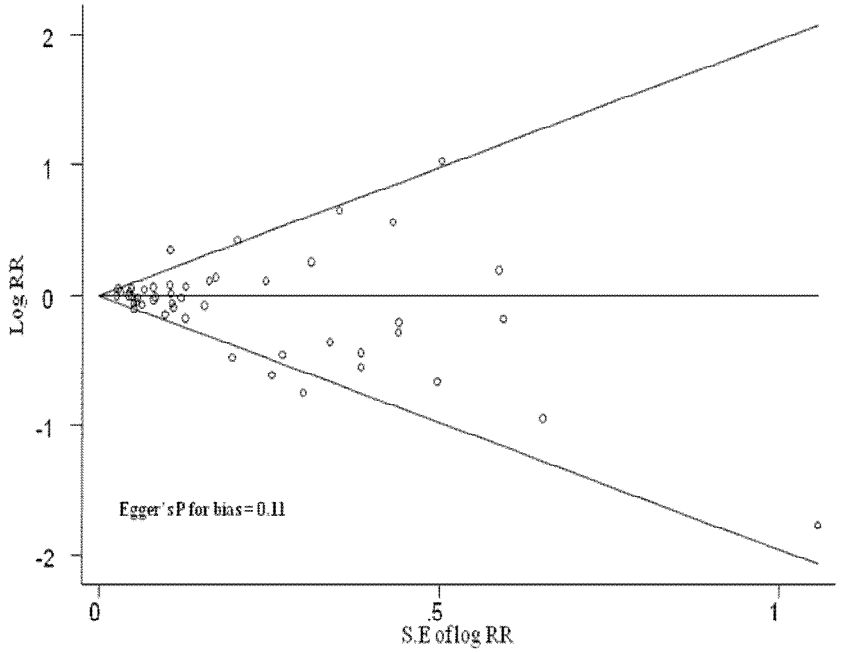


Figure 6. Begg's funnel plots and Egger's test for identifying publication bias. RR, Relative risk; S.E, Standard error.

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

Efficacy of vitamin or antioxidant supplements on cardiovascular disease in subgroup meta-analysis by various factors

Figures 2-5 and **Tables 3-5** 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 revealed that there was no significant association between vitamin or antioxidant supplements and the risk of the major cardiovascular events (**Figure 2**), while low-dose vitamin B6 supplementation slightly decreased the risk of major cardiovascular events (RR, 0.92; 95% CI, 0.85-0.99; I^2 = 35.0%; **Figure 4 and Table 3**) in the fixed-effects meta-analysis. Similarly, no significant association between them was found in the overall subgroup meta-analysis by type of supplements (**Figure 3 and Table 3**), type of outcome (cardiovascular death, fatal or nonfatal MI, stroke, or TIA), type of prevention (primary vs. secondary), type of study design (RDBPCT vs. OLRCT), methodological quality (high vs. low by score of 5), duration of treatment (<5 years vs. >5 years), funding source (independent organization vs. pharmaceutical industry), supply source for supplement (pharmaceutical industry vs. at cost or no mention), and type of control (placebo use vs. no use), while vitamin B6 and vitamin E supplements reduced the risk of cardiovascular death (RR, 0.91; 95% CI, 0.83-0.99; I^2 = 0%) and myocardial infarction (RR, 0.77; 95% CI, 0.65-0.91; I^2 = 76.2%), respectively, and

vitamin and antioxidant supplementation marginally increased the risk of angina pectoris (RR, 1.04; 95% CI, 1·00-1.08; I^2 = 35.5%) (**Tables 3-5**).

However, in the subgroup meta-analysis of high-quality RCTs within each category of low-dose vitamin B6 (RR, 0.94; 95% CI, 0.87-1.02; I^2 = 38.7%; fixed-effects model) and angina (RR, 1.01; 95% CI, 0.86-1.18; I^2 = 57.3%; random-effects model), beneficial or harmful effects disappeared (**Figure 4 and Table 4)**. Also, even though vitamin B6 supplementation decreased the risk of cardiovascular death in high-quality trials, and vitamin E supplementation decreased the risk of myocardial infarction, those beneficial effects were only shown in trials supplied with supplements by pharmaceutical industry **(Figure 5 and Table 3)**.

In the subgroup meta-analysis by the number of participants of each trial, vitamin or antioxidant supplements showed a trend toward a decreased (but not statistically significant) risk of the major cardiovascular events (RR, 0.97; 95% CI, 0.94-1.01; I^2 = 39.8%) in the subgroup meta-analysis of trials with <10000 participants, while those supplements showed an increased (but not statistically significant) risk of the major cardiovascular events (RR, 1.02; 95% CI, 0.99-1.04; I^2 = 39.2%) in the subgroup meta-analysis of those with ≥10000 participants (**Table 5**).

Table 6 shows the efficacy of vitamin and antioxidant supplements given singly or in combination with other vitamin or antioxidant supplements in the major cardiovascular events in subgroup meta-analyses. No significant beneficial effect of vitamin and antioxidant supplements was shown 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 (RR, 0.95; 95% CI, 0.90-1.00; I^2 = 45.8%).

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) (**Figure 6**).

Table 2. Methodological Quality of Trials Based on the Jadad Scale (n = 50).

	Source (Project Name)	Randomization	Description of randomization methods	Double-blind	Using identical placebo	Follow-up reporting	Total score
1	Korpela et al, 1989				n.a.		
2	Kuklinski et al, 1994				n.a.		
3	Steiner et al, 1995	1	0	1	1	1	4
4	Omenn et al, 1996 (CARET)	1	1	1	1	1	5
5	Stephens et al, 1996 (CHAOS)	1	1	1	1	1	5
6	Mark et al, 1996 (LNIT)	1	1	1	1	0	4
7	Hennekens et al, 1996 (PHS)	1	0	1	1	1	4
8	Greenberg et al, 1996 (SCP)	1	1	1	1	1	5

	Source (Project Name)	Randomization	Description of randomization methods	Double-blind	Using identical placebo	Follow-up reporting	Total score
9	Rapola et al, 1997 (ATBC)	1	1	1	1	1	5
10	Virtamo et al, 1998 (ATBC)	1	1	1	1	1	5
11	Marchioli et al, 1999 (GISSI)	1	1	0	0	1	3
12	Komulainen et al, 1999 (KOS)	1	0	1	1	1	4
13	Green et al, 1999 (NSCP)	1	0	0	1	1	3
14	Yusuf et al, 2000 (HOPE)	1	0	1	1	0	3
15	Boaz et al, 2000 (SPACE)	1	1	1	1	0	4

	Source (Project Name)	Randomization	Description of randomization methods	Double-blind	Using identical placebo	Follow-up reporting	Total score
16	Brown et al, 2001 (HATS)	1	0	1	1	1	4
17	Roncaglioni et al, 2001 (PPP)	1	1	0	0	1	3
18	You et al, 2001	1	0	1	1	1	4
19	Baker et al, 2002				n.a.		
20	Collins et al, 2002 (HPS)	1	1	0	1	1	4
21	Schnyder et al, 2002 (SHS)	1	0	1	1	1	4
22	Waters et al, 2002 (WAVE)	1	1	1	1	1	5
23	Liem et al, 2003 (Goes)	1	1	0	0	1	3

	Source (Project Name)	Randomization	Description of randomization methods	Double-blind	Using identical placebo	Follow-up reporting	Total score
24	Righetti et al, 2003	1	1	0	0	1	3
25	Trivedi et al, 2003	1	0	1	1	1	4
26	Lange et al, 2004	1	0	1	1	1	4
27	Hercberg et al, 2004 (SU.VI.MAX)	1	1	1	1	1	5
28	Toole et al, 2004 (VISP)	1	1	1	1	1	5
29	Wrone et al, 2004	1	1	1	1	1	5
30	Brazier et al, 2005	1	1	1	1	1	5
31	Lee et al, 2005 (WHS)	1	1	1	1	1	5
32	Zoungas et al, 2006 (ASFAST)	1	0	1	1	1	4

	Source (Project Name)	Randomization	Description of randomization methods	Double-blind	Using identical placebo	Follow-up reporting	Total score
33	Lonn et al, 2006 (HOPE-2)	1	1	1	1	1	5
34	Bonaa et al, 2006 (NORVIT)	1	1	1	1	1	5
35	Stranges et al, 2006 (NPC)	1	1	1	1	0	4
36	Jamison et al, 2007 (HOST)	1	1	1	1	1	5
37	Hsia et al, 2007 (WHI)	1	0	1	1	0	3
38	Berggren et al, 2008	1	0	0	0	1	2
39	Millman et al, 2008 (ICARE)	1	1	1	1	1	5
40	Prince et al, 2008	1	1	1	1	1	5

	Source (Project Name)	Randomization	Description of randomization methods	Double-blind	Using identical placebo	Follow-up reporting	Total score
41	Albert et al, 2008 (WAFACS)	1	0	1	1	1	4
42	Ebbing et al, 2008 (WENBIT)	1	1	1	1	1	5
43	Hodis et al, 2009 (BVAIT)	1	1	1	1	1	5
44	House et al, 2010 (DIVINe)	1	1	1	1	1	5
45	Heinz et al, 2010	1	0	1	1	1	4
46	Armitage et al, 2010 (SEARCH)	1	1	1	1	1	5
47	Galan et al, 2010 (SU.FOL.OM3)	1	1	1	1	1	5

	Source (Project Name)	Randomization	Description of randomization methods	Double-blind	Using identical placebo	Follow-up reporting	Total score
48	Graeme et al, 2010 (VITATOPS)	1	1	1	1	1	5
49	Bostom et al, 2011 (FAVORIT)	1	1	1	1	1	5
50	Sesso et al, 2008 (PHS2)	1	1	1	1	1	5

CARET, the Beta-Carotene and Retinol Efficacy Trial; CHAOS, the Cambridge Heart Antioxidant Study; LNIT, the Linxian Nutrition Intervention Trial; PHS, the Physicians' Health Study; SCP, the Skin Cancer Prevention Study; ATBC, the Alpha-tocopherol Beta-carotene Cancer Prevention Study; GISSI, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-Prevenzione trial; KOS, the Kuopio Osteoporosis Study; NSCP, the Nambour Skin Cancer Prevention trial; HOPE, the Heart Outcomes Prevention Evaluation Study; SPACE, Secondary Prevention with Antioxidants of Cardiovascular disease in Endstage renal disease; HATS, the HDL-Atherosclerosis Treatment Study; PPP, the Primary Prevention Project; HPS, the Heart Protection Study; SU.VI.MAX, the Supplemenatation en Vitamines et Mineraux Antioxydants; WHS, the Women's Health Study; ASFAST, the Atherosclerosis and Folic Acid Supplementation Trial; HOPE-2, The Heart Outcomes Prevention Evaluation 2 study; NORVIT, the Norwegian Vitamin Trial; NPC, the Nutritional Prevention of Cancer trial; WHI, the Women's Health Initiative; ICARE, the Israel Cardiovascular Events Reduction with Vitamin E trial; WAFACS, the Women's Antioxidant and Folic Acid Cardiovascular Study; WENBIT, the Western Norway B Vitamin Intervention Trial; BVAIT, the B-Vitamin Atherosclerosis Intervention Trial; DIVINe, the Diabetic Intervention with Vitamins to Improve Nephropathy; SEARCH, the Study of the Effectiveness of

Additional Reductions in Cholesterol and Homocysteine study; SU.FOL.OM3, the Supplémentation en Folates et Omega-3; VITATOPS, the Vitamins to Prevent Stroke trial; VISP, the Vitamin Intervention for Stroke Prevention randomized controlled trial; FAVORIT, the Folic Acid for Vascular Outcome Reduction in Transplantation trial.

Table 3. Efficacy of vitamin or antioxidant supplements in the prevention of the major cardiovascular events in subgroup meta-analyses by type of prevention and type of supplement.

Factor	No. of Trials	Summary RR (95% CI)	Heterogeneity, I^2	Model
All	50	1.00 (0.98-1.02)	41.6%	Fixed-effects
Prevention				
Primary	30	1.01 (0.98-1.03)	42.1%	Fixed-effects
Secondary	20	1.00 (0.97-1.03)	43.9%	Fixed-effects
Type of supplement				
Vitamins only	39	0.99 (0.97-1.01)	44.1%	Fixed-effects
Low quality	17	0.99 (0.96-1.02)	31.5%	Fixed-effects
High quality	22	0.99 (0.94-1.05)	52.9%	Random-effects

Factor	No. of Trials	Summary RR (95% CI)	Heterogeneity, I^2	Model
Antioxidants only	22	0.98 (0.96-1.02)	40.8%	Fixed-effects
Low quality	11	0.99 (0.96-1.03)	24.6%	Fixed-effects
High quality	9	0.97 (0.91-1.02)	48.5%	Fixed-effects
Vitamin A	2	0.98 (0.45-2.16)	87.2%	Random-effects
Low dose (10,000 IU/day)	1	0.63 (0.37-1.07)	n.a.	n.a.
High dose (25,000 IU/day)	1	1.41 (1.15-1.73)	n.a.	n.a.
Vitamin B6	16	0.96 (0.92-1.01)	33.1%	Fixed-effects
Low dose (3-25 mg/day)*	8	0.92 (0.85-0.99)	35.0%	Fixed-effects
Low quality*	3	0.76 (0.61-0.94)	0%	Fixed-effects

Factor	No. of Trials	Summary RR (95% CI)	Heterogeneity, I^2	Model
High quality	5	0.94 (0.87-1.02)	38.7%	Fixed-effects
High dose (40-100 mg/day)	8	0.99 (0.94-1.05)	22.0%	Fixed-effects
Vitamin B12	17	0.99 (0.95-1.02)	36.6%	Fixed-effects
Low dose (6 µg - 0.5 mg/day)	11	0.96 (0.90-1.02)	33.8%	Fixed-effects
High dose (1 - 2 mg/day)	6	1.00 (0.96-1.05)	42.8%	Fixed-effects
Folic acid	21	0.99 (0.95-1.02)	34.6%	Fixed-effects
Low dose (500 µg - 5 mg/day)	17	0.99 (0.96-1.03)	38.9%	Fixed-effects
High dose (10 - 40 mg/day)	4	0.89 (0.78-1.03)	0%	Fixed-effects
Vitamin C	7	0.99 (0.94-1.03)	10.2%	Fixed-effects
Low dose (120 - 250 mg/day)	3	0.99 (0.94-1.04)	30.6%	Fixed-effects

Factor	No. of Trials	Summary RR (95% CI)	Heterogeneity, I^2	Model
High dose (500 - 1000 mg/day)	4	0.98 (0.87-1.10)	27.8%	Fixed-effects
Vitamin D	7	1.02 (0.98-1.07)	22.9%	Fixed-effects
Low dose (120 - 250 mg/day)	2	1.05 (0.99-1.12)	0%	Fixed-effects
High dose (500 - 1000 mg/day)	5	0.94 (0.86-1.03)	0%	Fixed-effects
Vitamin E	17	0.97 (0.94-1.01)	44.0%	Fixed-effects
Low dose (60 IU - 250 mg/day)	13	0.96 (0.92-1.01)	34.9%	Fixed-effects
High dose (500 - 600 mg/day)	4	0.84 (0.52-1.35)	68.5%	Random-effects
Beta-carotene	11	1.04 (0.96-1.12)	55.2%	Random-effects

Factor	No. of Trials	Summary RR (95% CI)	Heterogeneity, I^2	Model
Low dose (6 - 25 mg/day)	6	0.99 (0.95-1.03)	6.8%	Fixed-effects
High dose (30 - 50 mg/day)	5	1.14 (0.96-1.35)	68.8%	Random-effects
Selenium	7	0.91 (0.77-1.06)	47.2%	Fixed-effects
Low dose (50 - 100 μg/day)	5	0.85 (0.70-1.04)	44.0%	Fixed-effects
High dose (122 - 200 μg /day)	2	0.57 (0.10-3.16)	66.5%	Fixed-effects

*Statistically significant, ** Marginally significant..

RDBPCT, randomized, double-blind, placebo-controlled trial; OLRCT, open-label, randomized controlled trial. For the subgroup meta-analysis of vitamin C and vitamin E, the data of the PHS2 article[83] published in 2008 were used because data are not available in the 2012 PHS article.

Table 4. Efficacy of vitamin or antioxidant supplements in the prevention of the major cardiovascular events in subgroup meta-analyses by type of cardiovascular outcome.

Factor	No. of Trials	Summary RR (95% CI)	Heterogeneity, I^2	Model
Cardiovascular death	32	1.01 (0.97-1.05)	40.6%	Fixed-effects
Vitamin A	2	0.98 (0.45-2.16)	87.2%	Random-effects
Vitamin B6*	8	0.91 (0.83-0.99)	0%	Fixed-effects
Low quality	4	0.93 (0.75-1.14)	11.5%	Fixed-effects
High quality*	4	0.90 (0.82-0.99)	0%	Fixed-effects
Trials not supplied with supplements by pharmaceutical industry	2	0.96 (0.84-1.10)	0%	Fixed-effects
Trials supplied with supplements by pharmaceutical industry*	2	0.85 (0.75-0.97)	0%	Fixed-effects
Trials not supplied with supplements	3	0.96 (0.83-1.10)	0%	Fixed-effects

Factor	No. of Trials	Summary RR (95% CI)	Heterogeneity, I^2	Model
by pharmaceutical industry				
Trials supplied with supplements by pharmaceutical industry*	5	0.88 (0.79-0.98)	0%	Fixed-effects
Vitamin B12	9	0.96 (0.90-1.03)	27.2%	Fixed-effects
Folic acid	11	0.96 (0.89-1.03)	11.3%	Fixed-effects
Vitamin C	6	1.03 (0.95-1.12)	26.6%	Fixed-effects
Vitamin D	3	0.90 (0.76-1.07)	27.3%	Fixed-effects
Vitamin E	15	0.98 (0.92-1.04)	37.3%	Fixed-effects
Beta-carotene	10	1.10 (0.96-1.27)	61.4%	Random-effects
Selenium	15	0.98 (0.92-1.04)	37.3%	Fixed-effects
Vitamin	2	0.98 (0.45-2.16)	87.2%	Random-effects

Factor	No. of Trials	Summary RR (95% CI)	Heterogeneity, I^2	Model
Angina**	10	1.04 (1.00-1.08)	35.5%	Fixed-effects
Low quality**	6	1.05 (1.00-1.09)	25.1%	Fixed-effects
High quality	4	1.01 (0.86-1.18)	57.3%	Random-effects
Vitamin B6	4	0.93 (0.72-1.20)	77.3%	Random-effects
Vitamin 12	4	0.93 (0.72-1.20)	77.3%	Random-effects
Folic acid	4	0.93 (0.72-1.20)	77.3%	Random-effects
Vitamin C	2	0.94 (0.85-1.03)	0.0%	Fixed-effects
Vitamin D	1	1.07 (0.93-1.23)	n.a.	n.a.

Factor	No. of Trials	Summary RR (95% CI)	Heterogeneity, I^2	Model
Vitamin E	3	1.15 (0.99-1.33)	0%	Fixed-effects
MI	34	1.00 (0.96-1.03)	0%	Fixed-effects
Vitamin B6	13	0.99 (0.91-1.07)	11.2%	Fixed-effects
Vitamin B12	14	0.99 (0.93-1.06)	4.1%	Fixed-effects
Folic acid	15	0.99 (0.93-1.06)	0%	Fixed-effects
Vitamin C	4	0.96 (0.87-1.07)	0%	Fixed-effects
Vitamin D	2	1.06 (0.92-1.21)	0%	Fixed-effects
Vitamin E*	12	0.77 (0.65-0.91)	76.2%	Random-effects
Low quality	5	0.76 (0.57-1.01)	80.5%	Random-effects
High quality*	7	0.75 (0.58-0.97)	75.3%	Random-

Factor	No. of Trials	Summary RR (95% CI)	Heterogeneity, I^2	Model
				effects
Trials not supplied with supplements by pharmaceutical industry	4	0.79 (0.53-1.17)	61.8%	Random-effects
Trials supplied with supplements by pharmaceutical industry*	3	0.67 (0.42-1.07)	86.4%	Random-effects
Primary prevention*	7	0.72 (0.54-0.95)	76.4%	Random-effects
Trials not supplied with supplements by pharmaceutical industry	3	0.79 (0.42-1.50)	54.9%	Random-effects
Trials supplied with supplements by pharmaceutical industry*	4	0.63 (0.42-0.97)	82.2%	Random-effects
Secondary prevention	5	0.79 (0.61-1.02)	79.7%	Random-effects

Factor	No. of Trials	Summary RR (95% CI)	Heterogeneity, I^2	Model
Trials not supplied with supplements by pharmaceutical industry	4	0.79 (0.53-1.17)	61.8%	Random-effects
Trials supplied with supplements by pharmaceutical industry*	8	0.73 (0.59-0.92)	81.7%	Random-effects
Beta-carotene	4	0.95 (0.80-1.14)	52.3%	Random-effects
Selenium	3	0.87 (0.59-1.28)	0%	Fixed-effects
Fatal MI	9	1.02 (0.92-1.12)	42.8%	Fixed-effects
Vitamin B6	1	1.00 (0.75-1.33)	n.a.	n.a.
Vitamin B12	1	1.00 (0.75-1.33)	n.a.	n.a.
Folic acid	1	1.00 (0.75-1.33)	n.a.	n.a.
Vitamin E	3	0.57 (0.32-1.03)	0%	Fixed-effects

Factor	No. of Trials	Summary RR (95% CI)	Heterogeneity, I^2	Model
Beta-carotene	1	1.05 (0.95-1.17)	n.a.	n.a.
Selenium	1	1.12 (0.43-2.87)	n.a.	n.a.
Nonfatal MI	13	0.83 (0.66-1.04)	89.3%	Random-effects
Vitamin B6	3	1.08 (0.90-1.30)	22.4%	Fixed-effects
Vitamin B12	4	1.03 (0.93-1.14)	1.0%	Fixed-effects
Folic acid	4	1.03 (0.93-1.14)	1.0%	Fixed-effects
Vitamin C	4	0.85 (0.70-1.04)	0%	Random-effects
Vitamin E	9	0.57 (0.32-1.03)	0%	Fixed-effects
Beta-carotene	4	0.95 (0.80-1.14)	52.3%	Random-effects

Factor	No. of Trials	Summary RR (95% CI)	Heterogeneity, I^2	Model
Selenium	3	0.82 (0.53-1.27)	0%	Fixed-effects
Stroke	32	0.97 (0.93-1.02)	0%	Fixed-effects
Vitamin B6	12	0.93 (0.85-1.01)	12.7%	Fixed-effects
Vitamin B12	5	0.91 (0.80-1.03)	7.7%	Fixed-effects
Folic acid	7	0.90 (0.79-1.01)	19.0%	Fixed-effects
Vitamin C	4	0.98 (0.88-1.09)	0%	Fixed-effects
Vitamin D	5	1.00 (0.88-1.13)	6.2%	Fixed-effects
Vitamin E	12	1.00 (0.93-1.09)	19.6%	Fixed-effects
Beta-carotene	2	0.98 (0.89-1.07)	0%	Fixed-effects
Selenium	1	1.09 (0.68-1.72)	n.a.	n.a.
TIA	5	1.12 (0.97-1.30)	0%	Fixed-effects

Factor	No. of Trials	Summary RR (95% CI)	Heterogeneity, I^2	Model
Vitamin B6	2	1.12 (0.88-1.42)	0%	Fixed-effects
Vitamin B12	2	1.12 (0.88-1.42)	0%	Fixed-effects
Folic acid	2	1.12 (0.88-1.42)	0%	Fixed-effects
Vitamin D	1	1.12 (0.96-1.42)	n.a.	n.a
Vitamin E	2	0.93 (0.59-1.47)	0%	Fixed-effects

Table 5. Efficacy of vitamin or antioxidant supplements in the prevention of the major cardiovascular events in subgroup meta-analyses by type of study design, methodological quality, duration of treatment, funding source, supply source for supplements, type of control, and number of participants in each trial.

Factor	No. of Trials	Summary RR (95% CI)	Heterogeneity, I^2	Model
Study design				
RDBPCT	45	1.00 (0.98-1.02)	46.1%	Fixed-effects
OLRCT	5	0.98 (0.89-1.07)	0.0%	Fixed-effects
Methodological quality				
High-quality (Jadad score = 5)	24	0.99 (0.96-1.03)	44.9%	Fixed-effects
Low-quality (Jadad score ≤4)	23	1.01 (0.98-1.03)	32.2%	Fixed-effects
Duration of treatment				
<5 years	34	0.97 (0.90-1.04)	51.5%	Random-

Factor	No. of Trials	Summary RR (95% CI)	Heterogeneity, I^2	Model
				effects
≥5 years	16	1.01 (0.98-1.03)	0%	Fixed-effects
Funding source				
Pharmaceutical industry	5	1.01 (0.96-1.07)	0.0%	Fixed-effects
Independent organization	42	1.00 (0.98-1.02)	42.1%	Fixed-effects
Supply source for supplements				
Pharmaceutical industry	29	0.99 (0.97-1.02)	33.3%	Fixed-effects
Not pharmaceutical industry	18	1.01 (0.98-1.05)	46.9%	Fixed-effects
Type of control				
Placebo	44	1.00 (0.98-1.02)	46.4%	Fixed-effects

Factor	No. of Trials	Summary RR (95% CI)	Heterogeneity, I^2	Model
No placebo	6	0.97 (0.89-1.06)	0.0%	Fixed-effects
Number of participants in each trial				
<10,000	40	0.97 (0.94-1.01)	39.8%	Fixed-effects
≥10,000	10	1.02 (0.99-1.04)	39.2%	Fixed-effects

Table 6. Efficacy of vitamin and antioxidant supplements given singly or in combination with other vitamin or antioxidant supplements in the prevention of the major cardiovascular events in subgroup meta-analyses.

Factor	No. of Trials	Summary RR (95% CI)	Heterogeneity, I^2	Model
All	50	1.00 (0.98-1.02)	41.6%	Fixed-effects
Type of supplementation				
Vitamin A				
Given singly	n.a.			
Given in combination with other vitamin or antioxidant supplements	2	0.98 (0.45-2.16)	87.2%	Random-effects
Vitamin B6				
Given singly	n.a.			

Factor	No. of Trials	Summary RR (95% CI)	Heterogeneity, I^2	Model
Given in combination with other vitamin or antioxidant supplements	16	0.96 (0.92-1.01)	33.1%	Fixed-effects
Low-quality trials	5	0.94 (0.73-1.21)	66.1%	Random-effects
High-quality trials	11	0.96 (0.91-1.01)	1.4%	Fixed-effects
Vitamin B12				
Given singly	n.a.			
Given in combination with other vitamin or antioxidant supplements	17	0.99 (0.95-1.02)	36.6%	Fixed-effects
Low-quality trials	5	0.94 (0.73-1.21)	66.1%	Random-effects
High-quality trials	12	0.98 (0.95-1.02)	17.9%	Fixed-effects
Folic acid				

Factor	No. of Trials	Summary RR (95% CI)	Heterogeneity, I^2	Model
Given singly	4	1.02 (0.84-1.23)	46.5%	Fixed-effects
Given in combination with other vitamin or antioxidant supplements	17	0.99 (0.95-1.02)	36.6%	Fixed-effects
Given singly or in combination with other vitamin or antioxidant supplements	21	0.99 (0.95-1.02)	34.6%	Fixed-effects
Low-quality trials	8	0.99 (0.90-1.08)	48.7%	Fixed-effects
High-quality trials	12	0.98 (0.95-1.02)	17.9%	Fixed-effects
Vitamin C				
Given singly	n.a.			
Given in combination with other vitamin or antioxidant supplements	7	0.99 (0.94-1.06)	15.6%	Fixed-effects
Low-quality trials	4	0.99 (0.94-1.04)	43.9%	Fixed-effects

Factor	No. of Trials	Summary RR (95% CI)	Heterogeneity, I^2	Model
High-quality trials	3	0.99 (0.88-1.11)	0.0%	Fixed-effects
Vitamin D				
Given singly	2	0.95 (0.86-1.05)	10.9%	Fixed-effects
Given in combination with other vitamin or antioxidant supplements	5	1.04 (0.99-1.10)	0.0%	Fixed-effects
Given singly or in combination with other vitamin or antioxidant supplements	7	1.02 (0.98-1.07)	22.9%	Fixed-effects
Low-quality trials	5	1.02 (0.98-1.08)	47.2%	Fixed-effects
High-quality trials	2	1.01 (0.45-2.27)	0.0%	Fixed-effects
Vitamin E				
Given singly	10	0.93 (0.85-1.01)	56.7%	Random-effects

Factor	No. of Trials	Summary RR (95% CI)	Heterogeneity, I^2	Model
Given in combination with other vitamin or antioxidant supplements	7	0.99 (0.94-1.04)	15.3%	Fixed-effects
Given singly or in combination with other vitamin or antioxidant supplements	17	0.97 (0.94-1.01)	44.0%	Fixed-effects
Low-quality trials	9	0.99 (0.95-1.03)	43.1%	Fixed-effects
High-quality trials*	8	0.95 (0.90-1.00)	45.0%	Fixed-effects
Beta-carotene				
Given singly	5	1.02 (0.96-1.08)	31.4%	Fixed-effects
Given in combination with other vitamin or antioxidant supplements	6	1.00 (0.81-1.23)	69.5%	Random-effects
Given singly or in combination with other vitamin or antioxidant supplements	11	1.04 (0.96-1.12)	55.2%	Random-effects

Factor	No. of Trials	Summary RR (95% CI)	Heterogeneity, I^2	Model
Low-quality trials	6	0.99 (0.95-1.03)	29.8%	Fixed-effects
High-quality trials	5	1.13 (0.98-1.29)	64.2%	Random-effects
Selenium				
Given singly	3	0.34 (0.06-2.05)	70.0%	Random-effects
Given in combination with other vitamin or antioxidant supplements	4	0.88 (0.72-1.08)	25.9%	Fixed-effects
Given singly or in combination with other vitamin or antioxidant supplements	7	0.91 (0.77-1.06)	47.2%	Fixed-effects
Low-quality trials	4	0.91 (0.73-1.12)	43.1%	Fixed-effects
High-quality trials	1	0.98 (0.77-1.24)	n.a.	n.a.

* Marginally significant. RDBPCT, randomized, double-blind, placebo-controlled trial; OLRCT, open-label, randomized controlled trial. For the subgroup

meta-analysis of vitamin C and vitamin E, the data of the PHS2 article[83] published in 2008 were used because data are not available in the 2012 PHS article.

DISCUSSION

In this large-scale meta-analysis of randomized controlled trials, we found that there was no evidence to support the use of vitamin or antioxidant supplements for the primary or secondary prevention of the major CV events. Further, these supplements did not reduce the risk of the major CV 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, supply source for supplement, type of control, number of participants in each trial, and supplements given singly or in combination with other vitamin or antioxidant supplements.

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] beta-carotene,[5] folic acid,[7, 8, 61, 62, 66] or selenium[6] and CVDs in randomized controlled trials.

However, our findings 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.

The “oxidative-modification hypothesis” of atherosclerosis, which proposes that the oxidation of low-density lipoprotein (LDL) initiates atherosclerosis, has explained these associations.[70] According to this hypothesis, accumulated

LDL in the subendothelial space of arteries is oxidized to minimally modified LDL by vascular cells, and then the minimally modified LDL induces accumulation of monocytes and macrophages, which stimulate further peroxdiation of LDL.[74] This reaction makes oxidized LDL more negatively charged and completely oxidized.[75] The uptake of completely oxidized LDL leads to massive uptake of cholesterol by the macrophages.[70] Also, oxidized LDL 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 findings indicate that there is a discrepancy in findings between *in vivo* animal or *in vitro* laboratory studies and randomized controlled trials with regard to the association between vitamin or antioxidants (natural forms in fruit and vegetables or synthetic forms) and CVD. Some explanations might be possible for this discrepancy. First, preclinical studies such as animal studies and in vitro laboratory studies may not represent the biological processes in the human body.[73] Thus, even though vitamin or antioxidant substances show benefits against for a certain disease in preclinical studies, they might show no benefit or could be harmful under clinical circumstances. Second, the beneficial effects of vitamin or antioxidant supplements might be related to the timing of their administration. For example, vitamin C is shown to have its beneficial effects in the early stages of atherosclerosis.[73] However, once the atherosclerotic plaque is already made, vitamin C had no beneficial effect.[77] In the trials included in the current analysis, the mean age of participants ranged from 49 to 82, the ages in which atherosclerotic plaques or

changes might be already formed.[73]

Also, a similar discrepancy in findings between case-control studies and randomized controlled trials was found. It might be explained by methodological biases of case-control studies. Case-control studies use retrospective assessment of each participant's information on fruit and vegetable consumptions and are, thus, susceptible to two potential biases, i.e., recall and selection.

Even though cohort studies are less biased than case-control studies, some important methodological issues exist in cohort studies and might explain the differences in findings between cohort studies and randomized controlled trials. The diet assessment tools such as food frequency questionnaire (FFQ) might not precisely assess an individual's long term diet or might not provide sufficient information on fruit and vegetables consumption. Also, more importantly, the use of vitamin or antioxidant supplements in randomized controlled trials should not be equated with 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 CVD might be obtained from the combination of various nutrients, not from one or several specific nutrients.

Importantly, our findings are similar to those of the previous meta-analysis of randomized 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 the use of vitamin A, vitamin E, or beta-carotene supplements increased mortality in a meta-analysis of 47 low-

bias (high-quality) trials with 180,938 participants, while vitamin C and selenium was not associated with mortality.[78] Regarding the negative effect of antioxidant supplements on mortality, they insisted that the elimination of free radicals in the human body through antioxidant supplementation interfere with essential defensive mechanisms such as apoptosis, phagocytosis, and detoxification and might lead to an increased mortality.[78] Their updated meta-analysis including the recent published trials also indicated the 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 and secondary preventive effect on cancer and even increased the risk of bladder cancer in the meta-analysis of 22 randomized controlled trials.[80]

Therefore, 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 type of quality (high vs. low), dose (low dose vs. high dose), and supplements given singly or in combination with other supplements, there was no overall association between vitamin or antioxidant supplements and the risk of major cardiovascular events, while vitamin and antioxidant supplementation marginally increased the risk of angina pectoris, and low-dose vitamin B6 supplementation slightly decreased the risk of major cardiovascular events.

However, in the subgroup meta-analysis of high-quality RCTs within each category, beneficial or harmful effects disappeared. Thus, we are unable to conclude that vitamin and antioxidant supplements are harmful for angina pectoris or vitamin B6 supplements are beneficial for major cardiovascular events. Also, even though vitamin B6 supplementation decreased the risk of cardiovascular death in high-quality trials, and vitamin E supplementation decreased the risk of myocardial infarction, those beneficial effects were only shown in trials supplied with supplements by pharmaceutical industry. We are unable to completely exclude the possibility that those supplies may have influenced the respective trial design, results, or interpretations.

We also found that there was a trend toward an increased (not statistically significant) risk of the major cardiovascular events for the supplementation group in subgroup meta-analysis of trials with ≥10000 participants, while there was a trend toward a decreased (not statistically significant) risk in subgroup meta-analysis of trials with <10000 participants. Given that a larger sample size is more accurate than a smaller size, we are unable to exclude that vitamin or antioxidant supplementation might increase the risk of CVD. Further large-scale trials are needed to confirm this.

There are several limitations in the current study. First, we investigated only the association between synthetic vitamin and antioxidant supplements and CVD. 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. Second, we were unable to evaluate if vitamin and antioxidant supplementation would be beneficial against CVD for the

populations who are deficient in vitamins or antioxidants at baseline. Further randomized controlled trials in those populations are needed. Third, we used the Jadad scale for the methodological quality of the trials, which has been criticized that it suffers from the generic problems of scales, has a strong emphasis on reporting rather than conduct, and does not cover allocation concealment, one of the important biases in RCTs.[81] Instead, the Cochrane Risk of Bias (RoB) tool has recently been introduced and used to evaluate internal validity of RCTs since 2008. However, Hartling et al reported that inter-rater agreement varied substantially across domains in the RoB tool, and the time to complete it was significantly longer than the Jadad scale.[82] Further validated tools for the assessment of quality are needed. Last, we assessed the methodological quality of the trials only based on the presented data in each article. Thus, we might not assess the actual performance or biases of each trial.

In summary, we found that there is no evidence to support the use of vitamin or antioxidants supplements in the prevention of CVD. Also, the recent meta-analyses showed that vitamin or antioxidant supplements increased mortality, had no preventive effect on cancer, or even increased some cancer. Most countries permit the pharmaceutical or food industry to sell these supplements under the name of functional food or medical food, and also many people have consumed vitamin or antioxidant supplements in the belief that these improve their health. However, based on the recent meta-analyses of randomized controlled trials including the current study, governments and regulating agencies for food and drug should consider

vitamin and antioxidant supplements as medicinal products and strictly evaluate those efficacy and safety before marketing.

REFERENCES

1. Mendis S, Lindholm LH, Anderson SG, Alwan A, Koju R, Onwubere BJ, et al. Total cardiovascular risk approach to improve efficiency of cardiovascular prevention in resource constrain settings. *J Clin Epidemiol* 2011;64:1451-62.

2. Dauchet L, Amouyel P, Dallongeville J. Fruits, vegetables and coronary heart disease. *Nat Rev Cardiol* 2009;6:599-608.

3. Lock K, Pomerleau J, Causer L, Altmann DR, McKee M. The global burden of disease attributable to low consumption of fruit and vegetables: implications for the global strategy on diet. *Bull World Health Organ* 2005;83:100-8.

4. Bhupathiraju SN, Tucker KL. Coronary heart disease prevention: nutrients, foods, and dietary patterns. *Clin Chim Acta* 2011;412:1493-514.

5. Vivekananthan DP, Penn MS, Sapp SK, Hsu A, Topol EJ. Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomized trials. *Lancet* 2003;361:2017-23.

6. Flores-Mateo G, Navas-Acien A, Pastor-Barriuso R, Guallar E. Selenium and coronary heart disease: a meta-analysis. *Am J Clin Nutr* 2006;84:762-73.

7. Lee M, Hong KS, Chang SC, Saver JL. Efficacy of homocysteine-lowering therapy with folic Acid in stroke prevention: a meta-analysis. *Stroke* 2010;41:1205-12.

8. Qin X, Huo Y, Langman CB, Hou F, Chen Y, Matossian D, et al.

Folic acid therapy and cardiovascular disease in ESRD or advanced chronic kidney disease: a meta-analysis. *Clin J Am Soc Nephrol* 2011;6:482-8.

9. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1-12.

10. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539-58.

11. Korpela H, Kumpulainen J, Jussila E, Kemilä S, Kääriäinen M, Kääriäinen T, et al. Effect of selenium supplementation after acute myocardial infarction. *Res Commun Chem Pathol Pharmacol* 1989;65:249-52.

12. Kuklinski B, Weissenbacher E, Fahnrich A. Coenzyme Q10 and antioxidants in acute myocardial infarction. *Mol Aspects Med* 1994;15 Suppl:s143-7.

13. Steiner M, Glantz M, Lekos A. Vitamin E plus aspirin compared with aspirin alone in patients with transient ischemic attacks. *Am J Clin Nutr* 1995;62(6 Suppl): 1381S-4S.

14. Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med* 1996;334:1150-5.

15. Stephens NG, Parsons A, Schofield PM, Kelly F, Cheeseman K, Mitchinson MJ. Randomized controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). *Lancet* 1996;347:781-6.

16. Mark SD, Wang W, Fraumeni JF, Jr., Li JY, Taylor PR, Wang GQ,

et al. Lowered risks of hypertension and cerebrovascular disease after vitamin/mineral supplementation: the Linxian Nutrition Intervention Trial. *Am J Epidemiol* 1996;143:658-64.

17. Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, Cook NR, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med* 1996;334:1145-9.

18. Greenberg ER, Baron JA, Karagas MR, Stukel TA, Nierenberg DW, Stevens MM, et al. Mortality associated with low plasma concentration of beta carotene and the effect of oral supplementation. *JAMA* 1996;275:699-703.

19. Rapola JM, Virtamo J, Ripatti S, Huttenen JK, Albanes D, Taylor PR, et al. Randomized trial of alpha-tocopherol and beta-carotene supplements on incidence of major coronary events in men with previous myocardial infarction. *Lancet* 1997;349:1715-20.

20. Virtamo J, Rapola JM, Ripatti S, Heinonen OP, Taylor PR, Albanes D, et al. Effect of vitamin E and beta carotene on the incidence of primary nonfatal myocardial infarction and fatal coronary heart disease. *Arch Intern Med* 1998;158:668-75.

21. GISSI-Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico). Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* 1999;354:447-55.

22. Komulainen M, Kröger H, Tuppurainen MT, Heikkinen AM, Alhava E, Honkanen R, et al. Prevention of femoral and lumbar bone loss with

hormone replacement therapy and vitamin D3 in early postmenopausal women: a population-based 5-year randomized trial. *J Clin Endocrinol Metab* 1999;84:546-52.

23. Green A, Williams G, Neale R, Hart V, Leslie D, Parsons P, et al. Daily sunscreen application and betacarotene supplementation in prevention of basal-cell and squamous-cell carcinomas of the skin: a randomized controlled trial. *Lancet* 1999;354:723-9.

24. Yusuf S, Dagenais G, Pogue J, Bosch J, Sleight P. Vitamin E supplementation and cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000;342:154-60.

25. Boaz M, Smetana S, Weinstein T, Matas Z, Gafter U, Iaina A, et al. Secondary prevention with antioxidants of cardiovascular disease in endstage renal disease (SPACE): randomized placebo-controlled trial. *Lancet* 2000;356:1213-8.

26. Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, Morse JS, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 2001;345:1583-92.

27. de Gaetano G; Collaborative Group of the Primary Prevention Project. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomized trial in general practice. *Lancet* 2001;357:89-95.

28. You WC, Chang YS, Heinrich J, Ma JL, Liu WD, Zhang L, et al. An intervention trial to inhibit the progression of precancerous gastric lesions: compliance, serum micronutrients and S-allyl cysteine levels, and toxicity.

Eur J Cancer Prev 2001;10:257-63.

29. Rafiee P, Shi Y, Kong X, Pritchard KA Jr, Tweddell JS, Litwin SB, et al. Activation of protein kinases in chronically hypoxic infant human and rabbit hearts: role in cardioprotection. *Circulation* 2002;106:239-45.

30. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomized placebo-controlled trial. *Lancet* 2002;360:23-33.

31. Schnyder G, Roffi M, Flammer Y, Pin R, Hess OM. Effect of homocysteine-lowering therapy with folic acid, vitamin B12, and vitamin B6 on clinical outcome after percutaneous coronary intervention: the Swiss Heart study: a randomized controlled trial. *JAMA* 2002;288:973-9.

32. Waters DD, Alderman EL, Hsia J, Howard BV, Cobb FR, Rogers WJ, et al. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial. *JAMA* 2002;288:2432-40.

33. Liem A, Reynierse-Buitenwerf GH, Zwinderman AH, Jukema JW, van Veldhuisen DJ. Secondary prevention with folic acid: effects on clinical outcomes. *J Am Coll Cardiol* 2003;41:2105-13.

34. Righetti M, Ferrario GM, Milani S, Serbelloni P, La Rosa L, Uccellini M, et al. Effects of folic acid treatment on homocysteine levels and vascular disease in hemodialysis patients. *Med Sci Monit* 2003;9:PI19-24.

35. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomized double blind controlled trial.

BMJ 2003;326:469.

36. Lange H, Suryapranata H, De Luca G, Börner C, Dille J, Kallmayer K, et al. Folate therapy and in-stent restenosis after coronary stenting. *N Engl J Med* 2004;350:2673-81.

37. Hercberg S, Galan P, Preziosi P, Bertrais S, Mennen L, Malvy D, et al. The SU.VI.MAX Study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. *Arch Intern Med* 2004;164:2335-42.

38. Toole JF, Malinow MR, Chambless LE, Spence JD, Pettigrew LC, Howard VJ, et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. *JAMA* 2004;291:565-75.

39. Wrone EM, Hornberger JM, Zehnder JL, McCann LM, Coplon NS, Fortmann SP. Randomized trial of folic acid for prevention of cardiovascular events in end-stage renal disease. *J Am Soc Nephrol* 2004;15:420-6.

40. Brazier M, Grados F, Kamel S, Mathieu M, Morel A, Maamer M, et al. Clinical and laboratory safety of one year's use of a combination calcium + vitamin D tablet in ambulatory elderly women with vitamin D insufficiency: results of a multicenter, randomized, double-blind, placebo-controlled study. *Clin Ther* 2005;27:1885-93.

41. Lee IM, Cook NR, Gaziano JM, Gordon D, Ridker PM, Manson JE, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. *JAMA*

2005;294:56-65.

42. Zoungas S, McGrath BP, Branley P, Kerr PG, Muske C, Wolfe R, et al. Cardiovascular morbidity and mortality in the Atherosclerosis and Folic Acid Supplementation Trial (ASFAST) in chronic renal failure: a multicenter, randomized, controlled trial. *J Am Coll Cardiol* 2006;47:1108-16.

43. Lonn E, Yusuf S, Arnold MJ, Sheridan P, Pogue J, Micks M, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med* 2006;354:1567-77.

44. Bønaa KH, Njølstad I, Ueland PM, Schirmer H, Tverdal A, Steigen T, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med* 2006;354:1578-88.

45. Stranges S, Marshall JR, Trevisan M, Natarajan R, Donahue RP, Combs GF, et al. Effects of selenium supplementation on cardiovascular disease incidence and mortality: secondary analyses in a randomized clinical trial. *Am J Epidemiol* 2006;163:694-9.

46. Jamison RL, Hartigan P, Kaufman JS, Goldfarb DS, Warren SR, Guarino PD, et al. Effect of homocysteine lowering on mortality and vascular disease in advanced chronic kidney disease and end-stage renal disease: a randomized controlled trial. *JAMA* 2007;298:1163-70.

47. Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, et al. Calcium/vitamin D supplementation and cardiovascular events. *Circulation* 2007;115:846-54.

48. Berggren M, Stenvall M, Olofsson B, Gustafson Y. Evaluation of a fall-prevention program in older people after femoral neck fracture: a one-

year follow-up. *Osteoporos Int* 2008;19:801-9.

49. Milman U, Blum S, Shapira C, Aronson D, Miller-Lotan R, Anbinder Y, et al. Vitamin E supplementation reduces cardiovascular events in a subgroup of middle-aged individuals with both type 2 diabetes mellitus and the haptoglobin 2-2 genotype: a prospective double-blinded clinical trial. *Arterioscler Thromb Vasc Biol* 2008;28:341-7.

50. Prince RL, Austin N, Devine A, Dick IM, Bruce D, Zhu K. Effects of ergocalciferol added to calcium on the risk of falls in elderly high-risk women. *Arch Intern Med* 2008;168:103-8.

51. Albert CM, Cook NR, Gaziano JM, Zaharris E, MacFadyen J, Danielson E, et al. Effect of folic acid and B vitamins on risk of cardiovascular events and total mortality among women at high risk for cardiovascular disease: a randomized trial. *JAMA* 2008;299:2027-36.

52. Ebbing M, Bleie Ø, Ueland PM, Nordrehaug JE, Nilsen DW, Vollset SE, et al. Mortality and cardiovascular events in patients treated with homocysteine-lowering B vitamins after coronary angiography: a randomized controlled trial. *JAMA* 2008;300:795-804.

53. Hodis HN, Mack WJ, Dustin L, Mahrer PR, Azen SP, Detrano R, et al. High-dose B vitamin supplementation and progression of subclinical atherosclerosis: a randomized controlled trial. *Stroke* 2009;40:730-6.

54. House AA, Eliasziw M, Cattran DC, Churchill DN, Oliver MJ, Fine A, et al. Effect of B-vitamin therapy on progression of diabetic nephropathy: a randomized controlled trial. *JAMA* 2010;303:1603-9.

55. Heinz J, Kropf S, Domröse U, Westphal S, Borucki K, Luley C, et al.

B vitamins and the risk of total mortality and cardiovascular disease in end-stage renal disease: results of a randomized controlled trial. *Circulation* 2010;121:1432-8.

56. Armitage JM, Bowman L, Clarke RJ, Wallendszus K, Bulbulia R, Rahimi K, et al. Effects of homocysteine-lowering with folic acid plus vitamin B12 vs placebo on mortality and major morbidity in myocardial infarction survivors: a randomized trial. *JAMA* 2010;303:2486-94.

57. Galan P, Kesse-Guyot E, Czernichow S, Briancon S, Blacher J, Hercberg S. Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases: a randomized placebo controlled trial. *BMJ* 2010;341:c6273.

58. VITATOPS Trial Study Group. B vitamins in patients with recent transient ischaemic attack or stroke in the VITAmins TO Prevent Stroke (VITATOPS) trial: a randomized, double-blind, parallel, placebo-controlled trial. *Lancet Neurol* 2010;9:855-65.

59. Bostom AG, Carpenter MA, Kusek JW, Levey AS, Hunsicker L, Pfeffer MA, et al. Homocysteine-lowering and cardiovascular disease outcomes in kidney transplant recipients: primary results from the Folic Acid for Vascular Outcome Reduction in Transplantation trial. *Circulation* 2011;123:1763-70.

60. Sesso HD, Christen WG, Bubes V, Smith JP, MacFadyen J, Schavartz M, et al. Multivitamins in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. *JAMA* 2012;308:1751-60.

61. Clarke R, Halsey J, Lewington S, Lonn E, Armitage J, Manson JE, et al. Effects of lowering homocysteine levels with B vitamins on cardiovascular disease, cancer, and cause-specific mortality: Meta-analysis of 8 randomized trials involving 37 485 individuals. *Arch Intern Med* 2010;170:1622-31.

62. Mei W, Rong Y, Jinming L, Yongjun L, Hui Z. Effect of homocysteine interventions on the risk of cardiocerebrovascular events: a meta-analysis of randomized controlled trials. *Int J Clin Pract* 2010;64:208-15.

63. Elamin MB, Abu Elnour NO, Elamin KB, Fatourechi MM, Alkatib AA, Almandoz JP, et al. Vitamin D and cardiovascular outcomes: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2011;96:1931-42.

64. Eidelman RS, Hollar D, Hebert PR, Lamas GA, Hennekens CH. Randomized trials of vitamin E in the treatment and prevention of cardiovascular disease. *Arch Intern Med* 2004;164:1552-6.

65. Shekelle PG, Morton SC, Jungvig LK, Udani J, Spar M, Tu W, et al. Effect of supplemental vitamin E for the prevention and treatment of cardiovascular disease. *J Gen Intern Med* 2004;19:380-9.

66. Zhou YH, Tang JY, Wu MJ, Lu J, Wei X, Qin YY, et al. Effect of folic acid supplementation on cardiovascular outcomes: a systematic review and meta-analysis. *PLoS One* 2011;6:e25142.

67. Parker RA, Sabrah T, Cap M, Gill BT. Relation of vascular oxidative stress, alpha-tocopherol, and hypercholesterolemia to early atherosclerosis in hamsters. *Arterioscler Thromb Vasc Biol* 1995;15:349-58.

68. Pratico D, Tangirala RK, Rader DJ, Rokach J, FitzGerald GA. Vitamin E suppresses isoprostane generation in vivo and reduces atherosclerosis in ApoE-deficient mice. *Nat Med* 1998;4:1189-92.

69. Crawford RS, Kirk EA, Rosenfeld ME, LeBoeuf RC, Chait A. Dietary antioxidants inhibit development of fatty streak lesions in the LDL receptor-deficient mouse. *Arterioscler Thromb Vasc Biol* 1998;18:1506-13.

70. Diaz MN, Frei B, Vita JA, Keaney JF Jr. Antioxidants and atherosclerotic heart disease. *N Engl J Med* 1997;337:408-16.

71. Ricciarelli R, Zingg JM, Azzi A. Vitamin E reduces the uptake of oxidized LDL by inhibiting CD36 scavenger receptor expression in cultured aortic smooth muscle cells. *Circulation* 2000;102:82-7.

72. Ulrich-Merzenich G, Metzner C, Schiermeyer B, Vetter H. Vitamin C and vitamin E antagonistically modulate human vascular endothelial and smooth muscle cell DNA synthesis and proliferation. *Eur J Nutr* 2002;41:27-34.

73. Farbstein D, Kozak-Blickstein A, Levy AP. Antioxidant vitamins and their use in preventing cardiovascular disease. *Molecules* 2010;15:8098-110.

74. Quinn MT, Parthasarathy S, Fong LG, Steinberg D. Oxidatively modified low density lipoproteins: a potential role in recruitment and retention of monocyte/macrophages during atherogenesis. *Proc Natl Acad Sci U S A* 1987;84:2995-8.

75. Henriksen T, Mahoney EM, Steinberg D. Enhanced macrophage degradation of low density lipoprotein previously incubated with cultured

endothelial cells: recognition by receptors for acetylated low density lipoproteins. *Proc Natl Acad Sci U S A* 1981;78:6499-503.

76. Schwartz CJ, Valente AJ, Sprague EA, Kelley JL, Nerem RM. The pathogenesis of atherosclerosis: an overview. *Clin Cardiol* 1991;14:I1-16.

77. Aguirre R, May JM. Inflammation in the vascular bed: importance of vitamin C. *Pharmacol Ther* 2008;119:96-103.

78. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. *JAMA* 2007;297:842-57.

79. Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C. Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases. *Cochrane Database Syst Rev* 2012;3:CD007176.

80. Myung SK, Kim Y, Ju W, Choi HJ, Bae WK. Effects of antioxidant supplements on cancer prevention: meta-analysis of randomized controlled trials. *Ann Oncol* 2010;21:166-79.

81. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 [updated February 2008]. *The Cochrane Collaboration*, 2008. Available from www.cochrane-handbook.org.

82. Hartling L, Ospina M, Liang Y, Dryden DM, Hooton N, Krebs Seida J, et al. Risk of bias versus quality assessment of randomized controlled trials: cross sectional study. *BMJ* 2009;339:b4012.

83. Sesso HD, Buring JE, Christen WG, Kurth T, Belanger C, MacFadyen J, et al. Vitamins E and C in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomised controlled trial. *JAMA* 2008;300:2123-33.

국문 초록

서론: 비타민 및 항산화보충제의 심혈관질환 예방에 대한 효능과 관련하여 그 동안 발표된 무작위배정비교임상시험의 결과는 일관되지 않았다. 본 연구는 무작위배정비교임상시험의 메타분석을 통해 비타민 및 항산화보충제의 심혈관질환 예방에 대한 효능을 알아보고자 하였다.

방법: 2012 년 6 월과 추가적으로 11 월에 PubMed, EMBASE, the Cochrane Library, Scopus, CINAHL 및 ClinicalTrials.gov 데이터베이스를 검색한 후 미리 정한 선택기준에 따라 두 명의 연구자가 독립적으로 문헌을 고찰한 후 기준에 적합한 무작위배정비교임상시험을 선택하였다. 무작위배정비교임상시험의 메타분석을 시행하였다.

결과: 데이터베이스와 개별연구에 언급된 문헌을 참고해 검색된 총 2,240 편의 논문 중에서 총 50 개의 무작위배정비교임상시험이 최종 분석에 포함되었으며 전체 연구대상자는 총 294,478 명(비타민 및 항산화보충제복용군 156,663 명, 대조군 137,815 명)이었다. 총

50 개의 무작위배정비교임상시험을 고정효과모형에 기반해 메타분석을 시행한 결과, 비타민 및 항산화보충제는 주요 심혈관 사건(major cardiovascular events)의 위험성을 줄이지 못 했다(상대위험도, 1.00; 95% 신뢰구간, 0.98-1.02; I^2 = 41.6%). 전체적으로 예방종류, 보충제의 종류, 심혈관 결과, 연구디자인, 방법론적 질, 치료기간, 연구비 출처, 보충제 제공 출처, 대조군 종류, 각 연구의 대상자수, 보충제 단독 혹은 병합투여에 따른 하위그룹메타분석(subgroup meta-analysis)에서도 비타민 및 항산화보충제의 유용한 효과는 관찰되지 않았다. 심혈관 결과 종류(cardiovascular outcomes)에 따른 하위그룹 메타분석에서 저용량 비타민 B6 보충제는 주요 심혈관 사건의 위험성을 약간 감소시켰지만, 비타민 및 항산화보충제는 경계성으로 협심증의 위험성을 높이는 것으로 나타났다. 하지만, 각 보충제 별 연구의 질적 수준이 높은 무작위배정비교임상시험의 하위그룹메타분석에서는 이러한 이로움 혹은 해로움은 관찰되지 않았다. 또한 비타민 B6 보충은 연구의 질적 수준이 높은 연구들에서 심혈관 사망의 위험성을 낮췄고, 비타민 E 보충 역시 심근경색의 위험성을 낮췄으나 제약회사로부터 보충제를 제공받은 임상시험의 경우에만 이러한 이로운 효과가 관찰되었다.

결론: 무작위배정비교임상시험의 메타분석결과, 비타민 및 항산화보충제 사용은 심혈관질환의 예방에 효과가 없었다.

주요어: 비타민 보충제, 항산화보충제, 심혈관질환, 메타분석, 무작위 배정비교임상시험

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