Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases (Review)

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[Intervention Review]

Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases

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ABSTRACT

Background

Animal and physiological research as well as observational studies suggest that antioxidant supplements may improve survival.

Objectives

To assess the effect of antioxidant supplements on mortality in primary or secondary prevention randomised clinical trials.

Search strategy

We searched *The Cochrane Library* (Issue 3, 2005), *MEDLINE* (1966 to October 2005), *EMBASE* (1985 to October 2005), and the *Science Citation Index Expanded* (1945 to October 2005). We scanned bibliographies of relevant publications and wrote to pharmaceutical companies for additional trials.

Selection criteria

We included all primary and secondary prevention randomised clinical trials on antioxidant supplements (beta-carotene, vitamin A, vitamin C, vitamin E, and selenium) versus placebo or no intervention. Included participants were either healthy (primary prevention trials) or had any disease (secondary prevention trials).

Data collection and analysis

Three authors extracted data. Trials with adequate randomisation, blinding, and follow-up were classified as having a low risk of bias. Random-effects and fixed-effect meta-analyses were performed. Random-effects meta-regression analyses were performed to assess sources of intertrial heterogeneity.

Main results

Sixty-seven randomised trials with 232,550 participants were included. Forty-seven trials including 180,938 participants had low risk of bias. Twenty-one trials included 164,439 healthy participants. Forty-six trials included 68111 participants with various diseases (gastrointestinal, cardiovascular, neurological, ocular, dermatological, rheumatoid, renal, endocrinological, or unspecified). Overall,

the antioxidant supplements had no significant effect on mortality in a random-effects meta-analysis (relative risk [RR] 1.02, 95% confidence interval [CI] 0.99 to 1.06), but significantly increased mortality in a fixed-effect model (RR 1.04, 95% CI 1.02 to 1.06). In meta-regression analysis, the risk of bias and type of antioxidant supplement were the only significant predictors of intertrial heterogeneity. In the trials with a low risk of bias, the antioxidant supplements significantly increased mortality (RR 1.05, 95% CI 1.02 to 1.08). When the different antioxidants were assessed separately, analyses including trials with a low risk of bias and excluding selenium trials found significantly increased mortality by vitamin A (RR 1.16, 95% CI 1.10 to 1.24), beta-carotene (RR 1.07, 95% CI 1.02 to 1.11), and vitamin E (RR 1.04, 95% CI 1.01 to 1.07), but no significant detrimental effect of vitamin C (RR 1.06, 95% CI 0.94 to 1.20). Low-bias risk trials on selenium found no significant effect on mortality (RR 0.90, 95% CI 0.80 to 1.01).

Authors' conclusions

We found no evidence to support antioxidant supplements for primary or secondary prevention. Vitamin A, beta-carotene, and vitamin E may increase mortality. Future randomised trials could evaluate the potential effects of vitamin C and selenium for primary and secondary prevention. Such trials should be closely monitored for potential harmful effects. Antioxidant supplements need to be considered medicinal products and should undergo sufficient evaluation before marketing.

PLAIN LANGUAGE SUMMARY

No evidence to support antioxidant supplements to prevent mortality in healthy people or patients with various diseases

Previous research on animal and physiological models suggest that antioxidant supplements have beneficial effects that may prolong life. Some observational studies also suggest that antioxidant supplements may prolong life, whereas other observational studies demonstrate neutral or harmful effects. Randomised trials have largely been neutral. We need evidence from randomised trials to decide if antioxidant supplements should be used for prevention.

BACKGROUND

Oxidative stress may play role in the pathogenesis of cancer and cardiovascular disease, the leading causes of death in middle- and high-income countries (Sies 1985; Halliwell 1999). Diet provides numerous vitamins and trace elements that are essential for good health. Several observational studies have shown a significant positive association between higher intake of fruits and vegetables and reduced risk of chronic diseases (Block 1992; Ames 1993; Willcox 2004). However, exactly which specific dietary constituents of fruits and vegetables might be beneficial is not clear. Furthermore, causal inferences are hard to establish from observational studies. Antioxidants have attracted most attention as promising preventive agents. Fruits and vegetables are sources of numerous micronutrients and some of these, including beta-carotene, vitamin A, vitamin C, vitamin E, and selenium have antioxidant potential. Many people take antioxidant supplements believing to improve their health (Balluz 2000; Millen 2004; Radimer 2004; Nichter 2006).

Whether antioxidant supplements are beneficial or harmful is uncertain (Herbert 1997; Caraballoso 2003; Vivekananthan 2003; Bjelakovic 2004; Stanner 2004; Miller 2005; Berger 2005). Antioxidants may play dual roles, acting as double-edged swords (Bjelakovic 2007b). Excessive antioxidants can adversely affect key physiological processes. The results of our recent systematic review and meta-analyses of the role of antioxidant supplements for prevention of gastrointestinal cancers were unforeseen (Bjelakovic 2004). We found that antioxidant supplements significantly increased mortality in the antioxidant group with the fixed-effect model meta-analysis but not with the random-effects meta-analysis (Bjelakovic 2004). The effect of antioxidant supplements on mortality has also been assessed in several large trials on primary and secondary prevention of diseases (HPS 2002Low; ATBC 2003Low; CARET 2004Low; SUVIMAX 2004Low; HOPE TOO 2005Low; WHS 2005Low). The results of the individual trials are equivocal. Furthermore, none of the trials had sufficient statistical power to identify the effect of antioxidants on mortality. Accordingly, we performed a systematic review of randomised trials on antioxidant supplements for primary and secondary prevention.

OBJECTIVES

Our aim was to assess the effect of antioxidant supplements (beta-carotene, vitamin A, vitamin C, vitamin E, and selenium) on overall mortality in primary or secondary prevention randomised clinical trials.

METHODS

Criteria for considering studies for this review

Types of studies

All primary and secondary prevention randomised clinical trials, irrespective of trial design, blinding, publication status, publication year, or language. From cross-over trials, only the first trial period was considered.

Types of participants

Adult participants (age 18 years or over) who were

- healthy participants or were recruited among the general population (primary prevention);
- diagnosed with a specific disease in a stable phase (secondary prevention).

We excluded tertiary prevention trials, ie, randomised trials in which antioxidant supplements were used to treat a specific disease or nutritional defects, like trials with patients with acute, infectious, or malignant diseases (except non-melanoma skin cancer). We excluded trials including children and pregnant women since they may be in need of certain antioxidant supplements.

Types of interventions

We considered for inclusion trials that compared antioxidant supplements (ie, beta-carotene, vitamin A, vitamin C, vitamin E, and selenium) at any dose, duration, and route of administration versus placebo or no intervention.
The antioxidants could have been administered

- separately or in any combination among themselves; or
- in combination with other vitamins; or
- in combination with trace elements without antioxidant function.

Concomitant interventions were allowed if used equally in both intervention arms of the trial.

Types of outcome measures

Our sole outcome measure was all-cause mortality.

Search methods for identification of studies

We searched the *Cochrane Central Register of Controlled Trials* (*CENTRAL*) in *The Cochrane Library* (Issue 3, 2005), *MEDLINE* (1966 to October 2005), *EMBASE* (*Excerpta Medica Database*) (1985 to October 2005), and the *Science Citation Index Expanded* (1945 to October 2005) (Royle 2003). We scanned bibliographies of relevant publications for additional trials. All search strategies are given in Appendix 1.
We sent letters by post or e-mail to major manufacturers of antioxidant supplements, ie, CBH in China, DSM in Switzerland, CVC4health in USA, and BASF in Germany, asking for unpublished randomised trials. No reply was received from any of the contacted manufacturers.

Data collection and analysis

The present review is based on our protocol on antioxidant supplements for preventing gastrointestinal cancers (Bjelakovic 2003) adopted to assess overall mortality. An abbreviated version of the review has previously been published (Bjelakovic 2007a).

Inclusion criteria application

Two of the three authors (GB and DN or RGS) independently assessed trial eligibility without blinding of the study authors. We listed excluded trials with the reasons for exclusion. Disagreement was resolved by discussion or in consultation with LLG or CG. We contacted authors of the trials for missing information.

Data extraction

Participant characteristics, diagnosis, and interventions

From each trial we recorded first author; country of origin; country income category (low, middle, high) (World Bank 2006); number of participants; characteristics of participants: age range (mean or median) and sex ratio; participation rate; dropout rate; trial design (parallel, factorial, or crossover); type of antioxidant; dose; duration of supplementation; duration of follow-up (ie, duration of intervention plus post-intervention follow-up); and co-interventions.

Trial characteristics

We recorded the date, location, sponsor of the trial (known or unknown and type of sponsor) as well as publication status.

Assessment of methodological quality

We defined the methodological quality as the confidence that the design and report restrict bias in the intervention comparison (Schulz 1995; Moher 1998; Kjaergard 2001). Due to the risk of overestimation of intervention effects in randomised trials with inadequate methodological quality (Schulz 1995; Moher 1998; Kjaergard 2001), we assessed the influence of methodological quality of the four components below as reported in the trials. When this information was not available, we asked the authors of the trial publications to provide it.

Generation of the allocation sequence

- Adequate, if the allocation sequence was generated by a computer or random number table. Drawing of lots, tossing of a coin, shuffling of cards, or throwing dice was considered as adequate if a person who was not

otherwise involved in the recruitment of participants performed the procedure.
- Unclear, if the trial was described as randomised, but the method used for the allocation sequence generation was not described.
- Inadequate, if a system involving dates, names, or admittance numbers were used for the allocation of patients.

Allocation concealment

- Adequate, if the allocation of patients involved a central independent unit, on-site locked computer, identically appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed envelopes.
- Unclear, if the trial was described as randomised, but the method used to conceal the allocation was not described.
- Inadequate, if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised.

Blinding (or masking)

- Adequate, if the trial was described as double blind and the method of blinding involved identical placebo or active drugs.
- Unclear, if the trial was described as double blind, but the method of blinding was not described.
- Not performed, if the trial was not double blind.

Follow-up

- Adequate, if the numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals.
- Unclear, if the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.
- Inadequate, if the number or reasons for dropouts and withdrawals were not described.

Trials with adequate generation of the allocation sequence, adequate allocation concealment, adequate blinding, and adequate follow-up were considered low-bias risk trials (high methodological quality) (Kjaergard 2001; Gluud 2006a). We appended 'Low' to the references of these trials. Trials with one or more unclear or inadequate quality components were classified as high-bias risk trials (low methodological quality) (Kjaergard 2001; Gluud 2006a). We also reported on whether the investigators had performed a sample-size calculation and used intention-to-treat analysis (Gluud 2001).

Statistical analyses

We performed the meta-analyses according to the recommendations of *The Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2006). For the statistical analyses, we used RevMan Analyses (RevMan 2003), STATA 8.2 (STATA Corp, College Station, Tex), Sigma Stat 3.0 (SPSS Inc, Chicago, Ill), and Stats-Direct (StatsDirect Ltd, Altrincham, England).

We analysed the data with both random-effects (DerSimonian 1986) and fixed-effect (DeMets 1987) model meta-analyses. We presented the results of random-effects model analyses. When statistically significant results are obtained in either the random- or fixed-effect model, we present both analyses. Results are presented as the relative risk (RR) with 95% confidence intervals (CI). We assessed heterogeneity with I^2, which describes the percentage of total variation across studies due to heterogeneity rather than chance (Higgins 2002).

Random-effects meta-regression analyses were performed to assess potential covariates that could predict intertrial heterogeneity, ie, which covariates that were statistically associated with estimated intervention effects. The included covariates were bias risk (low or high), type and dose of supplement, single or combined antioxidant experimental supplement regimen, duration of treatment, and type of prevention (primary or secondary). We also performed subgroup analyses comparing the primary and secondary prevention trials. Furthermore, we performed sensitivity analyses excluding trials using small dose antioxidant supplements in both the experimental and control study groups. The exclusion of trials using small dose antioxidant supplements in both the experimental and control study groups was based on the fact that addition of, eg, a vitamin pill could be a confounder. We observed that selenium seemed to have a beneficial effect on gastrointestinal cancer development (Bjelakovic 2004). The sensitivity analysis removing selenium trials from our analysis to evaluate their influence on our conclusions was therefore not a post hoc decision.

The influence of trials with zero events in the treatment or control group was assessed by re-calculating the random-effects meta-analyses with 0.5, 0.05, and 0.005 continuity corrections (Sweeting 2004; Bradburn 2007). We also performed additional meta-analyses including one large hypothetical trial with one event in the treatment and control group and a sample size corresponding to the total number of participants in the zero events trials.

All our analyses followed the intention-to-treat principle. We accounted all of the participants for each trial and performed the analyses irrespective of how the original trialists had analysed the data. Participants lost to follow-up were considered survivors. For trials with a factorial design, we based our results on 'at the margins' analysis, comparing all groups that received antioxidant supplements with groups that did not receive antioxidant supplements (McAlister 2003). This entails a risk of interaction between the antioxidant and the other intervention(s) assessed, whether significant or not in the individual trial. Due to the risk of confounding in factorial trials assessing other interventions, we conducted post-hoc sensitivity analysis including only factorial trial data, which

could not be affected of such confounding (ie, 'inside the table' analysis) (McAlister 2003). To determine the effect of a single antioxidant we also performed 'inside the table' analysis (McAlister 2003) in which we compared the single antioxidant intervention with the placebo or no intervention. In the trials with parallel group design with more than two arms and additional therapy, we compared only antioxidant intervention with placebo or no intervention. For cross-over trials we included only data from the first period (Higgins 2006).

Comparison of intervention effects was conducted with test of interaction (Altman 2003).

We performed adjusted rank correlation (Begg 1994) and regression asymmetry test (Egger 1997) for detection of bias. A $P < 0.10$ was considered significant.

RESULTS

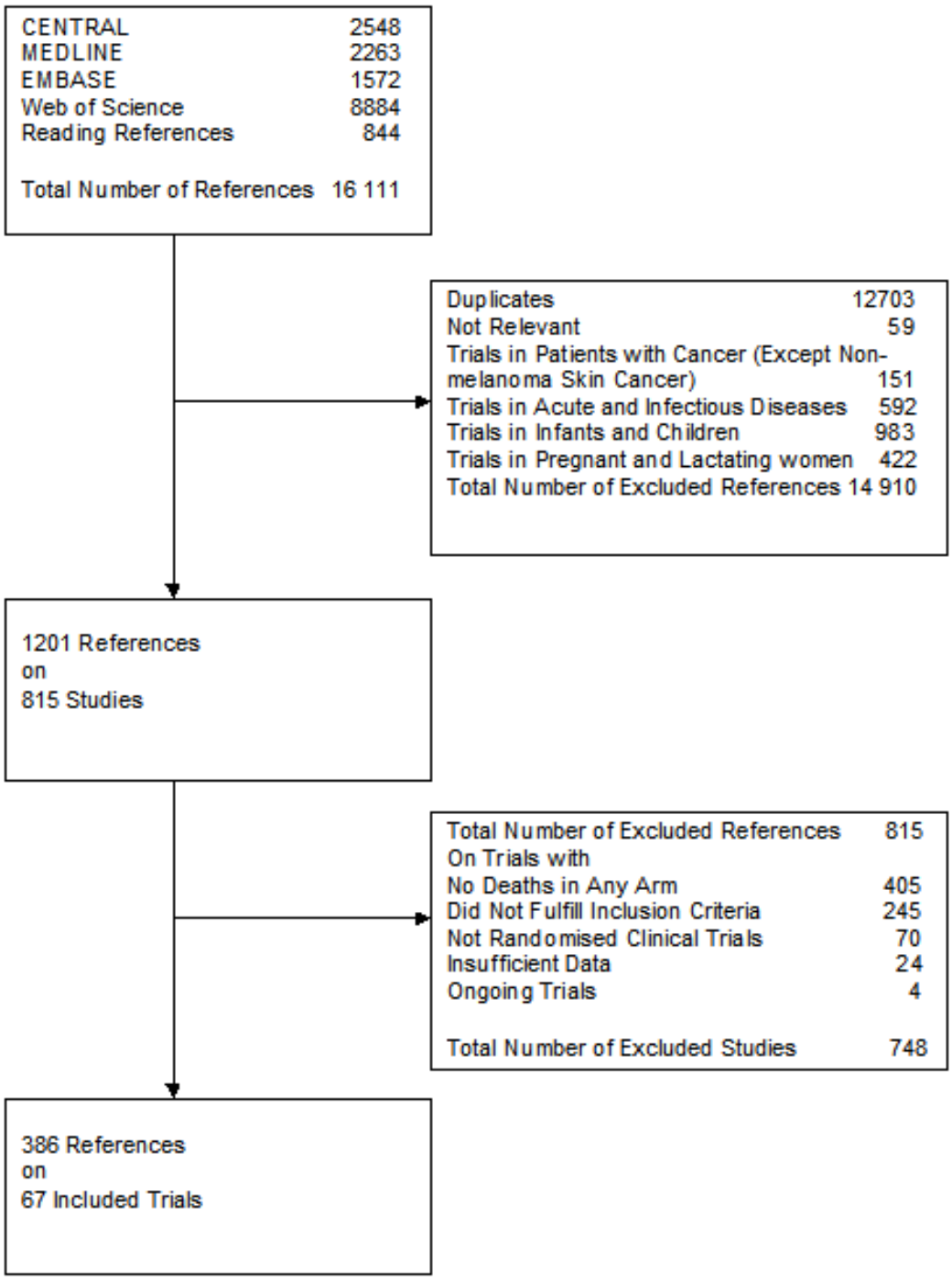
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Search results

Database searches yielded 16111 references (Figure 1). Exclusion of duplicates and irrelevant references left 1201 references describing 815 trials. To obtain additional information we wrote to authors of about 500 eligible trials. More than one hundred authors responded.

Figure 1. Flow diagram of identification of randomised trials for Inclusion



We excluded 815 references dealing with 748 studies. After further evaluation we excluded 339 studies because they were not randomised trials or did not fulfil our inclusion criteria. The remaining 409 were randomised trials examining antioxidant supplements. Four of these were still ongoing. The authors of the 405 trials did not report data on mortality (these trials are shown at http://ctu.rh.dk). The majority of these were small phase I or phase II trials with short duration of follow-up without assessment of clinical outcome measures. We contacted the authors and about one fifth of them confirmed that mortality was indeed zero.
We included 386 references describing 67 randomised trials fulfilling our inclusion criteria and able to provide data for our analyses (Table 1; Table 2) (http://ctu.rh.dk). This corresponds to a median of 6 references per included trial (range 1 to 44 references per trial).

Table 1. Characteristics of included trials with low risk of bias

Trial	Design	Number participants	Mean age	Suppl (Follow-up)-y	Beta-carotene (mg)	Vitamin A (IU)	Vitamin C (mg)	Vitamin E (IU)	Selenium (µg)
SCPS 1990	Parallel	1805	NA	5 (5)	50				
Murphy 1992	Parallel	109	NA	0.003 (0.25)		200000			
NIT2 1993	Parallel	3318	54	6 (6)	15	10000	180	60	50
PPS 1994	2 x 2	864	61	4 (4)	25		1000	440	
Pike 1995	Parallel	47	69	1 (1)		2666	90	45	
AMDS 1996	Parallel	71	72	1.5 (1.5)	12		750	200	50
CHAOS 1996	Parallel	2002	62	1.4 (1.4)				600	
NPCT 1996	Parallel	1312	63	4.5 (7.4)					200
PHS 1996	2 x 2	22071	53	12 (12.9)	25				

Table 1. Characteristics of included trials with low risk of bias (*Continued*)

SKICAP AK 1997	Parallel	2297	63	3.8 (3.8)		25000			
MINVI-TAOX 1999	2 x 2	725	84	2 (2)	6		120	16.5	100
NSCPT 1999	2 x 2	1621	49	4.5 (4.5)	30				
Correa 2000	2 x 2 x 2	976	51	6 (6)	30		2000		
Jacobson 2000	Parallel	112	42	0.5 (0.5)	12		500	400	
SPACE 2000	Parallel	196	65	1.42 (1.42)				800	
AREDS 2001	2 x 2	4757	68	6.3 (6.3)	15		500	400	
Desnuelle 2001	Parallel	288	64	1 (1)				500	
HATS 2001	2 x 2	160	53	3 (3)	25		1000	800	100
Graat 2002	2 x 2	652	NA	1 (1)	1.2	2000	60	272	25
HPS 2002	2 x 2	20536	NA	5 (5)	20		250	660	
REACT 2002	Parallel	297	68	3 (3)	18		750	660	
VEAPS 2002	Parallel	353	56	3 (3)				400	
WAVE 2002	2 x 2	423	65	3 (3)			1000	800	
White 2002	Parallel	100	63	0.23 (0.23)			1000	223	
Wluka 2002	Parallel	136	64	2 (2)				500	

Table 1. Characteristics of included trials with low risk of bias (*Continued*)

ASAP 2003	2 x 2	520	NA	6 (6)			250	272	
ATBC 2003	2 x 2	29133	57	6.1 (14.1)	20			50	
Collins 2003	2 x 2	52	67	0.5 (2.5)				400	
Prince 2003	Crossover	61	58	0.25 (0.25)	3		150	74.5	75
Allsup 2004	Parallel	164	83	0.15 (0.5)		2666	120	60	60
CARET 2004	Parallel	18314	58	4 (10)	30	25000			
DATOR 2004	Parallel	24	51	0.5 (4.5)				750	
LAST 2004	Parallel	61	75	1 (1)	10	2500	1500	500	200
Meydani 2004	Parallel	617	84	1 (1)				200	100
Mezey 2004	Parallel	51	48	0.25 (1)				1000	
SUVI-MAX 2004	Parallel	13017	49	7.54 (7.54)	6		120	33	100
VECAT 2004	Parallel	1193	66	4 (4)				500	
DATATOP 2005	2 x 2	800	61	2.6 (13)				2000	
Graf 2005	Parallel	160	58	1.5 (1.5)				5000	
HOPE TOO 2005	2 x 2	9541	66	4.5 (7)				400	

Table 1. Characteristics of included trials with low risk of bias (*Continued*)

Limburg 2005	2 x 2	360	47	0.83 (0.83)				200	
MAVIS 2005	Parallel	910	72	1 (1)		2666	60	10	
Mooney 2005	Parallel	284	37	1.25 (1.25)			500	400	
Tam 2005	Parallel	39	46	0.23 (2.67)			500	800	
WHS 2005	2 x 2	39876	55	10.1 (10.1)	25			300	
Witte 2005	Parallel	32	NA	0.75 (0.75)		2666	500	400	50
Rayman 2006	Parallel	501	67	0.5 (0.5)					200

Abbreviation:
NA, not available.
Blank cells indicate that the supplement was not part of the trial.

Table 2. Characteristics of included trials with high risk of bias

Trial	Design	Number participants	Mean age	Suppl (Y)	Beta-carotene (mg)	Vitamin A (IU)	Vitamin C (mg)	Vitamin E (IU)	Selenium (µg)
Gillilan 1977	Crossover	52	57	0.5				1600	
Mckeown-Eyssen 1988	Parallel	185	58	2			400	400	
Penn 1991	Parallel	30	84	0.077		8000	100	50	
Chandra 1992	Parallel	96	74	1	16	1333	80	44	20
NIT1 1993	1/2 (2 x 2 x 2 x 2)	29584	NA	5.25	15	5000	120	33	50

Table 2. Characteristics of included trials with high risk of bias (*Continued*)

de la Maza 1995	Parallel	74	50	1				500	
Takamatsu 1995	Parallel	147	47	6				136	
ter Riet 1995	2 x 2	88	NA	0.23			1000		
Hogarth 1996	2 x 2	106	83	0.083		8000	500		
ADCS 1 1997	2 x 2	341	73	2				2000	
Girodon 1997	2 x 2	81	84	2	6		120	15	100
Bonelli 1998	Parallel	304	NA	5		6000	180	30	200
GISSI 1999	2 x 2	11324	59	3.5				330	
de Waart 2001	Parallel	218	60	1.8				400	
PPP 2001	2 x 2	4495	64	3.6				330	
Stevic 2001	Parallel	28	57	1				1200	31.5
You 2001	2 x 2 x 2	3411	NA	3.25	15		500	200	75
Sasazuki 2003	2 x 2	439	57	5	15		500		
Takagi 2003	Parallel	93	63	5				600	
ADCS 2 2005	Parallel	516	73	3				2000	

Abbreviation:

NA, not available.

Blank cells indicate that the supplement was not part of the trial.

The years of follow-up are the same as the years of supplementation.

Included trials

The included trials are described in detail in the Table of included studies and in Table 1 to Table 3.

Table 3. Participants and outcome measures of included trials with a high risk of bias

Trial	Inclusion criteria	Outcome measures	Type of prevention
Gillilan 1977	Coronary artery disease	Improvement of angina pectoris	Secondary
Mckeown-Eyssen 1988	Removed colorectal adenomas	Newly diagnosed colorectal adenomas	Secondary
Penn 1991	Elderly long-stay patients	Cell-mediated immune function	Secondary
Chandra 1992	Elderly individuals	Infectuous morbidity	Primary
NIT1 1993	General population	Cancer incidence, cancer mortality, all-cause mortality	Primary
de la Maza 1995	Alcoholic cirrhosis	Liver function, mortality, hospitalisation rates	Secondary
Takamatsu 1995	General population	Any illness	Primary
ter Riet 1995	Nursing home patients with pressure ulcers	Wound status and clinometric changes	Secondary
Hogarth 1996	Elderly medical in-patients	Weight, serum albumin levels, activities of daily living, cognitive functioning, length of stay	Secondary
ADCS 1 1997	Probable Alzheimer disease	Death, institutionalisation, loss of ability to perform two of three basic activities of daily living	Secondary
Girodon 1997	Elderly individuals	Infectious morbidity	Primary
Bonelli 1998	Removed colorectal adenomas	Newly diagnosed colorectal adenomas	Secondary
GISSI 1999	Recent myocardial infarction	All-cause mortality, non-fatal myocardial infarction, non-fatal stroke, cardiovascular death	Secondary
de Waart 2001	Male cigarette smokers	Progression of atherosclerosis	Primary

Table 3. Participants and outcome measures of included trials with a high risk of bias (*Continued*)

PPP 2001	Elderly with at least one of the major cardiovascular risk factors	Cardiovascular death, non-fatal myocardial infarction and stroke, all-cause mortality, total cardiovascular events, angina pectoris, transient ischaemic attacks, peripheral artery disease, revascularization procedures	Primary
Stevic 2001	Probable or definitive amyotrophic lateral sclerosis	Survival and rate of disease progression	Secondary
You 2001	General population	Prevalence of dysplasia, gastric cancer, chronic atrophic gastritis, intestinal metaplasia	Primary
Sasazuki 2003	Chronic atrophic gastritis	Blood pressure	Secondary
Takagi 2003	Liver cirrhosis	Tumour free survival and cumulative survival rate	Secondary
ADCS 2 2005	Amnestic mild cognitive impairment	Alzheimer's disease	Secondary

Trial characteristics

Out of the 67 included trials, 39 trials used parallel-group design, 26 trials used factorial design (22 trials 2 x 2; 3 trials 2 x 2 x 2; 1 trial half replicate of 2 x 2 x 2 x 2), and 2 trials used cross-over design (Pocock 2004).

In 54 trials (81%), the antioxidants were provided at no cost from pharmaceutical companies. In the rest of the trials, funding was not reported.

The trials were conducted in Europe, North and South America, Asia, and Australia. Sixty-one trials came from high-income countries and 6 trials came from lower-middle-income countries (NIT1 1993; NIT2 1993Low; de la Maza 1995; Correa 2000Low; Stevic 2001; SIT 2001).

Participants

A total of 232,550 participants were randomly assigned in the 67 trials. The number of participants in each trial ranged from 24 to 39876 (Table 1; Table 2). The mean age was 62 years (range, 18 to 103 years). The mean proportion of women was 45% in the 63 trials reporting sex.

Twenty-one trials were primary prevention trials including 164,439 healthy participants; 46 trials were secondary prevention trials including 68111 participants with gastrointestinal (n = 10 trials), cardiovascular (n = 9), neurological (n = 6), ocular (n = 5), dermatological (n = 5), rheumatoid (n = 2), renal and cardiovascular (n = 1), endocrinological (n = 1), or unspecified (n = 7) diseases. Main outcome measures in the primary prevention trials were cancer and mortality (cause-specific and all-cause mortality), and in the secondary prevention trials they were progression of disease and mortality (cause-specific and all-cause mortality) (Table 4; Table 3).

Table 4. Participants and outcome measures of included trials with a low risk of bias

Trial	Inclusion criteria	Outcome measures	Type of prevention
SCPS 1990	History of BCC or SCC	Newly diagnosed BCC or SCC	Secondary
Murphy 1992	Elderly nursing-home residents	Bacterial infections	Secondary
NIT 2 1993	Esophageal dysplasia	Cancer incidence, cancer mortality, all-cause mortality	Secondary
PPS 1994	Removed colorectal adenomas	Newly diagnosed colorectal adenomas	Secondary

Table 4. Participants and outcome measures of included trials with a low risk of bias (*Continued*)

Pike 1995	Elderly individuals	Immune indices	Primary
AMDS 1996	Age-related macular degeneration	Outcome of age-related macular degeneration.	Secondary
CHAOS 1996	Coronary artery disease	Non-fatal myocardial infarction and cardiovascular death	Secondary
NPCT 1996	History of BCC or SCC	Incidence of SCC and BCC, cancer incidence, cancer mortality, all-cause mortality	Secondary
PHS 1996	Male physicians	Incidence of cancer and CVD and all-cause mortality	Primary
SKICAP AK 1997	History of BCC or SCC	Newly diagnosed SCC and BCC	Secondary
MINVITAOX 1999	Institutionalized elderly patients	Delayed-type hypersensitivity skin response, humoral response to influenza vaccine, and infectious morbidity and mortality	Secondary
NSCPT 1999	History of BCC or SCC	Newly diagnosed SCC and BCC	Secondary
Correa 2000	Multifocal atrophic gastritis with or without intestinal metaplasia and dysplasia	Change of gastric precancerous lesions	Secondary
Jacobson 2000	Heavy smokers	DNA damage	Primary
SPACE 2000	Stable haemodialysis patients with a documented medical history of CVD	Acute myocardial infarction (fatal and nonfatal), ishaemic stroke, peripheral vascular disease, unstable angina, CVD mortality, all-cause mortality	
AREDS 2001	Aged-related macular degeneration	Increase in nuclear, cortical or posterior subcapsular opacity grades, cataract surgery, loss of visual acuity	Secondary
Desnuelle 2001	Probable or definitive amyotrophic lateral sclerosis	Change in functional status, survival, bulbar function	Secondary

Table 4. Participants and outcome measures of included trials with a low risk of bias (*Continued*)

HATS 2001	Coronary artery disease	Change in coronary stenosis, first cardiovascular event (death, myocardial infarction, stroke or revascularization)	Secondary
Graat 2002	Elderly individuals	Acute respiratory tract infections	Primary
HPS 2002	Coronary and other occlusive arterial disease or diabetes	Major coronary events, fatal and non-fatal vascular events, cancer, other morbidity	Secondary
REACT 2002	Cataract	Cataract progression	Secondary
VEAPS 2002	Healthy individuals (serum LDL cholesterol >3.37 mmol/L)	Rate of change in the right distal common carotid artery intimamedia thickness	Primary
WAVE 2002	Coronary artery disease	Progression of coronary artery disease	Secondary
White 2002	Patients with Barrett's oesophagus on long-term acid suppression therapy	Prevention of potentially premalignant modifications to DNA in the human stomach	Secondary
Wluka 2002	Knee osteoarthritis	Change in cartilage volume	Secondary
Collins 2003	Patients with peripheral arterial diseaseWalking ability and perceived quality of life	Walking ability and perceived quality of life	Secondary
Prince 2003	Primary biliary cirrhosis	Change in patient fatigue	Secondary
ASAP 2003	Healthy individuals (serum cholesterol >5 mmol/L)	Progression of carotid atherosclerosis	Primary
ATBC 2003	Male cigarette smokers	Lung cancer and other major cancers, all-cause and cause specific mortality, incidence of other disease	Primary
Allsup 2004	Older institutionalised people	Response to influenza vaccine	Secondary
CARET 2004	Cigarette smokers, former smokers and workers exposed to asbestos	Lung cancer, other cancers, mortality	Primary

Table 4. Participants and outcome measures of included trials with a low risk of bias (*Continued*)

DATOR 2004	Type 1 diabetic patientsImpact on lipids and peroxidation during statin treatment	Impact on lipids and peroxidation during statin treatment	Secondary
LAST 2004	Age-related macular degenerationVisual function	Visual function	Secondary
Meydani 2004	Elderly individuals	Respiratory tract infections, emergency department visits, hospitalisation, and death	Primary
Mezey 2004	Alcoholic hepatitis	Clinical and laboratory parameters of liver function and markers of fibrogenesis	Secondary
SUVIMAX 2004	General population	Incidence of cancer and CVD and all-cause mortality	Primary
VECAT 2004	Early or no cataract	Age related cataract	Secondary
DATATOP 2005	Early Parkinson's disease not requiring levodopa	Level of functional disability for initiation of levo-dopa therapy	Secondary
Graf 2005	Probable or definitive amyotrophic lateral sclerosis	Survival	Secondary
HOPE TOO 2005	History of CVD or diabetes in the presence of at least one additional cardiovascular risk factor	Cancer incidence, cancer deaths, major cardiovascular events, unstable angina, congestive heart failure, revascularization or amputation, all-cause mortality	Secondary
Limburg 2005	Patients with oesophageal dysplasia	Change in histological grade of oesophageal dysplasia	Secondary
MAVIS 2005	Elderly individuals irrespective of chronic illness	Self reported days of infection, use of health services, quality of life	Primary
Mooney 2005	Cigarette smokers	Level of an intermediate cancer risk marker	Primary
Tam 2005	Systemic lupus erythematosus	Effects on markers of oxidative stress, antioxidant defence and endothelial function	Secondary

Table 4. Participants and outcome measures of included trials with a low risk of bias (*Continued*)

WHS 2005	Female health professionals	Invasive cancer, fatal and non-fatal myocardial infarction, stroke, mortality	Primary
Witte 2005	Stable chronic heart failure due to Ischaemic heart disease	Left ventricular function, levels of proinflammatory cytokines, quality of life	Secondary
Rayman 2006	General population	Mood, quality of life, plasma selenium levels	Primary

Abbreviations:
BBC, basal cell carcinoma.
CVD, cardiovascular disease.
SSCC, squamous cell carcinoma of the skin.
SI conversion: to convert cholesterol values to mg/dL, divide by 0.0259.

Experimental interventions

Antioxidants were administered either alone, or in combination with antioxidants, minerals, or other interventions (Table 1; Table 2). All antioxidant supplements were administered orally. The dose and regimen of the antioxidant supplements were: beta-carotene 1.2 to 50.0 mg (mean 18 mg), vitamin A 1333 to 200,000 IU (mean 20219 IU), vitamin C 60 to 2000 mg (mean 497 mg), vitamin E 10 to 5000 IU (mean 570 IU), and selenium 20 to 200 µg (mean 99 µg) daily or on alternate days for 28 days to 12 years (mean 2.8 years). In one trial (Murphy 1992Low), antioxidants were applied in a single dose and participants were followed up for three months thereafter. The mean duration of follow-up in all trials was 3.4 years (range, 28 days to 14.1 years) (Table 2; Table 1).

Beta-carotene was tested in 25 trials, vitamin A in 15, vitamin C in 33, vitamin E in 54, and selenium in 21 trials. Beta-carotene was tested singly in 6 trials, vitamin A in 2, vitamin E in 24, vitamin C and selenium in 3 trials each.

The antioxidant supplements were given in the following combinations:

- beta-carotene and vitamin A
- beta-carotene and vitamin C
- beta-carotene and vitamin E
- vitamin A and vitamin C
- vitamin C and vitamin E
- vitamin E and selenium
- selenium and zinc
- beta-carotene, vitamin C, and vitamin E
- beta-carotene, vitamin C, vitamin E, and selenium
- beta-carotene, vitamin C, vitamin E, selenium, and zinc
- vitamin A, vitamin C, vitamin E
- vitamin A, vitamin C, vitamin E, selenium, and zinc
- vitamin A, vitamin C, vitamin E, selenium, methionine, and ubiquinone.

Control interventions

Sixty-three trials used placebo and four trials used no intervention in the control group (ter Riet 1995; GISSI 1999; PPP 2001; Takagi 2003).

Concomitant interventions

In 11 trials, participants were supplemented with different mixtures of antioxidants as well as with vitamins and minerals without antioxidant properties (Chandra 1992; NIT1 1993; NIT2 1993Low; Pike 1995Low; Hogarth 1996; AMDS 1996Low; Graat 2002Low; Allsup 2004Low; LAST 2004Low; MAVIS 2005 Low; Witte 2005Low).

In nine trials, the experimental and control groups were supplemented with vitamins and minerals (with or without antioxidant properties) (Gillilan 1977; Murphy 1992Low; Takamatsu 1995; ter Riet 1995; HATS 2001Low; Sasazuki 2003; Meydani

2004Low; DATATOP 2005Low; ADCS 2 2005). In six of the trials, the supplementation was with vitamin E 4 IU (Takamatsu 1995; Meydani 2004Low), vitamin A 1000 IU (Murphy 1992Low), vitamin C 20 mg and 50 mg (ter Riet 1995; Sasazuki 2003); riboflavin 10 mg (Gillilan 1977); or niacin 100 mg (HATS 2001Low).

In some of the factorial designed trials, other interventions were administered to some of the participants in the antioxidant experimental arms and in the control arms. In the trials with factorial or parallel-group design, the additional interventions tested were multivitamins and minerals (zinc, copper, chromium); ubiquinone; L-methionine; omega-3 polyunsaturated fatty acids; citrus bioflavonoid complex; quercetin, bilberry extract, rutin (bioflavonoids); taurine; N-acetyl cysteine; L-glutathione; aged garlic; deprenyl-selegiline (selective monoamine oxidase B inhibitor); donepezil (acetylcholinesterase inhibitor); riluzole (modulator of glutamatergic neurotransmission); amoxicillin, metronidazole (antibiotics); bismuth subsalicylate; omeprazole (proton-pump inhibitor); aspirin; simvastatin (cholesterol-lowering drug); celecoxib (inhibitor of cyclooxygenase), and ramipril (angiotensin-converting enzyme inhibitor).

All-cause mortality

Fifty-eight of the trials published data on mortality. Mortality data were obtained from authors of a further nine trials (Jacobson 2000Low; de Waart 2001; Desnuelle 2001Low; White 2002Low; Collins 2003Low; Sasazuki 2003; Allsup 2004Low; DATOR 2004Low; Tam 2005Low). These trials represent the 67 included trials.

Excluded studies

The reason for exclusion of studies is given in the table 'Characteristics of excluded studies'.

Risk of bias in included studies

Forty-seven of the 67 trials (70.1%) had low-bias risk, ie, had adequate generation of the allocation sequence, allocation concealment, blinding, and follow-up. For an overview of the included trials with low risk of bias see Table 1 and Table 4.

Twenty trials had one or more unclear or inadequate methodological components. For an overview of the included trials with high risk of bias (low methodological quality) see Table 2 and Table 3.

Sixty-six trials reported losses to follow-up. The exact number of participants lost to follow-up separately for each group was reported in 65 trials. There was not a substantial difference in the losses to follow-up between the intervention group and the control group (2669 out of 108,480 (2.5%) versus 2593 out of 91168 (2.8%))

Effects of interventions

Mortality in all trials

A total of 17880 of 136,023 participants (13.1%) randomised to antioxidant supplements and 10136 of 96527 participants (10.5%) randomised to placebo or no intervention died. In random-effects meta-analysis, antioxidant supplements had no significant effect on mortality (RR 1.02, 95% CI 0.99 to 1.06). In fixed-effect meta-analysis, antioxidant supplements significantly increased mortality (RR 1.04, 95% CI 1.02 to 1.06). There was no significant intertrial heterogeneity (I^2 = 13.1%)(Analysis 1.1).

Sensitivity analyses taking trials with zero events into account

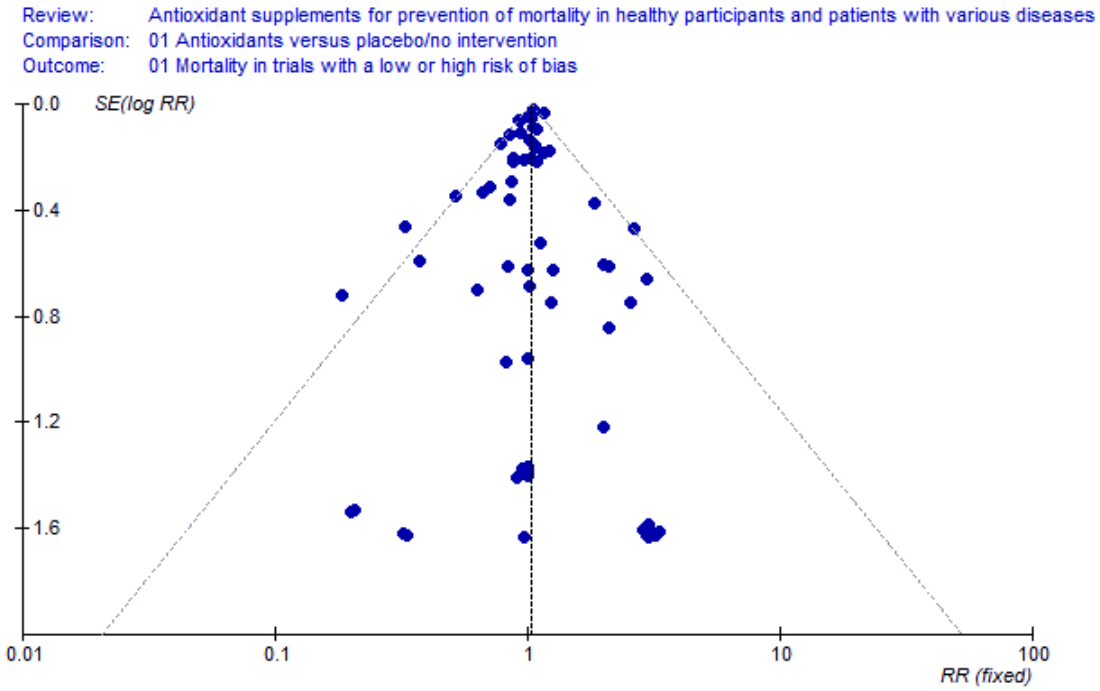
We included 14 trials with zero mortality in one arm. To account for the potential influence of these trials, we calculated the RR with 0.5, 0.05, and 0.005 as empirical continuity corrections (Sweeting 2004; Bradburn 2007). The random-effects model RR for the three continuity corrections were RR 1.02, RR 1.02, and RR 1.03. All three analyses were insignificant. The fixed-effect models with the same corrections were all showing significantly increased mortality in the antioxidant group and found the RR 1.04 in all three analyses.

Overall, 405 trials had zero mortality in both the experimental and control groups. These trials are excluded from the meta-analyses using RR as association measure. The total number of participants in these trials was about 40000. Therefore we performed exploratory analyses adding an imagined trial with 1 death and 20000 participants in each intervention group. The influence of zero events trials on our final result was not noticeable.

Analyses of bias risk

Inspection of the funnel plot in Figure 2 suggests potential bias (asymmetry). The adjusted-rank correlation test (P = 0.41) and regression asymmetry test (P = 0.21) found, however, no significant evidence of bias.

Figure 2. Funnel plot - overall mortality



Meta-regression analyses

Univariate meta-regression analyses revealed that the following covariates were significantly associated with estimated intervention effect on mortality: bias-risk (RR 1.17; 95% CI 1.05 to 1.30, P = 0.004) and dose of beta-carotene (RR 1.004, 95% CI 1.009 to 1.007; P = 0.013), dose of vitamin A (RR 1.000006, 95% CI 1.000002 to 1.000009, P = 0.003), and dose of selenium (RR 0.998, 95% CI 0.997 to 0.999, P = 0.005). None of the other covariates (dose of vitamin C; dose of vitamin E; single or combined experimental antioxidant regimen; duration of supplementation; and primary or secondary prevention) were significantly associated with estimated intervention effect on mortality.

In multivariate meta-regression analysis including all covariates, low bias risk of the trials was associated with significantly higher estimated intervention effect on mortality (RR 1.16, 95% CI 1.04 to 1.29, P = 0.007), and dose of selenium was associated with significantly lower estimated intervention effect on mortality (RR 0.999, 95% CI 0.997 to 1.000, P = 0.013). None of the other covariates was significantly associated with the estimated intervention effect on mortality.

Intervention effects according to bias risk of trials (Analysis 1.1)

In trials with low-bias risk, mortality was significantly increased in the supplemented group (RR 1.05, 95% CI 1.02 to 1.08, P = 0.003) without significant heterogeneity (I^2 = 7.5%). Exploratory analysis adding an imagined trial with 1 death and 20000 participants in each study group had no noticeable effect on the results.

In trials with high-bias risk (low-methodological quality) mortality was significantly decreased in the supplemented group (RR 0.92, 95% CI 0.85 to 0.99, P = 0.03) without heterogeneity (I^2 = 0%). Exploratory analysis adding an imagined trial with 1 death and 20000 participants in each study group had no noticeable effect on the results.

The difference between the estimate of antioxidants on mortality in low- and high-bias risk trials was statistically significant by test of interaction (z = 3.2, P = 0.0014).

Random-effects and fixed-effect model meta-analyses

For an overview of the effect of the different antioxidant supplements on mortality in a random-effects or fixed-effect model see Table 5 and Table 6.

Table 5. Effects of antiox. suppl. vs placebo or no interv. - random-effects model

Supplement	Number of trials	Participants number	RR (95%CI)	Heterogeneity (%)
Beta-carotene given singly	6	40977	1.05, 1.00-1.11	11.8

Table 5. Effects of antiox. suppl. vs placebo or no interv. - random-effects model (*Continued*)

Beta-carotene given in combination with other antioxidant supplements	21	139516	1.02, 0.95-1.08	50.6
Beta-carotene given singly or in combination with other antioxidant supplements	24	172755	1.02, 0.96-1.08	47.5
Beta-carotene given singly or in combination with other antioxidant supplements after exclusion of high-bias risk trials	19	150258	1.05, 1.00-1.10	38.4
Beta-carotene given singly or in combination with other antioxidant supplements after exclusion of high-bias risk and selenium trials	12	132610	1.07, 1.02-1.11	34
Beta-carotene given singly or in combination with other antioxidant supplements - high-bias risk trials	5	22497	0.81, 0.62-1.07	31.3
Vitamin A given singly	2	2406	1.18, 0.84-1.68	0
Vitamin A given in combination with other antioxidant supplements	14	42431	1.03, 0.90-1.19	33.9
Vitamin A given singly or in combination with other antioxidant supplements	16	44837	1.05, 0.93-1.19	26.1
Vitamin A given singly or in combination with other antioxidant supplements after exclusion of high-bias risk trials	11	25811	1.10, 0.96-1.26	14.8

Table 5. Effects of antiox. suppl. vs placebo or no interv. - random-effects model (*Continued*)

Vitamin A given singly or in combination with other antioxidant supplements after exclusion of high-bias risk and selenium trials	5	21677	1.16, 1.10-1.24	0
Vitamin A given singly or in combination with other antioxidant supplements - high-bias risk trials	5	19026	0.96, 0.84-1.08	0
Vitamin C given singly	3	826	0.88, 0.32-2.42	0
Vitamin C given in combination with other antioxidant supplements	32	69941	0.98, 0.91-1.06	10.2
Vitamin C given singly or in combination with other antioxidant supplements	33	70400	0.99, 0.92-1.06	68
Vitamin C given singly or in combination with other antioxidant supplements after exclusion of high-bias risk trials	23	46935	1.02, 0.96-1.08	5.9
Vitamin C given singly or in combination with other antioxidant supplements after exclusion of high-bias risk and selenium trials	13	29275	1.06, 0.94-1.20	10
Vitamin C given singly or in combination with other antioxidant supplements - high-bias risk trials	10	23210	0.93, 0.83-1.05	0
Vitamin E given singly	24	41341	1.02, 0.98-1.05	0

Table 5. Effects of antiox. suppl. vs placebo or no interv. - random-effects model (*Continued*)

Vitamin E given in combination with other antioxidant supplements	35	128681	1.02, 0.98-1.07	4.3
Vitamin E given singly or in combination with other antioxidant supplements	54	163454	1.02, 1.00-1.05	0
Vitamin E given singly or in combination with other antioxidant supplements after exclusion of high-bias risk trials	37	123761	1.04, 1.01-1.06	0
Vitamin E given singly or in combination with other antioxidant supplements after exclusion of high-bias risk and selenium trials	26	105065	1.04, 1.01-1.07	0
Vitamin E given singly or in combination with other antioxidant supplements - high-bias risk trials	17	39693	0.92, 0.85-0.99	0
Selenium given singly	3	1993	0.85, 0.68-1.07	0
Selenium given in combination with other antioxidant supplements	17	40924	0.91, 0.83-0.99	0
Selenium given singly or in combination with other antioxidant supplements	20	42916	0.90, 0.82-0.98	0
Selenium given singly or in combination with other antioxidant supplements after exclusion of high-bias risk trials	14	22446	0.90, 0.80-1.01	0

Table 5. Effects of antiox. suppl. vs placebo or no interv. - random-effects model (*Continued*)

Selenium given singly or in combination with other antioxidant supplements - high-bias risk trials	6	22390	0.90, 0.80-1.01	0
All antioxidant supplements given singly or in combination with other antioxidant supplements	67	232,550	1.02, 0.99-1.06	13.1

Table 6. Effects of antiox. suppl. vs placebo or no interv. - fixed-effect model

Supplement	Number of trials	Participants number	RR (95%CI)	Heterogeneity (%)
Beta-carotene given singly	6	40977	1.06, 1.02-1.10	11.8
Beta-carotene given in combination with other antioxidant supplements	21	139516	1.06, 1.03-1.09	50.6
Beta-carotene given singly or in combination with other antioxidant supplements	24	172755	1.05, 1.03-1.08	47.5
Beta-carotene given singly or in combination with other antioxidant supplements after exclusion of high-bias risk trials	19	150258	1.06, 1.04-1.09	38.4
Beta-carotene given singly or in combination with other antioxidant supplements after exclusion of high-bias risk and selenium trials	12	132610	1.07, 1.04-1.10	34.4
Beta-carotene given singly or in combination with other antioxidant supplements - high-bias risk trials	5	22497	0.88, 0.78-0.99	31.3

Table 6. Effects of antiox. suppl. vs placebo or no interv. - fixed-effect model (*Continued*)

Vitamin A given singly	2	2406	1.19, 0.84-1.68	0
Vitamin A given in combination with other antioxidant supplements	14	42431	1.10, 1.04-1.16	33.9
Vitamin A given singly or in combination with other antioxidant supplements	16	44837	1.10, 1.04-1.16	26.1
Vitamin A given singly or in combination with other antioxidant supplements after exclusion of high-bias risk trials	11	25811	1.14, 1.07-1.20	14.8
Vitamin A given singly or in combination with other antioxidant supplements after exclusion of high-bias risk and selenium trials	5	21677	1.16, 1.10-1.24	0
Vitamin A given singly or in combination with other antioxidant supplements - high-bias risk trials	5	19026	0.96, 0.84-1.08	0
Vitamin C given singly	3	826	0.89, 0.33-2.40	0
Vitamin C given in combination with other antioxidant supplements	32	69941	1.00, 0.95-1.06	10.2
Vitamin C given singly or in combination with other antioxidant supplements	33	70400	1.00, 0.95-1.05	68
Vitamin C given singly or in combination with other antioxidant supplements after exclusion of high-bias risk trials	23	46935	1.02, 0.96-1.08	5.9

Table 6. Effects of antiox. suppl. vs placebo or no interv. - fixed-effect model (*Continued*)

Vitamin C given singly or in combination with other antioxidant supplements after exclusion of high-bias risk and selenium trials	13	29275	1.05, 0.99-1.12	10.3
Vitamin C given singly or in combination with other antioxidant supplements - high-bias risk trials	10	23210	0.93, 0.82-1.04	0
Vitamin E given singly	24	41341	1.02, 0.98-1.05	0
Vitamin E given in combination with other antioxidant supplements	35	128681	1.03, 1.00-1.06	4.3
Vitamin E given singly or in combination with other antioxidant supplements	54	163454	1.02, 0.99-1.05	0
Vitamin E given singly or in combination with other antioxidant supplements after exclusion of high-bias risk trials	37	123761	1.03, 1.01-1.06	0
Vitamin E given singly or in combination with other antioxidant supplements after exclusion of high-bias risk and selenium trials	26	105065	1.04, 1.01-1.07	0
Vitamin E given singly or in combination with other antioxidant supplements - high-bias risk trials	17	39693	0.92, 0.85-0.99	0
Selenium given singly	3	1993	0.85, 0.68-1.07	0
Selenium given in combination with other antioxidant supplements	17	40924	0.90, 0.82-0.98	0

Table 6. Effects of antiox. suppl. vs placebo or no interv. - fixed-effect model (*Continued*)

Selenium given singly or in combination with other antioxidant supplements	20	42916	0.89, 0.82-0.97	0
Selenium given singly or in combination with other antioxidant supplements after exclusion of high-bias risk trials	14	20707	0.89, 0.79-1.00	0
Selenium given singly or in combination with other antioxidant supplements - high-bias risk trials	6	22390	0.90, 0.80-1.01	0
All antioxidant supplements given singly or in combination with other antioxidant supplements	67	232,550	1.04, 1.02-1.06	13.1

Primary and secondary prevention (Analysis 1.2)

In primary prevention trials with low-bias risk, mortality was not significantly increased in the supplemented group in random-effects analysis (RR 1.05, 95% CI 0.98 to 1.12, P = 0.18), but significantly increased in a fixed-effect analysis (RR 1.06, 95% CI 1.04 to 1.10, P < 0.0001) with significant heterogeneity (I^2 = 46.9%).

In primary prevention trials with high-bias risk, mortality was not significantly influenced by supplements (RR 0.95, 95% CI 0.85 to 1.06, P = 0.33, I^2 = 0%).

In secondary prevention trials with low-bias risk, mortality tended to be increased in the supplemented group (RR 1.03, 95% CI 0.98 to 1.08, P = 0.20, I^2 = 0%).

In secondary prevention trials with high-bias risk, mortality was significantly reduced by supplements (RR 0.89, 95% CI 0.80 to 1.00, P = 0.04) without significant heterogeneity (I^2 = 25.5%).

As stated above, meta-regression analysis did not find significant difference in the estimated intervention effects in primary and secondary prevention trials.

Sensitivity analyses excluding trials with co-administration of additional supplements to the experimental group (Analysis 1.3)

Sensitivity analyses excluding 11 trials that used co-interventions in the form of extra vitamins or trace elements with or without antioxidant functions in the experimental group did not noticeably change our results. In the 39 low-bias risk trials antioxidant supplements significantly increased mortality (RR 1.05, 95% CI 1.02 to 1.09, P = 0.0004) without significant heterogeneity (I^2 = 5.2%).

Sensitivity analyses excluding trials with co-administration of additional antioxidant supplements to both the experimental and control groups (Analysis 1.4)

Sensitivity analyses excluding nine trials that used co-interventions in the form of extra vitamins in both the experimental and control groups did not noticeably change our results. In the 43 low-bias risk trials antioxidant supplements significantly increased mortality (RR 1.05, 95% CI 1.01 to 1.08, P = 0.01) without significant heterogeneity (I^2 = 12.6%).

Sensitivity analysis excluding factorial trials testing collateral interventions (Analysis 1.5)

Sensitivity analysis excluding factorial trials testing collateral interventions which could lead to potential confounding did not noticeably change our results. In the 34 trials with low-bias risk, mortality was significantly increased in the supplemented group (RR 1.11, 95% CI 1.05 to 1.17, P < 0.0001, I^2 = 0%).

Sensitivity analysis excluding trials with co-administration of additional supplements to experimental and control groups, and factorial trials testing collateral interventions (Analysis 1.6)

Sensitivity analysis excluding trials with co-administration of additional supplements to the experimental and control groups, and factorial trials testing collateral interventions did not noticeably

change our results. In the 24 trials with low-bias risk, mortality was significantly increased in the supplemented group (RR 1.12, 95% CI 1.07 to 1.19, P < 0.0001, I^2 = 0%). These trials explored the influence of beta-carotene, vitamin A, vitamin C, vitamin E, and selenium.

The estimate of mortality risk in the 24 low-bias risk trials without potential confounding interventions (1.12, 95% CI 1.07 to 1.19) compared to the estimate of mortality risk in the 48 low-bias risk trials with potential confounding (1.05, 95% CI 1.02 to 1.08) was significantly increased (z = -2.09; P = 0.036).

Sensitivity analysis excluding trials with co-administration of additional supplements to the experimental and control groups, factorial trials testing collateral interventions, and selenium trials (Analysis 1.7)

Sensitivity analysis excluding trials with co-administration of additional supplements to the experimental and control groups, factorial trials testing collateral interventions, and selenium trials did not noticeably change our results. In the 19 trials with low-bias risk, mortality was significantly increased in the supplemented group (RR 1.16, 95% CI 1.09 to 1.23, P < 0.00001, I^2 = 0%).

The estimate of mortality risk in the 19 low-bias risk trials without any potential confounding interventions (1.16, 95% CI 1.09 to 1.23) compared to the estimate of mortality risk in the 48 low-bias risk trials with potential confounding (1.05, 95% CI 1.02 to 1.08) was significantly increased (z = -2.92; P = 0.0035).

Sensitivity analyses according to type of antioxidant supplement

Beta-carotene

Beta-carotene used singly or in combination with other antioxidants had no significant effect on mortality when including all 25 trials (RR 1.02, 95% CI 0.97 to 1.08, I^2 = 45%), 20 low-bias risk trials (RR 1.05, 95% CI 1.00 to 1.10, I^2 = 35%), or 5 high-bias risk trials (RR 0.81, 95% CI 0.62 to 1.07, I^2 = 31%)(Analysis 1.8). After exclusion of high-bias risk and selenium trials, however, beta-carotene singly or combined significantly increased mortality in 12 trials (RR 1.07, 95% CI 1.02 to 1.11, I^2 = 34%) (Analysis 1.13; Table 5).

A fixed-effect model analysis found a significant harmful effect of beta-carotene when including all 25 trials (RR 1.05, 95% CI 1.03 to 1.08) or 20 low-bias risk trials (RR 1.06, 95% CI 1.04 to 1.09), but a significant beneficial effect in 5 high-bias risk trials (0.88, 95% CI 0.78 to 0.99) (Table 6).

Vitamin A

Vitamin A used singly or in combination with other antioxidants had no significant effect on mortality when including all 15 trials (RR 1.05, 95% CI 0.93 to 1.19, I^2 = 31%), 11 low-bias risk trials, (RR 1.09, 95% CI 0.93 to 1.28, I^2 = 23%), or 5 high-bias risk trials (RR 0.96, 95% CI 0.84 to 1.08, I^2 = 0%) (Analysis 1.9). After exclusion of high-bias risk and selenium trials, however, vitamin A singly or combined significantly increased mortality in 5 trials (RR 1.16, 95% CI 1.10 to 1.24, I^2 = 0%) (Analysis 1.14; Table 5).

A fixed-effect model analysis found a significant harmful effect of vitamin A when including all 15 trials (RR 1.10, 95% CI 1.04 to 1.16) or 11 low-bias risk trials (RR 1.14, 95% CI 1.07 to 1.20) (Table 6).

Vitamin C

Vitamin C used singly or in combination with other antioxidants had no significant effect on mortality when including all 33 trials (RR 0.99, 95% CI 0.92 to 1.06, I^2 = 4.7%), 23 low bias-risk trials (RR 1.01, 95% CI 0.93 to 1.10, I^2 = 5.9%), or 10 high-bias risk trials (RR 0.93, 95% CI 0.83 to 1.05, I^2 = 0%) (Analysis 1.10) After the exclusion of high-bias risk trials and selenium trials vitamin C given singly or combined had no significant effect on mortality in 13 trials (RR 1.06, 95% CI 0.94 to 1.20, I^2 = 10%) (Analysis 1.15; Table 5).

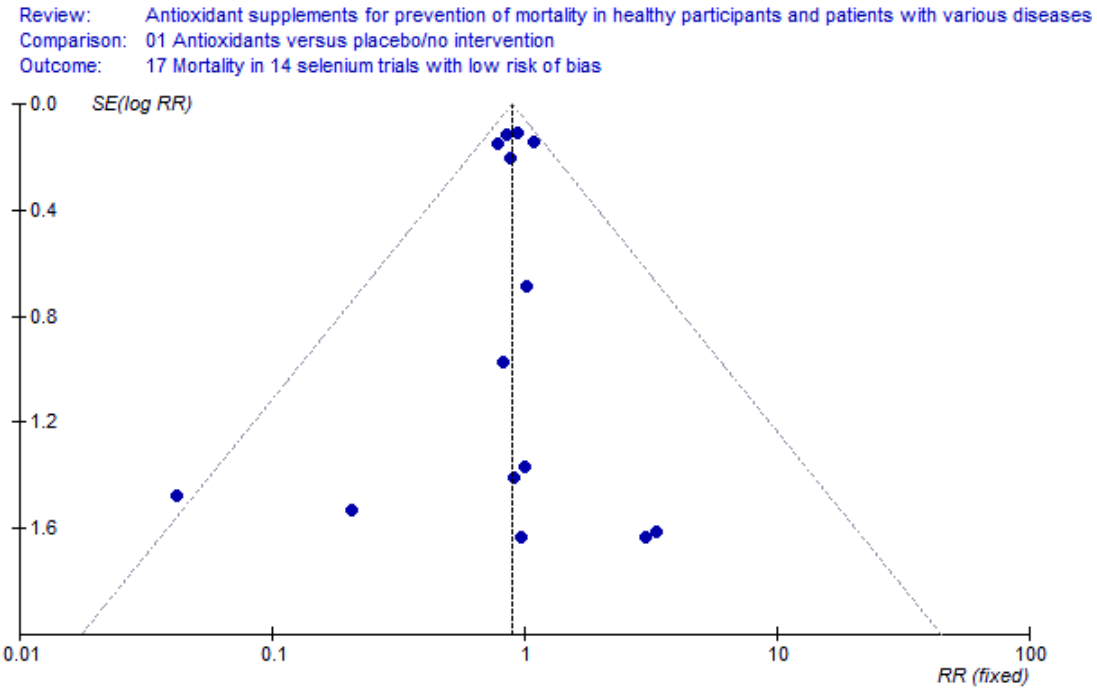
Vitamin E

Vitamin E used singly or in combination with other antioxidants had no significant effect on mortality when including all 54 trials (RR 1.02, 95% CI 1.00 to 1.05, I^2 = 0%). In 37 low-bias risk trials, vitamin E significantly increased mortality (RR 1.04, 95% CI 1.01 to 1.06, I^2 = 0%). In 17 high-bias risk trials, vitamin E significantly reduced mortality (RR 0.92, 95% CI 0.85 to 0.99, I^2 = 0%) (Analysis 1.11). Vitamin E given singly in high (more or equal to 1000 IU) or low dose (less than 1000 IU) did not significantly affect mortality (RR 1.07, 95% CI 0.91 to 1.25, I^2 = 0% and RR 1.01, 95% CI 0.98 to 1.05, I^2 = 0%, respectively). After exclusion of high-bias risk and selenium trials, vitamin E given singly or combined significantly increased mortality in 26 trials (RR 1.04, 95% CI 1.01 to 1.07, I^2 = 0%) (Analysis 1.16; Table 5).

Selenium

Selenium used singly or in combination with other antioxidants significantly decreased mortality when including all 20 trials (RR 0.90, 95% CI 0.83 to 0.98, I^2 = 0%). Selenium had no significant effect on mortality in 14 low-bias risk trials (RR 0.90 95% CI 0.80 to 1.01, I^2 = 0%), or 6 high-bias risk trials (RR 0.90, 95% CI 0.80 to 1.01, I^2 = 0%) (Analysis 1.12; Table 5). Inspection of funnel plot suggested asymmetry (Figure 3).

Figure 3. Funnel plot of 14 selenium trials with low risk of bias



DISCUSSION

Our systematic review contains a number of findings. Beta-carotene, vitamin A, and vitamin E given singly or combined with other antioxidant supplements significantly increase mortality. There is no evidence that vitamin C may increase longevity. We lack evidence to refute a potential negative effect of vitamin C on survival. Selenium tended to reduce mortality but only when high-bias risk trials were considered. Accordingly, we need more research on vitamin C and selenium. We confirmed that trials with inadequate bias control significantly overestimate intervention effects (Schulz 1995; Moher 1998; Kjaergard 2001; Bjelakovic 2004; Bjelakovic 2006). The detrimental effect of antioxidant supplements became significantly more pronounced when we excluded all trials with potential confounding. Our findings support and extend our previous findings regarding antioxidant supplements and increased mortality (Bjelakovic 2004).

Fixed-effect model and random-effects model meta-analyses

The fixed-effect model meta-analysis assumes that the true intervention effect is the same in every randomised trial, ie, the effect is fixed across trials. The random-effects model assumes that the effects being estimated based on the different randomised trials differ, but follow some general distribution. When there is no heterogeneity (I^2 = 0%), then fixed- and random-effects meta-analyses tend to give the same result. With increasing heterogeneity, then the estimated intervention effect as well as the corresponding 95% confidence interval will differ between the two models.

The meta-analyses we conducted included a heterogeneous set of randomised trials, eg, healthy participants or patients, single antioxidant supplement or combination, short duration of follow-up or long duration. These aspects could argue for only employing the random-effects model. We were requested to do so in our sister publication of the present review in JAMA (Bjelakovic 2007a). The standard random-effect model used in RevMan Analysis (RevMan 2003) is the DerSimonian and Laird method, which models the known differences between trials by incorporating a variance parameter tau^2 to account for across-trial variation (DerSimonian 1986). Adoption of the random-effects model in meta-analysis permits extension of inferences to a broader population of studies than the fixed-effect model does, which excludes the parameter tau^2 from the model.

The use of the random-effects model may come at a price. If there is between trial heterogeneity, then the weight of the large trials (usually providing more realistic estimates of intervention effects) becomes less. At the same time, the weight of small trials (usually providing more unrealistic estimates of intervention effects due to 'bias' (systematic errors) and 'chance' (random errors)) increases. We, therefore, also analysed our meta-analyses with the fixed-effect method. In all meta-analyses the pooled estimate of increased mortality in the antioxidant-supplemented group became more pronounced (Table 6). More of the meta-analyses became more significant or changed from non-significant to significant detrimental effects of vitamin A, beta-carotene, and vitamin E or borderline effects of selenium (Table 6).

The choice of statistical model for performing meta-analysis of sparse data is important (Sweeting 2004; Bradburn 2007). Because many methods are based on large sample approximations, they may be unsuitable when events are rare. Bradburn et al found that no method gives completely unbiased estimates (Bradburn 2007). At event rates below 1%, the Peto odds-ratio method appears to be the least biased and most powerful method when there is no substantial imbalance in treatment and control group sizes within trials, and treatment effects are not exceptionally large. Bradburn 2007 also demonstrated that the Peto odds ratio works well up to event rates around 10%. The calculation avoids addition of 0.5-event adjustments or any other adjustment. When we applied Peto odds ratio (a fixed-effect model analysis), we found even stronger support for detrimental effects of the supplements (for all 67 trials: 1.05; 95% CI 1.02 to 1.08; for the 47 low-bias risk trials: 1.07; 95% CI 1.04 to 1.10; after exclusion of high-bias risk trials and selenium trials, for beta-carotene: 1.09; 95% CI 1.06 to 1.13; for vitamin A: 1.20; 95% CI 1.12 to 1.29; for vitamin C: 1.06; 95% CI 0.99 to 1.14; and for vitamin E: 1.06; 95% CI 1.02 to 1.10). Again, our random-effects model analyses are supported and extended by the fixed-effect model analyses.

Strengths

Our review offers a number of strengths. It follows the overall plans of a published, peer reviewed Cochrane protocol (Bjelakovic 2003), taking into consideration our previous findings in a systematic review on antioxidant supplements for preventing gastrointestinal cancers (Bjelakovic 2004) and requests of having all preventive trials assessed (Forman 2004). Our review represents a comprehensive review of the topic, including 67 randomised trials with almost a quarter of a million participants. This increases the precision and power of our analyses (Higgins 2006).

Previous meta-analyses of preventive trials of antioxidant supplements have included less information (lung cancer, 4 trials with 109,394 participants (Caraballoso 2003); cardiovascular diseases, 8 trials with 138,113 participants (Vivekananthan 2003); gastrointestinal cancers, 14 trials with 170,525 participants (Bjelakovic 2004); colorectal adenoma, 8 trials with 17620 participants (Bjelakovic 2006); cancer or preinvasive lesions, 7 trials with 5112 participants (Davies 2006); mortality, 19 trials with 135,967 participants (Miller 2005); as well as their efficacy and safety, 5 trials with 47289 participants (Huang 2006). Previous meta-analyses either found no beneficial effect or no harmful effect of the supplements (Caraballoso 2003; Vivekananthan 2003; Bjelakovic 2006;

Davies 2006; Huang 2006) or reported a significantly increased mortality (Caraballoso 2003; Vivekananthan 2003; Bjelakovic 2004; Miller 2005).

We conducted a thorough review with methodology following the recommendations of The Cochrane Collaboration (Higgins 2006) and findings of methodological studies (Schulz 1995; Moher 1998; Kjaergard 2001). More than two thirds of the included trials with more than 180,000 participants fall in the group of low-bias risk trials. This highlights the validity of our results (Schulz 1995; Moher 1998; Kjaergard 2001). Antioxidant supplements not only seem to be one of the most researched topics in the world, they also seem to be one of the most adequately researched questions. Usually, only a small proportion of trials use adequate methodologies (Gluud 2006a; Gluud 2006b).

Our meta-analyses had little trial heterogeneity. This increases the trustworthiness of our findings. Our analyses were robust to sensitivity analyses involving different imputations of mortality in the zero-event study groups. We gave full account of all 405 identified trials assessing the supplements having zero events in both intervention groups. These trials were mostly assessing short-term supplement administration and surrogate outcome measures. Our results were robust to exploratory analyses adding an imagined trial with 20000 participants and one death in each intervention group. Accordingly, the increased mortality does not seem to be an artefact created by exclusion of trials with zero events in both intervention groups (Sweeting 2004; Bradburn 2007). Furthermore, all-cause mortality should generally be connected with unbiased estimates (Wood 2008).

Our estimates of increased mortality in low-bias risk trials increased significantly when we excluded factorial trials as well as other trials with collateral interventions. These trials may all suffer from potential confounding from the collateral interventions. This highlights the potential dramatic public health consequences of our results.

A large number of unpublished trials on supplements may exist. Their results are more likely to have been either neutral or negative than to have shown beneficial effects (Dickersin 2003). Accordingly, our estimates of increased mortality are likely to be conservative.

Limitations

Our systematic review has several limitations. As with all systematic reviews, our findings and interpretations are limited by the quality and quantity of available evidence on the effects of specific supplements on mortality. The examined populations varied. The effects of supplements were assessed in the general population or in patients with gastrointestinal, cardiovascular, neurological, skin, ocular, renal, endocrinological, rheumatoid, and undefined diseases. These populations mostly came from countries without overt deficiencies of specific supplements. Accordingly, we are unable to assess how antioxidant supplements affect mortality in populations with specific needs.

We have compared antioxidants with different properties, given at different doses and duration, singly or combined. We are aware of the potential risks in assessing the effects of different types of antioxidants together with different mechanisms of action, biotransformation, and bioavailability. There are pros (Palace 1999; Vertuani 2004; Kawanishi 2005) and cons (Maxwell 1999) in the literature about vitamin A being antioxidant. We fully acknowledge this. Most trials assessed combinations of different supplements, which reflects the way supplements are marketed, sold, and taken by people (Balluz 2000; Millen 2004; Radimer 2004; Nichter 2006).

All available non-enzymatic antioxidants work differently in the human body, and most of them exert effects that are non-antioxidant. We are not able to point to the specific biochemical mechanisms behind the detrimental effects. We found that trials examining the individual supplements singly were rare. It has been suggested that antioxidant supplements may show interdependency and may have effects only if given in combination (Hercberg 1998).

Most trials investigated the effects of supplements administered at higher doses than those commonly found in a balanced diet, and some of the trials used doses well above the recommended daily allowances and even above the tolerable upper intake levels (Anonymous 2000a; Anonymous 2000b) (see Figure 4 for overview of recommended dietary allowance, tolerable upper intake level, and experimental doses and regimen used). Our meta-regression analyses revealed significant effects of dose of beta-carotene, vitamin A, and selenium on mortality. The duration of supplementation and follow-up differed among the trials. However, we found no significant effect of treatment duration on our results.

Figure 4. Recommended dietary allowance, tolerable upper intake level, experimental doses, and regimen used in antioxidant supplements

Antioxidant supplements	RDA*		TUIL**	Experimental doses	Median doses	Regimen
	Man	Woman				
Beta-carotene	ND		ND	1.2 to 50 mg	15.5 mg	Daily or on alternate days
Vitamin A	900 µg	700 µg	3000 µg	400 to 7500 µg‡	1650 µg	Daily
Vitamin C	90 mg	70 mg	2000 mg	60 to 2000 mg	450 mg	Daily
Vitamin E	15 mg	15 mg	1000 mg†	10 to 5000 mg	400 mg	Daily or on alternate days
Selenium	55 µg	55 µg	400 µg	20 to 200 µg	87.5 µg	Daily

ND – not determined

RDA* The Recommended Dietary Allowance is the average daily dietary intake level that is sufficient to meet the nutrient requirement of nearly all (97 to 98 per cent) healthy individuals in a particular life stage and gender group. The RDA is intended to be used as a goal for daily intake by individuals. RDA for vitamin A from Anonymous 2000a, and RDA for the other antioxidants from Anonymous 2000b.

TUIL Tolerable Upper Intake Level** is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects in almost all individuals. TUIL for vitamin A from Anonymous 2000a, and TUIL for the other antioxidants from Anonymous 2000b.

† The European Commission Scientific Committee on Food published its opinion on the tolerable upper intake level of vitamin E (SCF 2003). The TUIL was established as 270 mg for adults, rounded to 300 mg.

‡ One trial (Murphy 1992Low) is excluded here as it only administered vitamin A once in a dose of 200000 IU (60000 µg).

We only assessed all-cause mortality. We are not able to determine the cause of the increased mortality. It is likely that increased cancer and cardiovascular mortality are the main reasons for the increased all-cause mortality (Caraballoso 2003; Vivekananthan 2003; Bjelakovic 2004; Lawson 2007). Further study of causes of mortality is needed. Our results extend previous reviews (Caraballoso 2003; Vivekananthan 2003; Bjelakovic 2004; Miller 2005; Bjelakovic 2006; Davies 2006; Huang 2006; Bjelakovic 2007a) and guidelines (Ritenbaugh 1999; Atkins 2002; McKevith 2003) suggesting that antioxidant supplements may not be beneficial.

Our overall analyses should be evaluated with care as they include data from trials in which bias is likely as well a data from trials in which bias is less likely. Furthermore, our review include several trials, in which we cannot exclude confounding by other interventions examined in these trials. By excluding data from such trials our relative mortality risk rose from 1.05 to 1.16 in low-bias risk trials.

Beta-carotene, administered singly or in combination with other antioxidants had no significant effect on mortality. After exclusion of high-bias risk and selenium trials, beta-carotene singly or combined significantly increased mortality. Recent studies have suggested that beta-carotene may act as a co-carcinogen (Lee 2003; Paolini 2003).

Vitamin A used singly or in combination with other antioxidants had no significant effect on mortality. After exclusion of high-bias risk and selenium trials, vitamin A singly or combined significantly increased mortality. Recent research revealed that vitamin A can cause oxidative damage to deoxyribonucleic acid (Murata 2000)

We found that vitamin E given singly or combined with four other antioxidants had no significant effect on mortality. However, after exclusion of high-bias risk trials, vitamin E given singly or combined significantly increased mortality. This is in agreement with a recent meta-analysis (Miller 2005). The dose of vitamin E was without significant effect on mortality in our analysis. The chance that vitamin E may benefit seems low (Brown 2005; Devaraj 2005; Guallar 2005).

The trials in which vitamin C was applied singly or in different combinations with beta-carotene, vitamin A, vitamin E, and selenium found no significant effect on mortality. According to the confidence intervals, small beneficial or large harmful effects cannot be excluded. We calculated the proportion of participants who died in the trials in which participants took vitamin C alone. In the control group it was 0.019 and in the vitamin C group it was 0.017. With alpha set to 0.05 and power to 0.90, and a minimal relevant difference of 2% the required sample size would be 186,000 participants. We are still far from having examined a sufficient sample. Studies have demonstrated that vitamin C may act as both a pro-oxidant and as an antioxidant in vivo (Podmore 1998; Duarte 2005), current and future trials should be monitored closely for harm.

Selenium given singly or in combination with other supplements seemed to significantly decrease mortality, but after exclusion of high-bias risk trials, the effect disappeared. Inspection of the funnel plot of the low-bias risk trials on selenium suggested asymmetry. Results of ongoing randomised trials with selenium will likely increase our understanding of the effects of selenium (Klein 2003). Recently, a randomised trial and an observational study have shown that selenium may carry health risks (Bleys 2007a; Bleys 2007b; Stranges 2007). Therefore, current and any future trials should be monitored closely for harm.

Our findings contradict the findings of observational studies, claiming that antioxidants improve health (Machlin 1987; Diplock 1994; van Poppel 1997; Diplock 1998). Considering that more than 10% to 20% of the adult population (80 million to 160 million people) in North America and Europe may consume the assessed supplements (Balluz 2000; Millen 2004; Radimer 2004; Nichter 2006) the public health consequences may be substantial. We are exposed to intense marketing. This is also reflected by the high number of publications per included randomised trial found in the present review.

There are several possible explanations for the increased mortality induced by antioxidant supplements. Although oxidative stress has a hypothesised role in the pathogenesis of many chronic diseases, it may be the consequence of pathological conditions (Halliwell 2000). By eliminating free radicals from our organism, we interfere with some essential defensive mechanisms like apoptosis, phagocytosis, and detoxification (Simon 2000; Salganik 2001; Kimura 2005). Recent evidence suggest that inhibition of reactive oxygen species formation in cells decrease the life span of nematodes (Schulz 2007). Antioxidant supplements are not subjected to the same rigorous toxicity studies as other pharmaceutical agents (Bast 2002). Better understanding of mechanisms and actions of antioxidants in relation to a potential disease is needed (Ratnam 2006).

The methodological quality of some of the trials was assessed using the published reports, which may not reflect the actual design and bias risk of the trials. Only some authors responded to our requests for further information.

Because we examined only the influence of antioxidant supplements, our findings should not be translated to potential effects of fruits and vegetables. Furthermore, we did not examine the treatment effect of antioxidant supplements (tertiary prevention) in specific patient groups or the preventive effects of antioxidant supplements for patient groups with verified specific need for antioxidant supplements. Other systematic reviews should address these issues.

AUTHORS' CONCLUSIONS

Implications for practice

We found no convincing evidence that antioxidant supplements decrease mortality. Even more, beta-carotene, vitamin A, and vitamin E seem to increase mortality. Therefore, we cannot recom-

mend the use of antioxidant supplements as a primary and secondary preventive measure in the population groups studied in the present review.

Implications for research

More randomised trials seem to be needed to more firmly establish the potential effects of vitamin C and selenium. Due to the risks that such antioxidant supplements may harm, such trials should have independent data monitoring and safety committees that should regularly review the accumulating data and incorporate these data with the data of our present review as well as other emerging evidence.

Our review highlights the necessity that national and international laws and regulations require that anything sold to the public claiming health benefits should be subjected to adequate assessment of benefits and harms before market release.

The significant association between unclear or inadequate methodological quality and overestimation of intervention effects has again focused on the need for more objective assessment of preventive and therapeutic interventions.

The published trials included in the systematic review lacked important information. We suggest that researchers in future trials should seriously consider adopting the CONSORT Statement (CONSORT - Consolidated Standards of Reporting Trials: www.consort-statement.org).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ADCS 1 1997

Methods	Alzheimer's Disease Cooperative Study (ADCS 1) Randomised, double-blind, placebo-controlled trial with two-by-two factorial design. Generation of the allocation sequence: unclear, not reported. Allocation concealment: unclear, not reported. Blinding: adequate, identical placebo pills. Follow-up: adequate. The losses to follow-up were 7% in the placebo group, 5% in the selegiline group, 9% in the alpha-tocopherol group, and 6% in the selegiline and alpha-tocopherol group. Intention-to-treat analysis: yes. Sample-size calculation: yes.
Participants	Country: United States of America. Number of participants randomised: 341, older than 18 years, mean age 73 years, 65% females from 23 centres participating in the Alzheimers Disease Co-operative Study Inclusion criteria: patients with probable Alzheimer's disease of moderate severity, as measured by a Clinical Dementia Rating of 2, free of other central nervous system diseases, were not taking psychoactive medications, and were residing either at home or in a supervised setting with a care giver but not in a skilled-nursing facility. Exclusion criteria: none stated.
Interventions	The patients were randomly assigned to receive: group 1: selegiline 5 mg (n = 87), group 2: alpha-tocopherol 1000 IU (n = 85), group 3: selegiline and alpha-tocopherol (n = 85), group 4: placebo (n = 84). Selegiline was given in a dose of 5 mg twice a day, and a racemic mixture of dl-alpha-tocopherol was given in a dose of 1000 IU twice a day. Both agents were given in the morning and in the afternoon for two years.
Outcomes	The primary outcome measure was: the time to the occurrence of any one of the following outcomes: death; institutionalisation; loss of the ability to perform at least two of three basic activities of daily living (ie, eating, grooming, using the toilet), as measured by part 2 of the Blessed Dementia Scale; and severe dementia, defined as a Clinical Dementia Rating of 3. Secondary outcome measures were: measures of cognition, function, behaviour, and the presence or absence of extrapyramidal signs.
Notes	Compliance was monitored in two ways. At each visit, unused medication was returned and the pills were counted. Measures to counter poor compliance included additional phone contact or review of the correct medication dosing schedule with the appropriate caregivers. Compliance was also monitored with surveillance of serum tocopherol concentrations, and the level of selegiline was monitored by measuring amphetamine, its major metabolite, in the urine. Compliance with treatment was good. Urine samples were available from 318 patients for analysis of amphetamine levels. The proportion of patients with positive tests for selegiline was 93% in the combined

ADCS 1 1997 (*Continued*)

	group, 98% in the selegiline group, 11% in the alpha-tocopherol group, and 13% in the placebo group. Serum samples were available from 332 patients. The proportion of patients with positive tests for alpha-tocopherol was 91% in the combined group, 93% in the alpha-tocopherol group, 9% in the selegiline group, and 12% in the placebo group. Follow-up was conducted one month after enrolment and at three-month intervals for the remainder of the two-year trial period. At each interval, every effort was made to assess primary and secondary outcomes, regardless of whether an outcome measure had been reached or the medication had been discontinued. Study agents were supplied by Somerset Pharmaceuticals, Tampa, Fla. (Selegiline) and Hoffmann-LaRoche, Nutley, N.J. (alpha tocopherol).

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

ADCS 2 2005

Methods	Alzheimer's Disease Cooperative Study (ADCS 2). Randomised, double-blind, placebo-controlled trial with parallel group design. Generation of the allocation sequence: unclear, not reported. Allocation concealment: unclear, not reported. Blinding: adequate, identical placebo pills. Follow-up: adequate. A total of 230 (29.9%) participants discontinued treatment during the double-blind phase; 92 in the donepezil group, 72 in the vitamin E group, and 66 in the placebo group. Intention-to-treat analysis: yes. Sample-size calculation: no.
Participants	Country: United States and Canada. Number of participants randomised: 769, 417 (54%) men and 352 (46%) women, aged 55-90 years, mean age 72.9 years. Inclusion criteria: amnestic mild cognitive impairment (MCI), age 55-90 years, inclusive, study informant available, mini-mental state examination (MMSE) 24-30, adequate vision and hearing for neuropsychological testing, normal vitamin B12 level and thyroid function studies and non-reactive rapid plasma reagin, electrocardiogram normal or no clinically significant abnormalities, a clinical dementia rating (CDR) of 0.5, all participants and study informants signed written consent Exclusion criteria: significant cerebral vascular disease, depression, central nervous system infarct, infection or focal lesions of clinical significance on computed tomography or magnetic resonance Imaging, medical diseases or psychiatric disorders that could interfere with study participation, pregnant, lactating or of child bearing potential, taking vitamin supplements, other supplements or a multi-vitamin, restrictions on concomitant medication usage, including those with significant cholinergic or anticholinergic effects or potential adverse effects on cognition.

ADCS 2 2005 (*Continued*)

Interventions	Participants were randomly assigned to receive: group 1: 2000 IU of vitamin E, placebo donepezil, and a multivitamin daily (n = 257); group 2: 10 mg of donepezil, placebo vitamin E, and a multivitamin daily (n = 253); group 3: placebo vitamin E, placebo donepezil, and a multivitamin daily (n = 259); over a period of 3 years. The multivitamin contained 15 IU of vitamin E. The initial dose of donepezil was 5 mg daily, and the dose was increased to 10 mg after six weeks. The initial dose of vitamin E was 1000 IU daily, and the dose was increased to 2000 IU (1000 IU twice daily) after six weeks. If a participant had difficulty tolerating the higher dose of vitamin E or donepezil, the investigator could reduce the dose of either medication temporarily and then rechallenge with the higher dose. On verification by a central review committee that a participant met clinical criteria for Alzheimer's disease, the participant stopped taking donepezil or matching placebo in a blinded fashion and was offered open-label donepezil until he or she completed the study at month 36.
Outcomes	The primary outcome measure was: the time to the development of possible or probable Alzheimer's disease. The secondary outcome measures were: the scores for the mini-mental state examination (MMSE); the Alzheimer's Disease Assessment Scale, cognitive subscale (ADASCog); the global CDR (Clinical Dementia Rating); the CDR sum of boxes (the sum of individual CDR domain scores); the ADCS Mild Cognitive Impairment Activities of Daily Living Scale; the Global Deterioration Scale; and a neuropsychological battery of tests.
Notes	Compliance with treatment is not described. Supported by a grant from Pfizer and Eisai. DSM Nutritional Products donated the vitamin E.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Allsup 2004Low

Methods	Randomised, double-blind, placebo-controlled trial with parallel group design. Generation of the allocation sequence: adequate, using a computer generated list of random numbers in the order in which consent was obtained. Allocation concealment: adequate, the identities of placebo and supplement were kept with the manufacturer (Recip AB, Arsta, Sweden) and were not revealed to the researchers until all data had been analysed. Blinding: adequate, active intervention and placebo had identical appearance. Follow-up: adequate. Analysed for primary outcome were 61 (75.3%) participants in the active and 57 (68.7%) participants in the placebo group. Overall, 20 participants in the active and 26 participants in the placebo group were lost to follow-up. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: Great Britain Number of participants randomised: 164, mean age 83 (37% males). Inclusion criteria: older people (60 or older) living in nursing and residential homes able to give informed consent (abbreviated mental test score > 7), not having neoplastic disease, and not prescribed immunosuppressant medication at the time of recruitment. Exclusion criteria: taking multivitamin supplements, vitamin C, or vitamin B, previous adverse reaction to influenza vaccine.
Interventions	Participants were randomly assigned to receive: group 1: multivitamin and trace element supplement (vitamin A 2666 IU, vitamin D3 400 IU, vitamin E 60 mg, vitamin B1 1.2 mg, vitamin B2 1.4 mg, vitamin B6 3.0 mg, nicotinamide 14 mg, folic acid 0.6 mg, vitamin B12 200 µg, biotin 30 mg, calciumpantothenate 5 mg, vitamin C 120 mg, iron 12 mg, zinc 14 mg, copper 2 mg, iodine 150 µg, manganese 1 mg, chromium 50 µg, selenium 60 µg, molybdenum 100 µg, calcium 240 mg, and magnesium 100 mg, n = 81; group 2: placebo, n = 83. Tablets were taken over an 8-week period. Influenza vaccine was administered 4 weeks after tablet commencement.
Outcomes	The primary outcome was: response to influenza vaccine.
Notes	The nursing staff at each home were responsible for the administration of tablets.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

AMDS 1996Low

Methods	Age Related Macular Degeneration Study (AMDS) Randomised, double-blind placebo-controlled trial with parallel group design. Generation of the allocation sequence: adequate, on a computer. Group one and group two patients were randomised between capsule number 1601 (starch placebo) and capsule number 1602 (Ocugard) at each centre by the optometrist co-investigator. Allocation concealment: adequate, coded bottles. Both the capsule for the placebo and antioxidant group (Ocuguard) were formulated by independent laboratories, and an intermediary company was responsible for assigning and maintaining the identity of codes, labelling and distributing masked bottles of capsules to each Medical Centre pharmacy service, informing the Medical Centre of capsule identity in case of adverse reaction, and breaking the code. None of the optometrist and the registered dietician co-investigators and the participants knew of the identity of the capsules. Blinding: adequate, identical looking capsules. Follow-up: adequate. Attrition data were as follows: 71 patients at baseline, 61 patients at 6 months, 59 patients at 12 months, and 59 patients at 18 months. Overall 2 participants from active intervention arm and 1 participant from placebo arm were lost to follow-up. Intention-to-treat analysis: no. Sample size calculations: no.
Participants	Country: United States. Number of participants randomised: 71, 66 men (93%) and 5 women (7%), mean age 72 years. Inclusion criteria: monocular one line drop of acuity, not attributable to cataract, amblyopia, systemic or ophthalmic disease, loss of macular reflex, Retinal Pigment Epithelium disruption and drusen observable by 90 degrees lens stereoscopic evaluation. Exclusion criteria: greater than 1 year prior use of vitamins, veterans who were former prisoners of war and veterans who were chronic alcoholics with tobacco/nutritional amblyopia or gastrointestinal absorption disorders.
Interventions	Patients were randomly assigned to receive: group 1: antioxidants (beta-carotene 20,000 IU; vitamin E 200 IU; vitamin C 750 mg; citrus bioflavonoid complex 125 mg; quercitin 50 mg; bilberry extract 5 mg; rutin 50 mg; zinc picolinate 12.5 mg; selenium 50 µg; taurine 100 mg; n-acetyl cysteine 100 mg; l-glutathione 5 mg; vitamin B2 25 mg; chromium 100 µg (n = 39); group 2: starch placebo (n = 32); for a period of 18 months.
Outcomes	The primary outcome was: non-exudative age-related macular degeneration.
Notes	Compliance with treatment was not described. Trial agents were provided by Twin Laboratories, Inc., Ronkonkoma, NY.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

AREDS 2001Low

Methods	Age Related Eye Disease Study (AREDS). Randomised, double-blind, placebo-controlled trial. Generation of the allocation sequence: adequate, centrally by the Co-ordinating Centre using the on-site computers, with procedures to protect the integrity of randomisation. Multiple levels of data encryption ensured the integrity of the treatment assignment files. Allocation concealment: adequate. Each centre had two treatment assignment databases: one for patients without age-related macular degeneration (AMD); (category 1) containing approximately 100 records consisting of bottle numbers for placebo (five bottle numbers) or antioxidants (five bottle numbers), and one for patients with some AMD (categories 2, 3, or 4) containing approximately 420 records consisting of a different sequence of bottle numbers for placebo and antioxidants (ten bottle numbers each) as well as for zinc and antioxidant and zinc formulations ten bottle numbers each). Each treatment assignment database residing on the hard drives at each Clinical Center is encrypted and includes check numbers to insure tamper-free operation and proper sequential treatment assignments. The computerised randomisation system identified which of the two randomisation tables (category 1 compared to categories 2, 3, or 4) should be used for assigning a treatment, and the participant was randomly assigned a bottle number from the appropriate list. Blinding: adequate, identical placebo tablets. Follow-up: adequate. About 2.3% of participants were lost to follow-up. The rate of participants withdrawal from the trial medication was 14% by 60 months and 15% by the end of trial. This rates include participants lost to follow-up and current smokers, 24% of whom withdrew from the trial medication after the results from the clinical trials of beta-carotene and lung cancer were announced. Overall, the vital status was known for 4753 out of 4757 particcipants. Intention-to-treat analysis: yes. Sample-size calculation: yes.
Participants	Country: United States of America. Number of participants randomised: 4757; 56% female, aged 55 to 80 years, median age 68 years. Inclusion criteria: participants free of any illness or condition that would make long-term follow-up or compliance with study medications unlikely or difficult. On the basis of fundus photographs graded by a central reading centre, best corrected visual acuity, and ophthalmologic evaluations, participants were enrolled in one of several AMD categories. At least one eye of each participant was free from eye disease that could complicate assessment of AMD, lens opacity progression, or visual acuity, and that eye could not have had previous ocular surgery (other than cataract surgery). Exclusion criteria: illness or disorders (eg, history of cancer with a poor 7-year prognosis, major cardiovascular or cerebrovascular event within the last year, haemachromatosis) that would make long term follow-up or compliance with the study protocol unlikely or difficult. Persons bilaterally aphakic or pseudophakic were ineligible for AMD category one.

Interventions	Participants were divided into two clinical trials:
	AMD Trial (n = 128) and
	Cataract Trial (n = 4629).
	In the Cataract Trial participants were randomly assigned to receive:
	group 1: placebo (n = 1456);
	group 2: zinc 80 mg (as zinc oxide) (n = 869);
	group 3: beta-carotene 15 mg, vitamin C 500 mg, vitamin E 400 IU, (n = 1451);
	group 4: beta-carotene 15 mg, vitamin C 500 mg, vitamin E 400 IU and zinc (n = 853).

AREDS 2001Low (*Continued*)

	Two study medication tablets were to be taken each morning and two each evening, to meet the total daily dose requirement. Tablets were to be taken with food to avoid potential irritation of an empty stomach by zinc. Participants were followed up for an average of 6.3 years.
Outcomes	Primary outcome measures were: an increase from baseline in nuclear, cortical, or posterior subcapsular opacity grades or cataract surgery, and at least moderate visual acuity loss from baseline (> 15 letters).
Notes	Compliance with treatment was checked by random serum assessments. Compliance with treatment was excellent. Overall adherence was estimated to be 75% or greater (participants took > 75% of their study tablets) for 70% of participants at five years. At 60 months, 20% of participants (20% both for current smokers and former or non-smokers) reported taking some multivitamin supplement containing at least one of the study medication. In 1994 and 1996, AREDS participants were informed of the results of the Alpha-Tocopherol, Beta Carotene Cancer Prevention Study and the Beta-Carotene and Retinol Efficacy Trial suggesting potential harmful effects of beta-carotene among smokers. The trial was supported from Bausch & Lomb Inc, Rochester, NY. Additional information received through personal communication with the authors.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

ASAP 2003Low

Methods	The Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) Study. Randomised, partially double-blind, placebo-controlled trial with two-by-two factorial design. Generation of the allocation sequence: adequate, computer generated randomisation lists. Participants were randomised separately in four strata of approximately equal size. Allocation concealment: adequate, the masking was carried out by the provider of the supplements and delivered to the data centre of the Field Centre, Research Institute of Public Health, University of Kuopio. Blinding: adequate, tablets were identical in appearance, size, and colour. Follow-up: adequate. Of the 520 participants randomised, 440 (84.6%) completed the study and underwent the 6-year re-examination. overall, 55 participants in the three vitamin groups and 25 participants in the placebo group were lost to follow-up. Intention-to-treat analysis: yes. Sample-size calculation: yes.
Participants	Country: Finland. Number of participants randomised: 520, 256 men and 264 postmenopausal women, smoking and non smoking, aged 45 to 69 years with serum cholesterol > 5 mmol/L (193 mg/dL). Inclusion criteria: participants with hypercholesterolemia defined as serum cholesterol levels > 5 mmol/L (193 mg/dL). Exclusion criteria: regular intake of antioxidants, acetosalicylate, or any other drug with antioxidative properties, severe obesity (body mass index >32 kg/m2), type 1 diabetes, uncontrolled hypertension (sitting diastolic blood pressure >105 mm Hg), any condition limiting mobility, or severe disease shortening life expectancy. Premenopausal women and those taking oral oestrogen therapy were also excluded.

ASAP 2003Low (*Continued*)

Interventions	The study consisted of 8-week dietary counselling and placebo lead-in phase, a 3-year double-masked treatment period, and a 3-year open treatment period. The participants were randomly allocated to receive twice daily with meal:
	group 1: d-alpha tocopherol 91 mg (corresponding to 100 mg of d-alpha-tocopheryl acetate and 136 IU of vitamin E) (n = 130);
	group 2: 250 mg slow-release vitamin C (n = 130);
	group 3: both d-alpha-tocopherol and slow-release ascorbic acid in a single tablet (CellaVie), (n = 130);
	group 4: placebo only (n = 130);
	for a period of 6 years.

Outcomes	The primary outcome measure was: progression of carotid atherosclerosis.
Notes	Compliance with treatment was checked by random serum assessments. Of the 390 participants randomised to supplementation, 335 continued the study after 3 years and 256 (76.4%) took the supplements as instructed for 6 years, whereas 62 participants stopped the supplements during the first 3 study years and additional 18 participants during the last 3 study years. The mean plasma alpha-tocopherol and ascorbate concentration increased in 6 years in the group randomised to supplementation, and in the unsupplemented group decrease. Ferrosan A/S, Denmark, provided the vitamin supplements.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

ATBC 2003Low

Methods	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC). Randomised, double-blind, placebo-controlled trial with two-by-two factorial design. Generation of the allocation sequence: adequate, centrally by computer. Randomisation performed in blocks of eight within each of the study areas. Allocation concealment: adequate, coded capsule packs maintained centrally. Blinding: adequate, identical placebo capsules. Follow-up: adequate, no losses to follow-up. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: Finland. Number of participants randomised: 29,133 males. Inclusion criteria: male smokers (five or more cigarettes daily), aged 50 to 69 years, averaged 57.2 years of age at study entry, who lived in south-western Finland. Exclusion criteria: men with a prior cancer or with other serious illness, or who used vitamin E, vitamin A, or beta-carotene supplements in excess of predefined doses (> 20 mg, > 20000 IU, or > 6 mg, respectively), or anticoagulants.

Interventions	Participants were randomly assigned in four groups to receive:
	group 1: alpha-tocopherol 50 mg (n = 7286);
	group 2: beta-carotene 20 mg (n = 7282);
	group 3: alpha-tocopherol and beta-carotene, (n = 7278);

ATBC 2003Low (*Continued*)

	group 4: placebo (n = 7287); daily for five to eight years (median 6.1 years). All participants took a single capsule daily. The four trial intervention groups were well balanced for all baseline characteristics evaluated. The two-by-two factorial design allowed assessment of the two intervention agents independently, with one-half of participants receiving alpha-tocopherol (n = 14,564) and the other half not (n = 14,569); similarly, half of the participants received beta-carotene (n = 14,560) and half did not (n = 14,573). The study was conducted between 1985 and 1993 (mean 6.1 years). The active intervention continued through April 30, 1993 and postintervention follow-up until April 30, 2001. Mean follow-up time regarding incident cancers and cause-specific deaths was 12.1 years and overall mortality 14.1 years.
Outcomes	The primary outcome measure was: incidence of lung cancer. Secondary outcome measures were: incidence of other major cancers, overall and cause specific mortality and incidence of other diseases.
Notes	Compliance with treatment was assessed by counts of the remaining capsules at each visit, by measurement of serum alpha-tocopherol and beta-carotene levels after three years of supplementation, and by measurements in random serum samples throughout the study. Compliance with treatment was excellent with four out of five active participants taking more than 95% of the scheduled capsules. Dropout rate and compliance were similar between all four groups. All capsules were supplied by Hoffmann-La Roche, Basel, Switzerland. Additional information received through personal communication with the authors.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Bonelli 1998

Methods	Randomised, double-blind, placebo-controlled trial with parallel group design. Generation of the allocation sequence: unclear, not reported. Allocation concealment: unclear, not reported. Blinding: adequate, active intervention and placebo had identical appearance. Follow-up: adequate. Of 304 patients randomised, 233 (76.6%) underwent at least one endoscopic follow-up examination. Overall, 30 participants in the active treatment group and 41 participant in the placebo group were lost to follow-up. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: Italy. Number of patients randomised: 304, patients who had histologically confirmed adenomatous polyps removed from the colon, aged 25 to 75 years. Inclusion criteria: age 25 to 75 years, at least one histologically confirmed colorectal adenoma endoscopically removed with a clean colon as a result of the work up.

Bonelli 1998 (*Continued*)

	Exclusion criteria: Familiar adenomatous polyposis, inflammatory bowel diseases, polypectomy performed more than six months before randomisation, adenoma with invasive carcinoma, previous colorectal resection, invasive cancer at any site, life-threatening chronic heart, liver or kidney diseases, current use of vitamin or calcium supplements, mental disability precluding informed consent to participate and adherence to the treatment, patients with 10 adenomas or more and those with large sessile adenomas (3 cm or more in diameter). The clean colon after polypectomy was assessed by means of total colonoscopy. When a total colonoscopy was not feasible a double contrast barium enema was performed. Colonoscopy was scheduled on years one, three and five after randomisation.
Interventions	Patients were randomly assigned to receive: group 1: selenium 200 µg (l-selenemethionine), zinc 30 mg, vitamin A 6000 IU, vitamin C 180 mg, vitamin E 30 mg (n = 147); group 2: placebo (n = 157); daily for 5 years.
Outcomes	The primary outcome measure was: occurrence of metachronous adenomas detected at follow-up endoscopic examinations.
Notes	The overall 5 year actuarial compliance to the treatment was 51%. Of the 304 randomised patients, 233 (76.6%) underwent at least one endoscopic follow up examination: 117 in the active compound group and 116 in the placebo group. Active intervention and placebo were provided by Pharma Nord. Additional information obtained through personal communication with authors.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

CARET 2004Low

Methods	The Beta-Carotene and Retinol Efficacy Trial (CARET). Randomised, double-blind, placebo-controlled trial with two-by-two factorial design in a pilot phase and then one-by-one. Generation of the allocation sequence: adequate, permuted block design with random block size chosen uniformly among 8, 10, 12, 14, and 16. Allocation concealment: adequate, locked central database with the link between study identifier and intervention assignment; all data analyses were performed centrally; the analyses that involved intervention assignment were performed only by the Co-ordinating Center's statisticians using coded intervention assignment unknown to the statisticians; analyses involving the coded intervention assignments were seen only by CARET's Data and Safety Monitoring Board, Co-ordinating Center statisticians, and a single CARET investigator who saw no participants. Blinding: adequate, identical placebo capsules provided by a sponsor. Follow-up: adequate. The losses to follow-up were less than 2% at the end of treatment. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: United States of America. Number of participants randomised: 18314; 12025 males and 6289 females. Inclusion criteria: smokers, former smokers, and workers exposed to asbestos at high risk of developing lung cancer. A total of 4060 male workers, mean age 57 years, exposed to asbestos and 14254 heavy smokers (44% of whom were women), mean age 58 years, were randomised. The participants agreed to limit their supplemental intake of vitamin A to less than 5500 IU per day and to take no supplemental beta-carotene.
Interventions	CARET builds on the experience of two pilot studies performed in Seattle (1985-1988). The first pilot study initiated a phase III trial of the safety and efficacy of the study vitamins in 816 asbestos-exposed participants randomised to a daily combination of 15 mg 13-carotene and 25,000 IU retinol or a placebo medication. Participants were eligible up to age 74 and were not required to have a history of cigarette smoking; otherwise, the eligibility criteria were the same as for the asbestos-exposed population in CARET. The second pilot study was a phase II trial of the comparative safety of the study vitamins in heavy smokers. The eligibility criteria were identical to those for heavy smokers in CARET. Overall 539 men and 490 women were randomised to one of four intervention groups: group 1: a daily combination of 30 mg 13-carotene and 25,000 IU retinol; group 2: 30 mg 13-carotene only; group 3: 25,000 IU retinol only; group 4: placebo medication. All 1845 participants in the two pilot studies continue to be followed for outcomes in CARET, together with approximately 16,000 additional participants. Participants of CARET trial were randomly assigned to receive: group 1: combination of 30 mg beta-carotene and 25,000 IU vitamin A (n = 9420); group 2: placebo, (n = 8894). Both formulations were given as capsules. Beta-carotene beadlets were combined with retinyl palmitate in a single capsule and dispensed in bottles, which were weighed and their content checked. The design projected active intervention until late 1997. The CARET active intervention was stopped 21 months earlier because of clear evidence of no benefit and substantial evidence of possible harm. The average duration of follow-up was 10.0 years
Outcomes	The primary outcome measure was: the incidence of lung cancer. Other outcomes reported are: mortality rates, and incidence of other cancers.
Notes	Compliance was assessed by weighing the returned bottles to estimate the number of capsules remaining (in 85% of the assessments), or by relying on the participants own estimates (in 15% of the assessments). Compliance with treatment was excellent. Among the active participants, the mean rate of capsule consumption was 93% through five years of follow-up, with no significant differences between the treatment groups. Participants who stopped receiving study vitamins for any reason other than death were defined as inactive participants and were still followed for outcomes and counted in the analysis. As of December 15, 1995 ascertainment of vital status for more than 98% was complete. Active agents and placebos were

CARET 2004Low (*Continued*)

	purchased from Hoffmann-La Roche and formulated by Tischon Corporation. Data were extracted from the primary publication, but additional information was received through personal communication with the authors.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Chandra 1992

Methods	Randomised, double-blind, placebo-controlled trial. Generation of the allocation sequence: adequate, four blocks of 24 random numbers. Allocation concealment: unclear, not reported. Blinding: adequate, the supplement and the placebo appeared identical and were prepared specifically for this study. Follow-up: adequate. Five participants on placebo and 3 participants from the supplemented group withdrew from the trial for personal reasons. Intention-to-treat analysis: yes. Sample-size calculation: no.
Participants	Country: Canada. Number of participants randomised: 96 independently living, healthy elderly individuals aged 66 to 86 years, mean age 74 years, 41 men and 55 women. Inclusion criteria: independently living, healthy elderly individuals over 65 years of age. Exclusion criteria: none stated.
Interventions	Participants were randomly assigned to receive: group 1: vitamin A 400 µg retinol equivalents, beta-carotene 16 mg, thiamin 2.2 mg, riboflavin 1.5 mg, niacin 16 mg, vitamin B6 3.0 mg, folate 400 µg, vitamin B12 4.0 µg, vitamin C 80 mg, vitamin D 4 µg, vitamin E 44 mg, iron 16 mg, zinc 14 mg, copper 1 .4 mg, selenium 20 µg, iodine 0.2 mg, calcium 200 mg, and magnesium 100 mg (n = 48); group 2: placebo, calcium 200 mg and magnesium 100 mg (n = 48) for one year. Influenza vaccine was given four weeks before the end of the study. Participants with infection were treated appropriately with antimicrobial agents and supportive measures.
Outcomes	The primary outcome measures were: immunocompetence and occurrence of infection related illness.
Notes	Compliance was verified by interview at fortnightly visits and counting of leftover medication. There was no report about the compliance.

Chandra 1992 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

CHAOS 1996Low

Methods	Cambridge Heart Antioxidant Study (CHAOS). Randomised, double-blind, placebo-controlled trial. Generation of the allocation sequence: adequate, computer-generated lists. Allocation concealment: adequate, computer programme that used a random-number database to allocate treatment by blocks of two after clinical data had been entered. Blinding: adequate, identical placebo capsules. Follow-up: adequate, complete follow-up data were available in 98% of participants. There were no differences between the groups in completeness of follow-up (98% placebo, 97.8% active treatment). Overall 23 participants in the active and 19 participants in the placebo group were lost to follow-up. Intention-to-treat analysis: yes. Sample-size calculation: yes.
Participants	Country: United Kingdom. Number of participants randomised: 2002; 1690 men and 312 women, mean age 61.8 years. Inclusion criteria: angiographically proven coronary artherosclerosis. Exclusion criteria: prior use of vitamin supplements containing vitamin E.
Interventions	Participants were randomly assigned to receive: group 1: vitamin E 800 IU, and then 400 IU (free 2R,4'R,8'R-alpha-tocopherol from natural sources in soya oil) (n = 1035): 546 patients received 800 IU daily for a median of 731 days (range 3 to 981), and 489 newly recruited patients received 400 IU daily for a median of 366 days (8 to 961). These two groups are not distinguished in the analysis. group 2: matching placebo (oil only), (n = 967). Median follow-up was 510 days (range 3 to 981).
Outcomes	The primary outcome measures were: non-fatal myocardial infarction alone and combination of non-fatal myocardial infarction and cardiovascular death.
Notes	Compliance with treatment was measured as the ratio of days that study medication was requested to per-protocol days prescribed. 73.2% of all prescribed alpha-tocopherol or placebo were requested as follow-up medications. There was no difference between treatment groups in the proportion of participants who were 100% compliant with the trial medication (48% placebo, 49% alpha-tocopherol). Study agents were supplied by Henkel Corporation (La Grange, Illinois, USA) Data were extracted from Mitchinson MJ, Stephens NG, Parsons A, Bligh E, Schofield PM, Brown MJ. Mortality in the CHAOS trial. Lancet 1999;353:381-2.

CHAOS 1996Low (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Collins 2003Low

Methods	Randomised, double-blind, placebo-controlled trial with two-by-two factorial design. Generation of the allocation sequence: adequate, using computer generated permuted blocks. Allocation concealment: adequate, for the vitamin E randomisation sequence was given to research pharmacist and the prescription bottles were coded. Experimental and control assignments were in sealed envelopes. Blinding: adequate, identical placebo capsules. Follow-up: adequate. Six randomised participants did not complete the study; 1 participant from the exercise and vitamin E group, 3 participants from exercise plus placebo group, and 2 participants from the placebo group. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: United States of America. Number of participants randomised: 52, mean age 67, 98% males. Inclusion criteria: current diagnosis of peripheral arterial disease, a history of intermittent claudication, and an ankle-brachial index < 0.95 at rest and/or < 0.85 after exercise. Exclusion criteria: taking any of the following drugs, vitamin E, Coumadin, or pentoxifylline.
Interventions	Participants were randomly assigned in four groups to receive: group 1: PoleStriding exercise with vitamin E (n = 13); group 2: PoleStriding exercise with placebo (n = 14); group 3: vitamin E without PoleStriding exercise (n = 13); group 4: placebo without exercise (n = 12). The dose of vitamin E was 400 IU daily. Participants were supplemented 0.5 year, and followed 2.5 years. PoleStriding is a form of walking that uses muscles of the upper and lower body in a continuous movement similar to cross country skiing.
Outcomes	The primary outcome was: walking ability and perceived quality of life.
Notes	Compliance with the study drug treatment was monitored in two ways: patient self-report and measured vitamin E levels. Vitamin E levels were obtained at baseline and 3 and 6 months. Investigators did not receive the measured vitamin E levels until the trial ended. For the first 3 months drug compliance was assessed biweekly by the study staff and monthly thereafter. Vitamin E and placebo capsules were provided by the Henkel Corporation, La- Grange, IL). Additional information received through personal communication with the authors.
Risk of bias	

Collins 2003Low (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Correa 2000Low

Methods	Randomised, controlled, partially double-blind, chemoprevention trial with two-by-two-by-two factorial design. Generation of the allocation sequence: adequate, computer-generated lists. Participants were randomly assigned in a single step, using a permuted block design, to one of eight different treatment regimens. Allocation concealment: adequate, coded capsules. Blinding: adequate, using identical placebo capsules. Follow-up: adequate, the average rate of loss was 4.3% per year over the six-year trial. Two hundred twenty-one participants withdrew from the study before their 72-month evaluation: 102 quitted treatment, 59 were lost to follow-up, 34 dropped out of the study because of pregnancy and other medical conditions, 18 died of causes unrelated to gastric cancer, and eight developed cancer other than gastric cancer. In one participant, the 72-month biopsy specimen was inadequate for histologic evaluation and determination of outcome. A total of 684 participants came to the 36-month biopsy; of those, 92% (631) came for the 72-month biopsy, there was a dropout rate of 2.6% per year for the last three years of the trial. Overall 24 participants from the placebo group, 25 from anti-Helicobacter pylori (anti-HP), 34 from the beta carotene (BC), 23 from the ascorbic acid (AA), 20 from the anti-HP + BC, 23 from anti-HP + AA, 17 from BC + AA, and 37 from anti-HP + BC + AA were lost to follow-up. Intention-to-treat analysis: no. Sample size calculations: no.
Participants	Country: Colombia. Number of participants randomised: 976; 46% males, aged 29 to 69 years, mean age 51.1 years. Inclusion criteria: preliminary histologic diagnosis of multifocal atrophic gastritis with or without intestinal metaplasia and dysplasia, good health. Exclusion criteria: normal histology, non-atrophic gastritis, gastric cancer. Before randomisation, participants were classified into one of three strata: atrophy (without metaplasia), intestinal metaplasia, or dysplasia, according to baseline histologic diagnosis.

Interventions	Participants were assigned to a dietary supplement of beta-carotene (30 mg once per day) and/or ascorbic acid (1 g twice a day) or their corresponding placebos, for a six-year period. The prevalence of Helicobacter pylori infection among all gastric biopsy specimens was 97%. Anti-Helicobacter pylori treatment consisting of amoxicillin (500 mg three times per day), metronidazole (375 mg three times per day), and bismuth subsalicylate (262 mg three times per day) was given for 14 days to half of the study participants assigned randomly. This treatment was not blinded or placebo controlled because an appropriate placebo was not available for bismuth subsalicylate.
	Participants were divided in eight treatment groups to receive:
	group 1: placebo (n = 117);
	group 2: anti-Helicobacter pylori treatment, which consisted of amoxicillin, metronidazole, and bismuth subsalicylate (n = 120);
	group 3: beta-carotene (n = 117);

Correa 2000Low (*Continued*)

	group 4: ascorbic acid (n = 130); group 5: Helicobacter pylori treatment, which consisted of amoxicillin, metronidazole, and bismuth subsalicylate, and additionally beta-carotene (n = 126); group 6: Helicobacter pylori treatment, which consisted of amoxicillin, metronidazole, and bismuth subsalicylate, and additionally ascorbic acid (n = 111); group 7: beta-carotene and ascorbic acid (n = 121); group 8: Helicobacter pylori treatment, which consisted of amoxicillin, metronidazole, and bismuth subsalicylate, and additionally beta-carotene and ascorbic acid (n = 134). Gastric biopsy specimens taken at baseline were compared with those taken at 72 months.
Outcomes	The primary outcome measures were: progression, no change or regression of gastric precancerous lesions (preliminary histologic diagnosis of multifocal atrophic gastritis with or without intestinal metaplasia and dysplasia). For our purposes we extracted data about the incidence of gastric cancer. We have also extracted data on overall mortality for all antioxidants as well as for beta-carotene and vitamin C.
Notes	Compliance with treatment was constantly encouraged and monitored by a social worker who interviewed the participants and recorded pill counts every three months. In addition, blood levels of beta-carotene and ascorbic acid were measured every three months in a 20% random sample of the participants. Compliance with treatment among participants who completed the study was high for all intervention modalities (mean compliance for ascorbic acid, 91.8%; for beta-carotene, 92.3%; and for anti-Helicobacter pylori treatment, 99.1%). Active medication and placebos were provided like identical coded tablets by Hoffmann-La Roche Inc. (Nutley, NJ). Additional information received through personal communication with the authors. Data were extracted from the article: Correa, et al. Re: Chemoprevention of gastric dysplasia: Randomized trial of antioxidant supplements and anti-Helicobacter pylori therapy. Journal of the National Cancer Institute 2001; 93: 559.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

DATATOP 2005Low

Methods	The Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP). Randomised, double-blind, placebo-controlled secondary prevention trial with two-by-two factorial design. Generation of the allocation sequence: adequate, centrally by computer. Allocation concealment: adequate, coded capsule packs maintained centrally. Blinding: adequate, identical placebo capsules. Follow-up: adequate, losses to follow-up almost equal in each treatment group. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: United States and Canada. Number of patients randomised: 800, 530 men and 270 women, 66% men, mean age 61 years. Inclusion criteria: early Parkinsons disease not requiring levodopa without severe postural instability (Parkinsons Disease at Hoehn and Yahr stage 1 or 2) within a 5 years of symptom onset and not yet requiring symptomatic therapy. Exclusion criteria: important comorbid illness, cognitive impairment (Mini Mental State examination score of < 23, or severe tremor (tremor score of >3 on the Unified Parkinsons Disease Rating Scale.
Interventions	Patients were randomly assigned to receive: group 1: vitamin E (dl-alpha-tocopherol; all-racemic) 1000 IU; group 2: deprenyl 5 mg; group 3: tocopherol and deprenyl; group 4: placebo; twice daily with morning and evening meals. 401 participants were assigned to tocopherol and 399 participants to deprenyl. Participants were instructed to take one tablet and one capsule twice daily with morning and evening meals. A standard multivitamin containing vitamin E (30 IU) was provided to all participants. Median duration of vitamin E exposure during the randomised phase was 2.6 years. Preliminary analysis in the fall of 1989, after an average 1.5 years of follow-up, indicated unexpectedly striking effects of deprenyl in postponing PD disability as measured by the need for levodopa therapy. After this disclosure, all active trial participants, whether or not they required levodopa therapy, were placed on open-label deprenyl, 10 mg/day, for about 3.5 years, from fall 1989 to spring 1993. Blinded tocopherol treatment assignments were maintained for about 3 years after the initial randomisation. Participants began taking levodopa (with carbidopa, a peripheral dopa decarboxylase inhibitor) in addition to their experimental treatments at any point in the trial when they were judged clinically to require therapy for emerging disability. Investigators adjusted levodopa dosage to achieve optimal clinical benefits and avoid dopaminergic adverse effects. Because of concerns about the sustained benefit of deprenyl, a second randomisation was undertaken in spring 1993. Consenting research participants who required levodopa were randomised, independently of their original randomisation, to continue deprenyl (50%) or to switch to deprenyl placebo (50%). Further adjustments of levodopa dosage were permitted after the second randomisation. This additional placebo-controlled phase of deprenyl assignment was continued for 2 years until the last formal (face-to-face) clinical evaluation in spring 1995. The 800 participants have therefore been followed at least annually for an average of 8.2 years. Participants who underwent the second randomisation had a minimum of 3.2 years and a maximum of 7.3 years of exposure to active deprenyl. Participants were followed 13 years.
Outcomes	The primary outcome in the trial occurred when, in the judgement of the enrolling investigator, a participant reached a level of functional disability sufficient to warrant the initiation of levo-dopa therapy. Operationally, the primary response variable in the trial was defined as the time from randomisation to the end point. After the outcome, the experimental treatments were withdrawn in blinded fashion, and approximately 30 days later the participants received a final evaluation.

DATATOP 2005Low (*Continued*)

Notes	Monitoring of compliance was carried out in follow-up evaluations in which unused doses return by the subject were counted, the serum tocopherol levels measured, and the urinary levels of amphetamine and metamphetamine metabolites of deprenyl determined. The results of the compliance monitoring were not shared with the participants or the investigators. Compliance in taking experimental medications was excellent among all treatment groups. The overall compliance rate, as a percentage of the doses dispensed that were actually taken, ranged from 97.9 to 99.5 percent for both tocopherol and deprenyl. Tablets of l-deprenyl and matching placebos were provided by Someret Pharmaceuticals, Denville; N.J. Capsules of d-l-alpha tocopherol and matching placebos were provided by Hoffman-LaRoche, Nutley, N.J. A standard vitamin (One-A-Day) by Miles Laboratories, Elkhart, Ind.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

DATOR 2004Low

Methods	Randomised, single-blind, placebo-controlled trial with parallel group design. Generation of the allocation sequence: adequate, block randomisation using the Geigy manual randomisation tables. Allocation concealment: adequate, sealed envelopes. Blinding: adequate, identical placebo capsules. Follow-up: adequate. During the course of the trial, 1 participant from each group dropped out - 1 participant due to thyroid dysfunction and 1 participant due to an accident. Intention-to-treat analysis: no. Sample size calculations: no.
Participants	Country: Belgium. Number of participants randomised: 24, mean age 51, 86% males. Inclusion criteria: type 1 diabetic patients attending the outpatient diabetes clinic having history of high serum cholesterol, (total cholesterol > 4.9 and LDL cholesterol > 3.0 mmol/L but Triglycerides < 4.5 mmol/L) and normal blood levels of thyroxin (9.7-23.4 pmol/L) and TSH (0.47-4.7µU/mL). Exclusion criteria: none reported.
Interventions	Participants were randomly assigned to receive: group 1: Atorvastastin® 20 mg together with 750 IU (504 mg) d-alpha-tocopherol; group 2: Atorvastastin® with placebo (280 mg soybean oil containing 0.25 mg tocopherol per capsule), daily. Participants were supplemented 0.5 years and followed 4.5 years.
Outcomes	The primary outcome measure was: impact on lipids and peroxidation during statin treatment.

DATOR 2004Low (*Continued*)

Notes	Omega-Pharma NV is acknowledged for the supply of alpha-tocopherol and placebo. Additional information received through personal communication with the authors. Due to the addition of 0.25 mg tocopherol to the control group, the 'placebo' control of the trial can be discussed.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

de la Maza 1995

Methods	Randomised, double-blind, placebo-controlled trial with parallel group design. Generation of the allocation sequence: unclear, not reported. Allocation concealment: unclear, not reported. Blinding: adequate, identical placebo tablets. Follow-up: adequate: 7 randomised participants were removed from the trial due to lack of compliance. Intention-to-treat analysis: no. Sample size calculations: no.
Participants	Country: Chile. Number of participants randomised: 74, mean age 50, 85% males. Inclusion criteria: clinical evidence of alcoholic liver disease at the time of enrolment (two or more of the following): jaundice, encephalopathy, ascites, oedema, spider nevi, marked collateral circulation, bleeding disorders, esophageal varices on endoscopy; a history of > 5 years of heavy alcohol consumption (daily alcohol intake > 150 g); absence of hepatitis B surface antigen; absence of significant renal, pulmonary or cardiac disease, clinical diabetes or malignant tumours (including hepatoma). Exclusion criteria: none mentioned.
Interventions	Patients were randomly assigned to receive: group 1: vitamin E 500 mg (in the form of alpha-tocopheryl acetate, n = 37; group 2: placebo, n = 37. Participants were supplemented and followed 1 year.
Outcomes	The primary outcome measure was: the liver function, mortality, and hospitalisation rates.
Notes	Patients were seen once a month by a nurse practitioner at the liver disease clinic. Patients were asked about compliance to the treatment, which was assessed by counting the leftover tablets. Blood samples were obtained at the beginning of the study and every 3 months to measure serum levels of vitamin E. Financing was provided by Roche and Saval Laboratories.

Risk of bias

de la Maza 1995 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

de Waart 2001

Methods	Randomised, double-blind, placebo-controlled trial with parallel group design. Generation of the allocation sequence: unclear, not reported. Allocation concealment: unclear, not reported. Blinding: adequate, identical looking capsules. Follow-up: adequate, 29 participants (13 in active and 16 in placebo groups) were lost to follow-up. Intention-to-treat analysis: no. Sample size calculations: no.
Participants	Country: The Netherlands. Number of patients randomised: 218 men, aged from 50 to 76 years, mean age 60 years. Inclusion criteria: male cigarette smokers aged 50 to 76 years. Exclusion criteria: diabetes patients, users of (multi)vitamin-, vitamin E, vitamin C, beta-carotene, garlic, or fish oil supplements, users of vitamin K antagonists (phenprocoumon, acenocoumarol), individuals with current illness interfering with participation, and unwillingness to participate.
Interventions	Participants were randomly assigned to receive: group 1: vitamin E (dl-alpha-tocopherol) 400 IU (n = 109); group 2: placebo (n = 109) for a period of 2 years. Mean follow-up time was 1.8 years.
Outcomes	The primary outcome measure was: progression of atherosclerosis in lifelong male smokers measured by 2-year change of the common carotid intima media thickness as measured by B-mode ultrasonography.
Notes	Compliance with treatment is not reported. Vitamin E or placebo capsules were provided by F Hoffman La Roche Ltd, Basel.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Desnuelle 2001Low

Methods	Amyotrophic Lateral Sclerosis riluzole-tocopherol study (ALSRT). Randomised, double-blind, placebo-controlled trial with parallel group design. Generation of the allocation sequence: adequate, randomisation schedule prepared by laboratory. Randomisation was balanced by centre. Allocation concealment: adequate, randomisation schedule prepared by laboratory and coded bottles. Blinding: adequate, identical looking capsules and tablets. Follow-up: adequate, no losses to follow-up. One hundred and forty-six patients (74 in the placebo group and 72 in the alpha-tocopherol group) did not complete the one-year treatment period. Intention-to-treat analysis: yes. Sample-size calculation: yes.
Participants	Country: France. Number of participants randomised: 288, 158 men and 130 women, mean age 64 years. Inclusion criteria: probable or definitive amyotrophic lateral sclerosis (ALS), according to El Escorial criteria, over 18 years of age at recruitment, to be able to fully understand the study information, have been treated with riluzole 950 mg b.i.d. for at least three months without presenting side effects. Exclusion criteria: signs of dementia and/or major psychiatric disorders, another concomitant serious disease, or handicap likely to interfere with their assessment of survival, forced vital capacity of less than 60%, monoclonal gammopathy, conduction blocks of motor nerves on electromyography, hepatic or renal disfunction, pregnancy or breast feeding, creatinine plasma concentration above 200 µM, alanine aminotransferase and/or aspartate transaminase activity greater than twice the upper limit of the normal range, known hepatic disease, taking drugs known to be hepatotoxic, enzyme-inducing or enzyme-inhibiting, taking vitamin E.

Interventions	Participants were randomly assigned to receive:
	group 1: vitamin E 500 mg plus riluzole 50 mg (n = 144);
	group 2: placebo (n = 144) plus riluzole 50 mg;
	one capsule (vitamin E) and one tablet (Riluzole) daily for one year.

Outcomes	The primary outcome measure was: change in functional status of each patient using the modified Norris limb scale. The secondary outcome measures were: survival (defined as the time to death or tracheostomy), bulbar function assessed with the Norris bulbar scale (total possible score 39) and manual muscle testing.
Notes	Compliance with treatment was checked by measuring the plasma vitamin E levels. Compliance with treatment good. In the vitamin E group, a highly significant increase in plasma levels of vitamin E was observed after 3 months of treatment. Study agents were supplied by: alpha-tocopherol (Toco 500R) Laboratories Rhone-Poulenc Rorer (now trading under the name Laboratories Aventis); riluzole Rhone-Poulenc Rorer. Additional information received through personal communication with the authors.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Gillilan 1977

Methods	Randomised, double-blind, placebo-controlled cross-over trial. Generation of the allocation sequence: unclear, not reported. Allocation concealment: unclear, not reported. Blinding: identical looking placebo capsule. Follow-up: adequate, 48 participants (of 52) completed the trial. There were no losses to follow-up. Intention-to-treat analysis: no. Sample size calculations: no.
Participants	Country: United States. Number of patients randomised: 52. Inclusion criteria: typical, stable, effort-related angina pectoris, and Q wave electrographic evidence of previous myocardial infarction and/or positive coronary arteriograms as defined by 75% obstruction at least one major coronary artery (31 patients). Exclusion criteria: none stated.

Interventions	Participants were randomly assigned to receive:
	group 1: vitamin E (d-alpha-tocopherol succinate) 1600 IU (n = 26);
	group 2: placebo (containing 2.5 mg of riboflavin), (n = 26);
	three capsules of vitamin E (400 IU) or placebo daily for a period of six months, and then cross-over.
	The mean duration of double-blind therapy was 189 days of vitamin E and 192 days of placebo.

Outcomes	The primary outcome measure was: any improvement of angina pectoris.
Notes	Drug adherence was followed by capsule count and a urine fluorescence test. Serum vitamin E levels were measured at baseline and at the end of the first and six months of each treatment phase. The capsule count data shows a mean consumption of 88% of the prescribed capsules during vitamin E phase, and 84% consumption during placebo therapy. The percent of urine specimens with fluorescence indicate 78% of taking placebo prescribed medication. The serum tocopherol levels were significantly higher during the supplementation. Vitamin E and placebo capsules supplied by Wilson and Wolfer Pharmaceutical Manufacturers and Distributors, Detroit, Michigen.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Girodon 1997

Methods	Randomised, double-blind, placebo-controlled trial with parallel group design. Generation of the allocation sequence: unclear, not reported. Allocation concealment: unclear, not reported. Blinding: adequate, identical looking capsules. Follow-up: adequate. There were no losses to follow-up. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: France. Number of participants randomised: 81 elderly participants, 20 males and 61 females, aged 65 to 102 years, with an average age of 84 years. Inclusion criteria: at least 65 years of age, only age related diseases (osteoarthritis, hypertension, residual stroke etc.), that required chronic care. Exclusion criteria: history of cancer, taking medication that might interfere with nutritional status, immunocompetence, or vitamin or mineral supplements.

Interventions	Participants were randomly assigned to receive:
	group 1: placebo (n = 20);
	group 2: trace elements (zinc 20 mg in a form of zinc sulfate; selenium 100 µg in a form of selenite) (n = 20);
	group 3: vitamins (vitamin C 120 mg; beta-carotene 6 mg; vitamin E 15 mg) (n = 20);
	group 4: combination of trace elements and vitamins at equal doses (n = 21);
	daily (one capsule a day) for a period of 2 years.
	Mean duration of follow-up was 730 days.

Outcomes	The primary outcome measure was: impact of a trace element and vitamin supplementation on infectious morbidity.
Notes	Compliance with treatment was checked by measuring the plasma vitamin levels and counting of the returned capsules. Compliance was good. After 6 months of supplementation, a significant increase in vitamin and trace element serum levels was obtained in the corresponding treatment groups: a plateau was then observed for the whole study. No changes appeared in the placebo group. Study agents were provided by Produits Roche SA.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

GISSI 1999

Methods	GISSI-Prevenzione trial (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico). Randomised clinical secondary prevention trial with two-by-two factorial design. Generation of the allocation sequence: adequate, computer programme based on the biased-coin algorithm, stratified by hospital. Allocation concealment: adequate, central randomisation over the telephone and by computer network. Randomisation data kept at the co-ordinating centre. Blinding: inadequate, there is no intervention in the control arm. Follow-up: adequate. Information on the vital status of patients at the end of the trial was available for 99.9% of the population. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: Italy. Number of participants randomised: 11324; 9659 males and 1665 females, mean age 59 years. Inclusion criteria: recent (< 3 months) myocardial infarction, informed written consent. Age limits were not defined. Exclusion criteria: contraindications to the dietary supplements (ie, known allergy to n-3 PUFA or alpha-tocopherol, or known congenital defects of coagulation), unfavourable short-term outlook (eg, overt congestive heart failure, cancers, etc).

Interventions	Patients were randomly assigned to four treatment groups to receive:
	group 1: n-3 PUFA alone (as 1 gelatin capsule containing 850 mg to 882 mg eicosapentaenoic acid and docosahexaenoic acid as ethyl esters in the average ratio of 1:2), 1 g daily (n = 2836);
	group 2: vitamin E alone, 300 mg daily (n = 2830);
	group 3: n-3 PUFA and vitamin E combined (n = 2830);
	group 4: no supplement (n = 2828);
	for 3.5 years.

Outcomes	The primary outcome measures were: cumulative rate of all-cause death, non-fatal myocardial infarction, and non-fatal stroke; and the cumulative rate of cardiovascular death, non-fatal myocardial infarction, and nonfatal stroke.
Notes	Compliance with treatment was measured by refilling drug supplies every three months. Compliance with assigned treatment was excellent. At year one and at the end of the study, 11.6% and 28.5% of patients receiving n-3 PUFA and 7.3% and 26.2% of those receiving vitamin E, respectively, had permanently stopped taking the study drug. Conversely, during the whole course of the study, only two patients not assigned vitamin E and 26 patients not assigned n-3 PUFA were receiving these drugs. The trial was supported by grants from Bristol-Myers Squibb, Pharmacia-Upjohn, Società Prodotti Antibiotici, and Pfizer. Pharmacia-Upjohn and Società Prodotti Antibiotici supplied marketed capsules containing 850 to 882 mg EPA/DHA ethyl esters. Vitamin E (acetyl d, l-a- tocopherol) was supplied by Bracco.

Risk of bias

Item	Authors' judgement	Description

GISSI 1999 (*Continued*)

Allocation concealment?	No	C - Inadequate

Graat 2002Low

Methods	Randomised, double-blind, placebo-controlled trial with two-by-two factorial design. Generation of the allocation sequence: adequate, a computer-generated, 4-per-block, randomisation list. Allocation concealment: adequate, randomisation list was created by the pharmacy allocating treatment to participant number. Numbered boxes containing identical looking capsules were transported from the pharmacy to the Wageningen University. At enrolment, boxes were assigned consecutively to participants. Treatment allocation was kept at the pharmacy exclusively in sealed opaque envelopes while participant identity was known exclusively at the Wageningen University. None of the treatment codes was broken during the study period. Blinding: adequate, identical looking placebo capsules. Follow-up: adequate. In total, 16% of the participants discontinued the treatment. Overall, 26 participants assigned to receive multivitamin-mineral, 25 to vitamin E, 26 to multivitamin-mineral plus vitamin E, and 20 to placebo were lost to follow-up. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: The Netherlands. Number of participants randomised: 652, 325 men and 327 women, older than 60 years. Inclusion criteria: noninstitutionalized elderly persons older than 60 years. Exclusion criteria: used immunosuppressive treatment, anticoagulants interfering with vitamin K metabolism, or dietary supplements in the previous 2 months or if they had a history of cancer, liver disease, or fat malabsorption during the 5 years before randomisation.

Interventions	Participants were randomly assigned to receive:
	group 1: multivitamins and minerals (n = 163);
	group 2: vitamin E 272 IU (n = 164);
	group 3: multivitamins and minerals plus vitamin E (n = 172);
	group 4: placebo (n = 153).
	The multivitamin-mineral capsule contained: retinol (600 µg), beta-carotene (1.2 mg), ascorbic acid (60 mg), vitamin E (10 mg), cholecalciferol (5 µg), vitamin K (30 µg), thiamin mononitrate (1.4 mg), riboflavin (1.6 mg), niacin (18 mg), pantothenic acid (6 mg), pyridoxine (2.0 mg), biotin (150 µg), folic acid (200 µg), cyanocobalamin (1 µg), zinc (10 mg), selenium (25 µg), iron (4.0 mg), magnesium (30 mg), copper (1.0 mg), iodine (100 µg), calcium (74 mg), phosphor (49 mg), manganese (1.0 mg), chromium (25 µg), molybdenum (25 µg), and silicium (2 µg). The vitamin E capsule contained 200 mg/dL of alpha-tocopheryl. Placebo capsules contained soybean oil. Quality control of the capsules after treatment showed no decrease in the original contents.
	Each participant received 2 capsules per day to be ingested with dinner for a maximum of 15 months.

Outcomes	The primary outcomes were: incidence and severity of acute respiratory tract infections.

Graat 2002Low (*Continued*)

Notes	Compliance with treatment was checked by measuring the plasma vitamin levels and counting of the returned capsules. Baseline plasma samples were collected for determination of alpha-tocopherol, ascorbic acid, retinol, and carotenoids. To monitor compliance, these assessments were repeated in a postintervention sample of a subset (n = 300). Returned capsules were counted for all participants. After treatment, ascorbic acid, total carotenoids, alpha-tocopherol, and cholesterol-adjusted alpha-tocopherol levels increased significantly in the multivitamin-mineral and multivitamin-mineral plus vitamin E group, while gamma-tocopherol decreased significantly. In the vitamin E group, alpha-tocopherol and cholesterol-adjusted alpha-tocopherol levels increased significantly, while gamma-tocopherol levels decreased significantly. In the placebo group, none of the measured vitamins changed significantly. 94% of the participants met the compliance criteria of 80% capsule intake. Trial agents were provided by Roche Vitamins, Europe, Basel, Switzerland.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Graf 2005Low

Methods	Randomised, double-blind, placebo-controlled trial with parallel group design. Generation of the allocation sequence: adequate, computer generated. Allocation concealment: adequate, central independent unit. Blinding: adequate, identical looking capsules. Follow-up: adequate, no losses to follow-up. Intention-to-treat analysis: yes. Sample size calculations: no.
Participants	Country: Germany. Number of participants randomised: 160, 104 males and 56 females, mean age 58 years with probable or definite amyotrophic lateral sclerosis (ALS). Inclusion criteria: patients with probable or definite amyotrophic lateral sclerosis (ALS) treated with riluzole and disease duration of less than 5 years. Exclusion criteria: none stated.
Interventions	Patients were randomly assigned to receive: group 1: vitamin E (alpha-tocopherol), 5000 mg (five times daily one capsule of 1000 mg) (n = 83); group 2: placebo (n = 77); for a period of 18 months.
Outcomes	Primary outcome measure was: survival, calculating time to death, tracheostomy, or permanent assisted ventilation. Secondary outcome measures were: the rate of deterioration of function assessed by the modified Norris limb and bulbar scales, manual muscle testing, spasticity scale, ventilatory function and the Sickness Impact Profile.

Graf 2005Low (*Continued*)

	Additional information obtained through personal communication with authors.
Notes	Compliance with treatment was checked by measuring the plasma vitamin E levels. Vitamin plasma levels were, as expected, significantly higher in the high dose vitamin E group than in the placebo group. Trial agents were provided by Schwarzhaupt, Cologne, Germany. Additional information obtained with personal communication with authors.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

HATS 2001Low

Methods	The HDL-Atherosclerosis Treatment Study (HATS). Randomised, double-blind, placebo-controlled trial with two-by-two factorial design. Generation of the allocation sequence: adequate, random numbers generated by computer. Allocation concealment: adequate, central independent unit. Blinding: adequate, identical placebo capsules. Follow-up: adequate. Vital status was ascertained at 38 months for all 160 patients enrolled. Follow-up information for 159 patients was complete, including records of events from the patient's physicians. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: United States and Canada. Number of participants randomised: 160, mean age 53 years, 13 % female. Inclusion criteria: men (younger than 63 years of age) and women (younger than 70 years of age) with clinical coronary disease (defined as previous myocardial infarction, coronary interventions, or confirmed angina) and with at least three stenoses of at least 30 percent of the luminal diameter or one stenosis of at least 50 percent. All had low levels of HDL cholesterol (35 mg per decilitre [0.91 mmol per litre] or lower in men and 40 mg per deciliter [1.03 mmol per litre] in women), LDL cholesterol levels of 145 mg per deciliter (3.75 mmol per litre) or lower, and triglyceride levels below 400 mg per decilitre (4.52 mmol/L). Exclusion criteria: lipid levels outside of the specified ranges, coronary bypass surgery, severe hypertension, recent gout, or liver, thyroid, or kidney disease, or uncontrolled diabetes.

Interventions	Patients were randomly assigned to receive:
	group 1: simvastatin (10 mg to 20 mg) plus niacin (500 mg to 4 g), (n = 33);
	group 2: antioxidant vitamins, 800 IU of vitamin E (as d-alpha-tocopherol), 1000 mg of vitamin C, 25 mg of natural beta-carotene, and 100 µg of selenium;
	group 3: simvastatin plus niacin plus antioxidants (n = 40).
	group 4: all placebos (n = 34);
	for three years.

HATS 2001Low (*Continued*)

	Simvastatin therapy began at 10 mg per day for patients with an LDL cholesterol level of 110 mg per decilitre (2.84 mmol per litre) or lower on screening and 20 mg per day for those with an LDL cholesterol level higher than 110 mg per decilitre. The dose was increased by 10 mg per day in patients whose LDL cholesterol level was higher than 90 mg per decilitre (2.33 mmol per litre) in any sample during the first year of the study and was reduced by 10 mg per day if the LDL cholesterol level fell below 40 mg per decilitre (1.03 mmol per litre) at any time during the study. During treatment, patients receiving the matching placebo were given 10 mg of simvastatin if their LDL cholesterol level was 140 mg per decilitre (3.62 mmol per litre) or higher; the target level was 130 mg per decilitre (3.37 mmol per litre) or lower. The dose of slow-release niacin was increased linearly from 250 mg twice daily to 1000 mg twice daily at four weeks. Patients whose HDL cholesterol levels had not increased by at least 5 mg per decilitre (0.13 mmol per litre) at 3 months, at least 8 mg per decilitre (0.21 mmol per litre) at 8 months, and at least 10 mg per decilitre at 12 months were switched to crystalline niacin the dose of which was gradually increased to 3 g per day or, at most, 4 g per day in order to meet the target levels. Niacin "placebo" tablets (taken at a dose of 50 mg twice daily) were active, provoking flushing without affecting lipid levels.
Outcomes	The primary outcome measures were: arteriographic evidence of a change in coronary stenosis and the occurrence of a first cardiovascular event (death, myocardial infarction, stroke, or revascularisation).
Notes	Compliance with the trail regimens, measured by means of pill counts, ranged between 80 percent and 95 percent. The mean doses of simvastatin and niacin taken by patients were 13 ± 6 mg per day and 2.4 ± 2.0 g per day, respectively. Plasma vitamin concentrations increased significantly in 75 patients who received active vitamin therapy. The active agents and placebos were provided by: Simvastatin (Zocor, Merck, West Point, Pa.) slow-release niacin (Slo-Niacin, Upsher-Smith, Minneapolis) crystalline niacin (Niacor, Upsher-Smith).

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Hogarth 1996

Methods	Randomised, double-blind, placebo-controlled trial with two-by-two factorial design. Generation of the allocation sequence: unclear, not reported. Allocation concealment: unclear, not reported. Blinding: adequate, identical placebo capsules and solution. Follow-up: adequate, 87 patients completed the trial (13 died, 6 withdrew). Three participants in supplemented group and 3 participants in placebo group withdrew. Intention-to-treat analysis: no. Sample size calculations: yes.

Hogarth 1996 (*Continued*)

Participants	Country: UK. Number of participants randomised: 106, 64 (44%) men and 42 (56%) women, mean age 82.65 years. Inclusion criteria: elderly medical in-patients. Exclusion criteria: already taking nutritional supplements, had diabetes mellitus, dysphagia, or a body mass index > 25 or < 15 kg/m2.
Interventions	Participants were randomly assigned to receive: group 1: active energy and active vitamin supplementation (n = 31); group 2: active energy and placebo vitamin supplementation (n = 24); group 3: placebo energy and active vitamin supplementation (n = 23); group 4: placebo energy and placebo vitamin supplementation (n = 28); for one month period. Supplementation was provided as 750 ml glucose drink (2317,5 kJ, 540 kcal) (Lucozade), and capsules containing vitamins A 8000 IU, B1 15 mg, B2 15 mg, B3 50 mg, B6 10 mg, C 500 mg. Matching placebos were Nutrasweet drinks or capsules of maize, starch and lactose.
Outcomes	The primary outcome measures were: weight, serum albumin levels, and activities of daily living, cognitive functioning and length of stay.
Notes	Compliance with the energy supplement (active or placebo) was monitored by measuring unconsumed fluid each day during admission. Following discharge, patients or carers were asked to complete a form estimating the volume of fluid (in quarters) remaining in each bottle each day. Vitamin compliance was monitored by tablet count at the end of the 1-month period at the final assessments. Compliance was poor with the liquid energy supplement with only one-third of patients consuming > 50% of offered drinks during the study period (17/55 patients, active group; 16/51 patients, placebo group). Vitamin capsule compliance was higher with approximately 90% of patients taking more than 50% of the capsules provided (48/52 patients, active group; 49/54 patients, placebo group). The energy supplement (Lucozade) and placebo preparation were provided by SmithKline and Beecham.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

HOPE TOO 2005Low

Methods	The Heart Outcomes Prevention Evaluation Study (HOPE). Randomised, double-blind, placebo-controlled trial with two-by-two factorial design. Generation of the allocation sequence: adequate, by computer. Allocation concealment: adequate, randomisation is done by a telephone call to a central office. After receipt of appropriate baseline data over the telephone, the patient is randomised. Blinding: adequate, identical placebo capsules. Follow-up: adequate. At the end of the initial HOPE trial, vital status was ascertained for 9535 (99.9%) of 9541 randomized patients. At the end of the HOPE-TOO trial, vital status was ascertained for 4724 (99.8%) of 4732 patients who participated in the extension trial. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: International, North America, South America, Europe (19 countries) Number of participants randomised: 9541; 6996 males and 2545 females, 55 years old or older, mean age 66 years. Inclusion criteria: 55 years or older, had a history of CV disease (coronary artery disease, stroke or peripheral arterial disease) or diabetes in the presence of at least one additional CV risk factor (total cholesterol > 5.2 mmol/l, HDL cholesterol =0.9 mmol/l, hypertension, defined as use of medications to treat high blood pressure, or blood pressure at time of recruitment > 160 mmHg systolic or > 90 mmHg diastolic, known microalbuminuria, or current smoking). Exclusion criteria: Dipstick-positive proteinuria, diabetic nephropathy, serum creatinine > 200 mmol/l, history of congestive heart failure, or known left ventricular ejection fraction (< 40%), hyperkalaemia, uncontrolled hypertension, myocardial infarction, unstable angina or stroke within 1 month before study enrolment, and use of or intolerance to vitamin E or angionetsin-converting-enzyme (ACE) inhibitors.
Interventions	Patients were randomly assigned to receive either group 1: 400 IU of vitamin E (RRR-a-tocopheryl acetate) daily from natural sources (n = 4761); or group 2: matching placebo (n = 4780); or group 3: an angiotensin-converting-enzyme inhibitor (ramipril 10 mg) (n = 4645); or group 4: matching placebo (n = 4652), once a day for a four to six years, mean 4.5 years. The Heart Outcomes Prevention Evaluation [HOPE] trial is conducted between December 21, 1993, and April 15, 1999. The Heart Outcomes Prevention was extended (HOPE-The Ongoing Outcomes [HOPE-TOO]) between April 16, 1999, and May 26, 2003. Of the initial 267 HOPE centres that had enrolled 9541 patients, 174 centres participated in the HOPE-TOO trial. Of 7030 patients enrolled at these centres, 916 were deceased at the beginning of the extension of the trial, 1382 refused participation, 3994 continued to take the study intervention, and 738 agreed to passive follow-up. The mean follow-up period was 7 years.
Outcomes	The primary outcome measures were: cancer incidence, cancer deaths, major cardiovascular events (myocardial infarction, stroke, and cardiovascular death). The secondary outcomes were: unstable angina, congestive heart failure, revascularisation or amputation, death from any cause, complications of diabetes, and cancer.
Notes	Compliance with treatment was checked by measuring the plasma vitamin E levels in randomly selected patients. The rate of compliance with the assigned regimen was high throughout the study. The percentages of patients who were taking vitamin E in the vitamin E and placebo groups, respectively, were 94.2% and 1.0% at 1 year, 93.3% and 1.7% at 2 years, 91.3% and 2.0% at 3 years, 90.2% and 2.7% at 4 years, and 89.2% and 3.4% at the final visit. There was no significant interaction between the study treatments (ramipril and vitamin E) for the primary, secondary, and other study outcomes. At the end of the initial HOPE trial, vital status was ascertained for 9535 (99.9%) of 9541 randomised patients. Funded by the Medical Research Council of Canada, Natural Source Vitamin E Association, Negma, Hoechst-Marion Roussel, AstraZeneca, King Pharmaceuticals, and the Heart and Stroke Foundation of Ontario.

HOPE TOO 2005Low (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

HPS 2002Low

Methods	Heart Protection Study. Randomised, double-blind, placebo-controlled trial with two-by-two factorial design. Generation of the allocation sequence: adequate, computer generated random numbers. Allocation concealment: adequate, central telephone randomisation system. Blinding: adequate, identical placebo capsules. Follow-up: adequate. 99.7% of the participants were with complete follow-up for average of 5 years in vitamins allocated group and 99.6% in placebo group. Overall, 25 participants allocated to vitamins group and 35 participants to placebo group were lost to follow-up. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: United Kingdom. Number of participants randomised: 20,536; 15,454 males and 5082 females at an age 40 to 80 years. Inclusion criteria: adults with coronary disease, other occlusive arterial disease, or diabetes, and non-fasting blood total cholesterol concentrations of at least 3.5 mmol/L. Exclusion criteria: other life-threatening conditions, such as chronic liver disease, severe renal disease, severe heart failure, severe chronic airways disease, or diagnosed cancer (other than non-melanoma skin cancer). In addition, anyone already taking high-dose vitamin E supplements, or in whom such supplements were considered indicated, was not to be randomised.
Interventions	Participants were randomly assigned to receive: group 1: 600 mg vitamin E, 250 mg vitamin C, and 20 mg beta-carotene daily (n = 10,269); or group 2: matching placebo capsules (n = 10,267), daily during the scheduled 5-year treatment period.
Outcomes	The primary outcome measures were: major coronary events (for overall analyses) and fatal or non-fatal vascular events (for subcategory analyses), with subsidiary assessments of cancer and of other major morbidity.
Notes	Compliance with treatment was assessed at each follow-up by reviewing the calendar packed tablets remaining and, for those who had stopped, the reasons for doing so were sought. An average of 83% of participants in each treatment group remained compliant during the scheduled five-year treatment period. To assess the effects of the treatment allocation on blood concentrations of the vitamins being studied, assays were performed in non-fasting samples collected from about 5% of participants at the initial screening visit and at an average of about three years of follow-up (the approximate mid-point of the study). Vitamins were provided by Roche.

HPS 2002Low (*Continued*)

	Data were extracted from the primary publication, but additional information was received through personal communication with the authors.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Jacobson 2000Low

Methods	Randomised, double-blind, placebo-controlled trial with parallel group design. Generation of the allocation sequence: adequate, computer-generated random number sequence. Allocation concealment: adequate, a three-letter code was written on the bottles to distinguish treatment from placebo without indicating which was which. The specimens were labelled by study ID and whether it was the first, second, third, etc., specimen. The numbers were scrambled according to a set formula to keep the technicians blind to which specimen it was. Blinding: adequate, identical placebo tablets. Follow-up: adequate, 73 participants completed the trial. Drop-out rates were high in both groups, but were higher in the placebo (53%) than in the treatment (35%) group. Intention-to-treat analysis: no. Sample size calculations: no.
Participants	Country: United States of America. Number of participants randomised: 121, mean age 42, 58% males. Inclusion criteria: adults 18 years of age and older who smoked one or more packs of cigarettes per day and were not currently taking the study vitamins. Exclusion criteria: nondetectable polycyclic aromatic hydrocarbon PAH-DNA adduct levels in mononuclear cells and plasma vitamin levels higher than 1.0 mg/dl for vitamin C, 15 mg/dl for beta-carotene, and 1.2 mg/dl for alpha-tocopherol at the first study visit.
Interventions	Participants were randomly assigned to receive: group 1: vitamin C 500 mg, alpha-tocopherol400 IU, beta-carotene 6 mg, n = 60; group 2: placebo, n = 61. Participants were supplemented and followed 0.5 years.
Outcomes	The primary outcome measure was: DNA damage.
Notes	Compliance with treatment was not reported. Additional information received through personal communication with the authors.

Risk of bias

Jacobson 2000Low (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

LAST 2004Low

Methods	Lutein Antioxidant Supplementation Trial (LAST). Randomised, double-blind placebo-controlled trial with parallel group design. Generation of the allocation sequence: adequate, by consecutive random card-3-choice, allocation sequence. Allocation concealment: adequate, manufacturer of the capsules maintained and concealed the blinding and four digit allocation codes. Bottles with masked four-digit allocation codes were sent to the assigned research pharmacist at DVA Medical Centre, North Chicago. All personnel at the DVA Medical Centre were unaware of the masked allocation codes during the 12-month clinical study. Participants were provided with opaque capsules of identical appearance in numbered containers. Blinding: adequate, identical looking capsules. Follow-up: adequate. During the one year clinical trial, 1, 2, and 1 participants were lost to follow-up from each group. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: United States of America. Number of participants randomised: 90, 86 men and 4 women, mean age 74.7 years. Inclusion criteria: diagnosis of atrophic age-related macular degeneration (ARMD) by stereo bio-ophtalmoscopy and at least one vision-degrading visual-psychophysical abnormality associated with ARMD in one or both eyes; clear non-lenticular ocular media (cornea, aqueous and vitreous), free of advanced glaucoma and diabetes or any other ocular or systemic disease that could affect central or parafoveal macular visual function. Exclusion criteria: recent (within 6 months) cataract or retinal surgery; taking photosenzing drugs (such as phenotiazines and chloroquine).

Interventions	Patients were randomly assigned to receive:
	group 1: lutein 10 mg (n = 29);
	group 2: lutein 10 mg, and antioxidants/vitamins and minerals broad spectrum supplementation formula (n = 30);
	group 3: placebo (maltodextrin) (n = 31);
	taken as three capsules twice per day with food, over a period of 12 months.
	The OcuPower supplement consists of: lutein 10 mg; vitamin A 2,500 IU; natural beta-carotene 15,000 IU (Betatene R); vitamin C 1500 mg (as calcium ascorbate-Ester C R); vitamin D3 400 IU; natural vitamin E (d-alpha tocopherol succinate) 500 IU; vitamin B1 50 mg; vitamin B2 10 mg; vitamin B3 70 mg; vitamin B5 50 mg; vitamin B6 50 mg; vitamin B12 500 µg; folic acid 800 µg; biotin 300 mcg; calcium 500 mg; magnesium 300 mg; iodine 75 µg; zinc (as zinc L-methionine-L-Optizinc R) 25 mg; copper 1 mg; manganese 2 mg; selenium 200 µg; chromium 200 µg; molibdenum 75 µg; lycopene 600 µg; bilberry extract (standardized to 25% anthocyanosides); alpha lipoic acid 150 mg; N-acetyl cysteine 200 mg; quercetin 100 mg; rutin 100 mg; citrus bioflavonoids 250 mg; plant enzymes 50 mg; black

LAST 2004Low (*Continued*)

	pepper extract (Bioperine R) 5 mg; malic acid 325 mg; taurine 900 mg; L-glycine 100 mg; L-glutathione 10 mg; boron 2 mg.
Outcomes	The primary outcome measures were: visual function and symptoms in atrophic age-related macular degeneration (ARMD).
Notes	Compliance was assessed by telephone at one week, two weeks, four weeks, six weeks, three months, and 12 months. Compliance with treatment was good. During one-year study, 96% of the participants took approximately 92% of their assigned capsules. There was no difference in compliance among the three groups. Lutein (Floraglo R) was provided by Kemin Foods International, Des Moines, Iowa); lutein in combination with additional antioxidants and nutrients (OcuPower R) and placebo were provided by Nutraceutical Sciences Institute, Boynton Beach, Florida.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Limburg 2005Low

Methods	Randomised, double-blind, placebo-controlled trial with two-by-two factorial design. Generation of the allocation sequence: adequate, the random allocation sequences by sex were generated by the US data-coordinating centre before the baseline evaluation by computer. Allocation concealment: adequate, the masked code linking agent bottles to intervention group assignments was retained by data-coordinating centre staff and concealed from all but the study statisticians until completion of the study analyses. Blinding: adequate, identical placebo capsules. Follow-up: adequate. Vital status was ascertained at the trial end in all patients in the vitamin E group and in 99.9% in the placebo group. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: China. Number of participants randomised: 360, mean age 47, 42% males. Inclusion criteria: at least 1 grossly visible oesophageal lesion with biopsy-proven mild or moderate squamous dysplasia, according to histological interpretation by a single pathologist. Exclusion criteria: history of cancer (except nonmelanoma skin cancer), symptoms suggestive of an upper gastrointestinal tract malignancy, recently treated peptic ulcer disease, or contraindications to the intervention agent(s) or study-related procedures. Subjects were also excluded if a grossly visible lesion could not be confirmed during the baseline EGD or if the worst histological diagnosis at baseline was less than mild or greater than moderate dysplasia.

Limburg 2005Low (*Continued*)

Interventions	Participants were randomly assigned into four groups to receive: group 1: selenium 200 μg and celecoxib 400 mg, n = 90; group 2: celecoxib 400 mg, n = 90; group 3: selenium 200 μg, n = 90; group 4: placebo, n = 90. Participants were supplemented and followed 10 months.
Outcomes	The primary outcome measure was: change in histological grade of squamous dysplasia (determined by comparing the most advanced histological diagnosis for each subject at the baseline and end-of-trial evaluations) and was categorised as regression, stable, or progression.
Notes	Compliance was assessed by pill counts and by direct observation by the village doctors who watched all participants take 2 morning pills each day throughout the intervention period. Compliance was further assessed biochemically by comparing baseline and end-of-trial serum selenium concentrations. Compliance with the single daily dose of selenomethionine (or placebo) and 1 of the 2 daily doses of celecoxib (or placebo) was in excess of 99% by both direct observation and pill counts. Pfizer, Incorporated, provided active and placebo celecoxib agent supplies.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

MAVIS 2005 Low

Methods	Mineral And Vitamin Intervention Study (MAVISl) Randomised, double-blind placebo-controlled trial with parallel group design. Generation of the allocation sequence: adequate, participants were randomly allocated to intervention or placebo by batch numbers generated by a password protected computer program. Allocation concealment: adequate, the computer program used for randomisation could be accessed by only the data programmer, blind to treatment allocation. The identity of the tablets was concealed in a double envelope sent by the manufacturer, which was kept locked in a cabinet during the trial. Blinding: adequate, identical placebo tablets. Follow-up: adequate, only 13% (n = 121) of the participants were lost to follow-up or reported stopping taking tablets. At least 1 diary was provided by 99% (901) of participants, 6 diaries by 93% (846), and 12 diaries by 89% (808). Losses to follow-up was equal in the active and the placebo (n = 22) groups. Fourteen participants in the active group and 18 participants in the placebo group withdrew. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: Scotland Number of participants randomised: 910, 479 men and 431 women, aged 65 or over who did not take vitamins or minerals.

MAVIS 2005 Low (*Continued*)

	Inclusion criteria: all people aged 65 or over who were registered with the practices were eligible, irrespective of chronic illness, unless their doctors considered them too unwell. Exclusion criteria: use of vitamin, mineral, or fish oil supplements in the previous three months (one month in the case of water soluble vitamins) or vitamin B12 injection in the past three months.
Interventions	Participants were randomly assigned to receive: group 1: multivitamin and multimineral supplement (800 µg vitamin A (acetate), 60 mg vitamin C, 5 µg vitamin D3, 10 mg vitamin E (D, L alpha-tocopheryl acetate), 1.4 mg thiamin (mononitrate), 1.6 mg riboflavin, 18 mg niacin (nicotinamide), 6 mg pantothenic acid (calcium D-pantothenate), 2 mg pyridoxine (hydrochloride), 1µg vitamin B12, 200 µg folic acid, 14 mg iron (fumurate), 150 µg iodine (potassium iodide), 0.75 mg copper (gluconate), 15 mg zinc (oxide), and 1 mg manganese (sulphate); or group 2: matched sorbitol placebo, one tablet daily for one year. Tablets were purchased from a commercial supplier.
Outcomes	The primary outcome measures were: number of contacts with primary care (doctor and other primary care workers, in person or by phone) for infection, number of self reported days of infection, and health related quality of life measured by the EuroQol and SF-12. The secondary outcome measures were: number of antibiotic prescriptions in primary care, number of days that antibiotics were prescribed, number of hospital admissions (including those related to infection), number of days in hospital with infection, number of infection related and all outpatient visits, adverse events reported by participants, and compliance with trial drugs (from diaries submitted monthly in all participants and tablet count at six and 12 months in a random sample of 10% of participants).
Notes	Compliance with treatment was assessed by self-report and was consistent with tablet counting. There were no differences between the groups for compliance with drug taking. Compliance in participants still taking tablets and returning information in diaries was over 91% throughout the trial.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

McKeown-Eyssen 1988

Methods	Randomised, double-blind, placebo-controlled trial with parallel group design. Generation of the allocation sequence: unclear, not reported. Allocation concealment: unclear, not reported. Blinding: adequate, identical placebo pills. Follow-up: adequate, the losses to follow-up were 14.1% in the vitamins group and 11.9% in the placebo group. Seventeen participants of 96 assigned to receive vitamins withdrew, and 5 were lost to follow-up. Of 89 participants assigned to placebo, 15 withdrew and 4 were lost to follow-up. Intention-to-treat analysis: no. Sample size calculations: no.
Participants	Country: Canada. Number of participants randomised: 200. Fifteen participants had to be excluded after initial randomisation because none of the polyps was adenomatous. Of the 185 participants, 121 were males and 64 females. Mean age was 58 years. Inclusion criteria: At least one polyp in the colon or rectum identified by colonoscopy and removed at two Toronto hospitals between 1979 and 1984. Patients who used supplements of vitamin C or E agreed to discontinue their use for the duration of the trial. Of the 185 eligible participants 137 completed the study with a second colonoscopic examination.
Interventions	Participants were randomly assigned to receive: group 1. vitamin C 400 mg; vitamin E 400 mg (n = 96). group 2: lactose placebos (n = 89); over a period of two years. Second colonoscopic examination was performed approximately two years after the initial examination, but could be performed earlier if judged clinically necessary. The physician assessed the presence and location of polyps, and any observed were removed.
Outcomes	The primary outcome measure was: recurrence of colorectal polyps.
Notes	Compliance with treatment was assessed by random urine samples collected at each visit from which urinary vitamin C levels were assessed, using a dipstick, as an index of compliance. The compliance to the vitamin supplements appears to be good. Of the 185 eligible participants, 137 (75%) completed the study with second colonoscopic examination conducted when most participants (81,5% of those on vitamins and 82,3% of those on placebos) had been receiving supplements for 12 to 30 months. Trial agents were supplied by H. Newmark of Roche, New Jersey and Roche, Canada.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Meydani 2004Low

Methods	Randomised, double-blind placebo-controlled trial with parallel group design. Generation of the allocation sequence: adequate, in blocks of 4 according to lists generated by the trial's statistician, who used a computer program. Six randomisation lists were constructed. Allocation concealment: adequate, those enrolling the participants had no access to the randomisation lists. Participants were unknown to the statistician. Blinding: adequate, identical looking placebo capsules. Capsules were in 2 equal batches, soft gel and identical in colour and taste. Follow-up: adequate. Of the 617 randomised persons, 37% in the vitamin E and 36% in the placebo groups, respectively, completed the 1-year trial period. Forty-one participants in the vitamin group and 42 participants in the placebo group were lost to follow-up. The losses to follow-up were equal in both groups. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: United States. Number of participants randomised: 617, 169 men and 448 women, mean age 84 years. Inclusion criteria: aged 65 years or older; life expectancy greater than 6 months; no anticipated discharge within 3 months; not room-bound for the past 3 months; absence of active neoplastic disease; no tube feeding, no kidney dialysis; no intravenous or urethral catheters for the last 30 days; no tracheostomy or chronic ventilator; antibiotic-free for more than 2 weeks; no long-term steroid treatment greater than 10 mg/d, no use of immunosuppressive drugs, or greater than the recommended daily allowance (RDA) level of supplements of vitamins E, C, or B6, selenium, zinc, beta-carotene, or fish oil; body mass index of at least 18; serum albumin at least 3.0 g/dL; able to swallow pills; willing to receive influenza vaccine; and willing to provide informed consent (for patients with dementia, family members provided informed consent).
Interventions	Participants were randomly assigned to receive: group 1: 200 IU of vitamin E (dl-alpha-tocopherol) (n = 311); group 2: placebo 4 IU of vitamin E (n = 306); both in soybean oil, one capsule daily for a period of one year. All participants received a capsule containing half the recommended daily allowance of essential vitamins and minerals. All participants received influenza vaccine.
Outcomes	Primary outcomes of the trial were: incidence of, number of persons with, and number of days with respiratory tract infections (upper and lower), and number of new antibiotic prescriptions for respiratory tract infection. Secondary outcomes included emergency department visits, hospitalisation, and death. A post hoc subgroup analysis was performed to determine the effect of vitamin E on common colds.
Notes	Adherence to trial protocol was verified by nursing home medication records, returned pill count, and quarterly measurement of plasma vitamin E levels. Ninety-eight percent of those completing the trial consumed the capsules for at least 330 days (> 90% of the 1-year supplementation period). The number of missed supplements did not differ statistically between the vitamin E and placebo groups. Capsules were manufactured by Tishcon Corporation (Westbury, NY). The capsules were packed by Pharmasource Healthcare Inc (Marlboro, Mass).

Meydani 2004Low (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Mezey 2004Low

Methods	Randomised, double-blind placebo-controlled trial with parallel group design. Generation of the allocation sequence: adequate, on a computer in blocks of 4. Allocation concealment: adequate. The vitamin E capsules and placebo capsules were prepared and labelled by the hospital pharmacies. For each patient entered into the trial the investigators opened a consecutive sealed container which had a 3-month supply of capsules. Blinding: adequate, capsules were identical in looks, smell, and taste. Follow-up: adequate. During the initial 3-month period of therapy, one patient in the treatment group withdrew from the trial. Four patients, 2 in each group, died during the initial 3 months. Five patients in the treatment group and 4 patients in the placebo group were lost between 3 and 12 months to follow up. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: United States and Spain. Number of participants randomised: 51, 34 men and 17 women, mean age 48 years, Inclusion criteria: age (18 years to 70 years), recent history of heavy alcohol ingestion and clinical and laboratory characteristics adopted by the International Informatics Hepatology Group for the diagnosis of alcoholic hepatitis. These criteria included moderate elevation of the serum aspartate aminotransferase AST (< 10 times above normal), an AST/alanine aminotransferase (ALT) ratio greater than 1.0 and no evidence of liver disease due to viral hepatitis, autoimmune disease, haemochromatosis, Wilsons disease or drug-induced hepatitis. Exclusion criteria: pregnancy, breast feeding, cardiovascular, pulmonary, kidney disease, pancreatitis, type I diabetes, recent (within 1 month) gastrointestinal bleeding, peptic ulcer disease, concurrent infection, history of thrombophlebitis, HIV positivity and history of ingestion of more than 100 IU vitamin E for the prior month.
Interventions	Participants were randomly assigned to receive: group 1: vitamin E (dl-alpha-tocopheryl acetate) 1000 IU (n = 25) group 2: placebo (n = 26); one capsule daily 3 months. The patients were followed for 1 year after entry into the trial.
Outcomes	The primary outcome measures was: clinical and laboratory parameters of liver function and on markers of fibrogenesis.
Notes	Compliance with treatment was checked by serum assessments. Plasma alpha-tocopherol levels increased in patients on vitamin E. The authors published results of shorter (3 months) and longer (1-year) follow-up period.

Mezey 2004Low (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

MINVITAOX 1999Low

Methods	MIN.VIT.AOX geriatric network. Randomised, double-blind placebo-controlled trial with two-by-two factorial design. Generation of the allocation sequence: adequate, random numbers generated by computer program. Allocation concealment: adequate, central independent unit. Blinding: adequate, identical placebo capsules. Follow-up: adequate, losses to follow-up were approximately 2.2% in each treatment group. Three participants from the vitamin group, 3 participants from the vitamin and trace elements group, 4 participants from the trace elements group, and 4 participants from the placebo group withdrew before the end of the trial. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: France. Number of participants randomised: 725 institutionalised elderly patients from 25 geriatric centres, 185 men and 540 women, aged 65 to 103 years, mean age 83.9 years. Inclusion criteria: no acute illnesses and at least 65 years of age. Age-related diseases were allowed. Exclusion criteria: patients with a history of cancer or those taking medication that might interfere with nutritional status, immunocompetence, or vitamin or mineral supplementation.
Interventions	Participants were randomly assigned to receive: group 1: trace elements zinc sulfate and selenium sulfide (providing 20 mg of zinc and 100 μg of selenium), (n = 182); group 2: vitamin group - ascorbic acid (120 mg), beta-carotene (6 mg), and alpha-tocopherol (15 mg) (n = 180); group 3: trace element and vitamin supplements (n = 181); group 4: placebo capsules (n = 182). Participants received one capsule daily, with their breakfast for two years.
Outcomes	The primary outcome measures were: delayed-type hypersensitivity skin response, humoral response to influenza vaccine, and infectious morbidity and mortality.
Notes	Compliance with treatment was assessed first by the nursing teams that administered the pills every morning and then at the end of each six months by counting the remaining capsules in the pillboxes, and by random serum assessments. High compliance (> 85%) was observed. The supplements and placebo were provided by Produits Roche SA, Fontenay-aux-Roses, France. Additional information received through personal communication with the authors.

MINVITAOX 1999Low (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Mooney 2005Low

Methods	Randomised, double-blind placebo-controlled parallel group trial Generation of the allocation sequence: adequate, sample IDs were generated sequentially for each patient at each visit, without reference to treatment group by computer. Allocation concealment: adequate, uniformly coded bottles. Participants, interviewers, and laboratory personnel were blinded to treatment group and did not have access to the randomisation code. Blinding: adequate, identical placebo pills. Follow-up: adequate, 83 of 142 (58%) in the treatment group and 93 of 142 (66%) in the placebo group completed 15 months of treatment. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: United States. Number of participants randomised: 284, 55% men and 45% women were aged 18 or older, mean age 36.8 years. Inclusion criteria: men and women ages > 18 years who smoked at least 10 CPD, did not take vitamin supplements or use a nicotine patch in the 3 months before enrolment, had no prior history of cancer or liver disease, lived at a permanent address, owned a home telephone, were willing to comply with the 2-year protocol, and completed a 1-month placebo run-in. Exclusion criteria: none stated.

Interventions	Participants were randomly assigned to receive:
	group 1: vitamin C 500 mg and vitamin E 400 IU (n = 142);
	group 2: placebo (n = 142);
	for a period of 1.25 years.

Outcomes	The primary outcome measure was: level of benzo(a)pyrene [B(a)P]-DNA adducts as an intermediate cancer risk marker.
Notes	Treatment compliance was assessed by serum vitamin measurements and pill counts. Compliance with treatment did not differ by gender measured by blood levels of {alpha}-tocopherol at 15 months of follow-up or by pill counts. At all time points after randomisation, in all participants, the treatment group had significantly higher levels of vitamin E than the placebo group. However, in women, the blood levels of vitamin E did not plateau until the 9-month time point. Trial agents were provided by Hoffman-LaRoche.
Risk of bias	

Mooney 2005Low (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Murphy 1992Low

Methods	Randomised, double-blind, placebo-controlled trial with parallel group design. Generation of the allocation sequence: unclear, not reported. Allocation concealment: adequate, participants were given a content of a single capsule by a research assistant who was not involved with outcome ascertainment. Patients, their regular physicians, and study team members remained masked to the capsule contents for the duration of the trial. Blinding: adequate, identical placebo tablets. Follow-up: adequate, 2 patients from vitamin A group were lost to follow-up. Intention-to-treat analysis: yes. Sample size calculations: no.
Participants	Country: United States of America. Number of participants randomised: 109, 37 men and 72 women, mean age 73 years. Inclusion criteria: patients on the chronic medical and skilled/intermediate care wards of an academically affiliated nursing home. Exclusion criteria: patients in the rehabilitation unit.
Interventions	Participants were randomly assigned to receive: group 1: vitamin A 60,000 µg retinol equivalent (200,000 IU) (n = 53); group 2: placebo (vitamin A 300 retinol equivalents (1000 IU) as retinyl palmitate in arachis oil (n = 56). All capsules contained 40 IU of vitamin E as an antioxidant. Patients receiving multivitamin preparations at the onset of the trial continued to receive them. No patient was commenced on vitamin A-containing supplements during the follow-up period. A content of a single capsule was given to participants by research assistant. Participants were followed-up for 90 days.
Outcomes	The primary outcome measure was: incidence of antibiotic treated bacterial infections among elderly nursing-home residents.
Notes	Participants were given a content of a single capsule by a research assistant. Due to the administration of vitamin A in the control group, the 'no intervention' in that group can be discussed. Trial capsules were provided by Roche, Basel, Switzerland.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

NIT1 1993

Methods	Nutrition Intervention Trial (NIT); The General Population Trial, in Linxian, China. Randomised, placebo-controlled trial with one-half replicate of a two-by-two-by-two-by-two factorial design. Generation of the allocation sequence: adequate, random numbers generated by independent data management centre in USA. The randomisation sequence was known only at data management centre until the intervention concluded. Allocation concealment: adequate, sequentially numbered coded bottles. Pill containers were labelled in the USA at the pill distribution centre. Blinding: adequate, identical placebo pills. Follow-up: inadequate, losses to follow-up not reported. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: China, Henan Province of north central China, Linxian County. Number of participants randomised: 29584; 45% males, aged 40 to 69 years. Inclusion criteria: residents willing to take part in a multi-year, daily pill-taking regimen. Exclusion criteria: debilitating disease or prior oesophageal or stomach cancer.
Interventions	Participants were randomly assigned to receive one of eight vitamin/mineral supplement combinations in the form of individual oral tablets. The eight intervention groups (each with 3677 to 3709 participants) were derived from a one-half replicate of a two-by-two-by-two-by-two factorial design which allowed to asses four factors (ie, nutrient combinations) in a single experiment. The four factors designated by the letters A, B, C, D were: A - retinol (as palmitate) 5000 IU, zinc (as zinc oxide) 22.5 mg; B - riboflavin (vitamin B2) 3.2 mg and niacin (vitamin B3) 40 mg; C - ascorbic acid 120 mg and molybdenum (as molybdenum yeast complex) 30 µg; D - beta carotene 15 mg, selenium (as selenium yeast) 50 µg, and alpha-tocopherol 30 mg. Doses of each nutrient varied from one to two times US Recommended Daily Allowances (RDAs). The eight intervention groups were defined by the following combinations of supplements; AB, AC, AD, BC, BD, CD, ABCD, or placebo and packed in coded bottles containing a one-month supply. Bottles were distributed monthly beginning in March 1986 and continuing through May 1991, average 5.25 years.
Outcomes	The primary outcome measures were: cancer incidence, cancer mortality, and overall mortality.
Notes	Compliance with study treatment was assessed by monthly pill counts and biochemical measures. Compliance was excellent throughout the study. The overall pill disappearance rate was 93% for all participants, with no difference by treatment group (range 92% to 93%) and little change during the trial. All vitamin/mineral supplements and placebos were provided by Hoffmann-La Roche, Basel, Switzerland and Lederle Laboratories, Inc. Data were extracted from the primary publication. Additional information received through personal communication with the authors.

Risk of bias

Item	Authors' judgement	Description

NIT1 1993 (*Continued*)

Allocation concealment?	Yes	A - Adequate

NIT2 1993Low

Methods	The Dysplasia Trial. Randomised, placebo-controlled trial with parallel group design. Generation of the allocation sequence: adequate, random numbers generated by independent data management centre in USA. Allocation concealment: adequate, sequentially numbered coded bottles. Pill containers were labelled in the USA at the pill distribution centre. Blinding: adequate, identical placebo pills. Follow-up: adequate, the morbidity and mortality follow-up rates were 99%. Intention-to-treat analysis: yes. Sample size calculation: yes.
Participants	Country: China, Henan Province of north central China, Linxian County. Number of participants randomised: 3318; 1461 males and 1857 females at age 40 to 69 years, mean age 54 years. Inclusion criteria: place of living in one of the three northern Linxian communes (Yaocun, Rencun, or Donggang), provided consent, diagnosis of oesophageal dysplasia on a balloon cytology examination. Exclusion criteria: taking vitamins of any type regularly, or antitumour B (a traditional Chinese drug consisting of a mixture of six medical herbs), history of malignancy or other debilitating disease.
Interventions	Participants were randomly assigned to receive: group 1: 14 vitamins and 12 minerals (vitamin A (acetate) 10000 IU; vitamin E (dl-alpha tocopherol acetate) 60 IU, vitamin C (ascorbic acid) 180 mg, vitamin B1 5 mg, vitamin B2 5.2 mg, vitamin B6 6 mg, vitamin B12 18 µg, vitamin D 800 IU; beta-carotene 15 mg, folic acid 800 µg, niacinamide 40 mg, biotin 90 µg, pantothenic acid 20 mg, calcium 324 mg, phosphorus 250 mg, iodine 300 µg, iron 54 mg, magnesium 200 mg, copper 6 mg, manganese 15 mg, potassium 15.4 mg, chloride 14 mg, chromium 30 µg, molybdenum 30 µg, selenium (sodium selenate) 50 µg, and zinc (n = 1657); group 2: placebo (n = 1661); for a period of 6 years. The doses were typically two to three times the US Recommended Daily Allowances (RDAs), but ranged from 0.26 to seven times the RDA depending on the vitamin or mineral. Each participant was given three pills daily, including one capsule beta-carotene or placebos and two tablets of vitamin/mineral supplement, or placebos.
Outcomes	The primary outcome measures were: cancer incidence, cancer mortality, and overall mortality.
Notes	Compliance with treatment was assessed by counting unused pills for all trial participants and by assessing nutrient levels in blood collected from samples of individuals randomly selected without replacement every three months throughout the trial. Compliance with treatment was excellent. The overall pill disappearance rate was 94% in both groups with slight decline (from 96% in year 1 to 92% in year 6 in both groups) over the duration of the trial. Data were extracted from the primary publication.

NIT2 1993Low (*Continued*)

	Active medications and placebos were provided: beta-carotene as Solatane by Hoffmann-La Roche, Inc., Nutley, N.Y., and vitamin/mineral supplement as Centrum Lederle Laboratories, Inc., Pearl River, N.Y. Additional information received through personal communication with the authors.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

NPCT 1996Low

Methods	Nutritional Prevention of Cancer Trial (NPCT). Randomised, double-blind, placebo-controlled trial with parallel group design. Generation of the allocation sequence: adequate, computer generated random numbers. Allocation concealment: adequate, treatment group assignment was made centrally. The co-ordinating centre held all treatment information in blinded form. Medications were distributed using sealed pill bottles. Follow-up: adequate. At the end of the blinded period of treatment no participants were lost to vital follow-up, and only 7 participants (3 in the selenium group and 4 in the placebo group) declined to provide additional information about the illness. Blinding: adequate, identical placebo tablets. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: United States of America. Number of participants randomised: 1312; 75% males, aged 18 to 80 years, mean age 63 years. Inclusion criteria: history of two or more basal cell skin cancers (BCC) or one squamous cell skin cancer (SCC), with one of this occurring within the year prior the randomisation, life expectancy of at least five years and no internal malignancies treated within the previous five years. Exclusion criteria: history of significant liver or kidney disorders. Recruitment began on September 15, 1983 and continued each year through 1991.
Interventions	Patients were randomly assigned to receive: group 1: 200 μg of selenium supplied in a 0.5 g high-selenium bakers yeast tablet (n = 653); group 2: placebo (n = 659); The end of a blinded period of treatment was on February 1, 1996. Mean length of treatment was 4.5 years and follow-up 7.4 years.
Outcomes	The primary outcome measures were: incidences of basal cell and squamous cell carcinoma of the skin. In 1990 secondary outcome measures were identified, which included: total mortality and cancer mortality, as well as the incidence of the lung, colorectal, and prostate cancers.

NPCT 1996Low (*Continued*)

Notes	Compliance with treatment: excellent, 79.3% of the participants (80.3% in the placebo group and 78.4% in the selenium group) missed taking a pill less than twice a month. Trial medications were provided by Nutrition 21 (La Jolla, CA), through 1995 and by Cypress Systems (Fresno, CA) thereafter.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

NSCPT 1999Low

Methods	Nambour Skin Cancer Prevention Trial (NSCPT). Randomised, double-blind, placebo-controlled trial with two-by-two factorial design. Generation of the allocation sequence: adequate, randomisation computer program. Allocation concealment: adequate, the treatment code was known only to the investigator who generated it and the two people who packaged the tablets for distribution. None of these people had contact with participants. Blinding: adequate, identical looking placebo tablets of beta-carotene. Follow-up: adequate. At the end of the trial after 5 years, 15% participants had withdrawn without a complete skin examination by a dermatologist in the follow-up period. Fifty participants, assigned to sunscreen and beta carotene, 70 assigneed to sunscreen and placebo, 59 assigned to no sunscreen and beta carotene, and 59 assigned no sunscreen and placebo were lost to follow-up. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: Australia. Number of participants randomised: 1621, 708 men and 913 women, aged between 20 and 69 years, mean age 48.8 years. Inclusion criteria: examination by a dermatologist with removal of all diagnosed skin cancers, written informed consent. Exclusion criteria: taking vitamin supplements containing beta-carotene and those who reported that they were already applying sunscreen on a strict daily basis.

Interventions	Patients were randomly assigned to receive:
	group 1: sunscreen and beta-carotene (30 mg) (n = 404);
	group 2: sunscreen and oral placebo (n = 408);
	group 3: beta-carotene (n = 416);
	group 4: oral placebo (n = 393);
	one tablet daily for a period of 4.5 years.
	Use of a placebo skin cream is considered unethical from two points of view: an oil-in-water emulsion with no active chemicals may enhance ultraviolet damage after evaporation of the water component; and people in the trial may use the placebo skin cream rather than a protective sunscreen in situations that

NSCPT 1999Low (*Continued*)

	lead to sunburn. The treatment protocol involves the self-application of an adequate layer of sunscreen to all exposed sites on the head, neck, and upper limbs every morning, after heavy sweating or bathing.
Outcomes	The primary outcomes were: incidence of basal-cell and squamous-cell carcinomas both in terms of people treated for newly diagnosed disease and in terms of the numbers of tumours that occurred. Analysis of the effect of sunscreen was based only on skin cancers that developed on sites of daily application.
Notes	Compliance is assessed on a 3-monthly basis when supplies of sunscreens and tablets are replenished comparing the weight of sunscreen used to an empirical standard usage rate, by counting the remaining tablets, and by determining serum beta-carotene in a random sample of participants at 12 and 54 months. At the end of the trial, 75% of participants who were assigned daily sunscreen use were applying sunscreen to their head, neck, arms, and hands at least 3 or 4 days per week. Of those people not assigned to the sunscreen group, 74% were applying sunscreen to head, neck, and arms either not at all or no more than 1 or 2 days per week. Self-reported frequency of sunscreen application was well correlated with estimated daily weight of sunscreen used (averaged across the entire intervention period) in the sunscreen group. On the basis of counts of returned tablets, 72% of the beta-carotene group and 70% of the placebo group took at least 80% of the prescribed tablet intake over the entire intervention period. The beta-carotene group had significantly greater mean skin reflectance on the palm at follow-up than at baseline and their follow-up values were greater than those of the placebo group. Study agents were supplied by Hoffman-La Roche, Nutley, NJ (beta-carotene), and broad-spectrum, sun protection factor 15+ sunscreen supplied by Woolworths Limited, Sydney, Australia, under the brand Auscreen Ultrablock Lotion SPE 15+ Ross Cosmetics, Melbourne, Australia.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Penn 1991

Methods	Randomised, double-blind, placebo-controlled trial with parallel group design. Generation of the allocation sequence: unclear, not reported. Allocation concealment: unclear, not reported. Blinding: adequate, identical vitamin cocktail. Follow-up: adequate, 1 patient from each group was lost to follow-up. Intention-to-treat analysis: no. Sample size calculations: no.
Participants	Country: United Kingdom. Number of participants randomised: 30; 20% males, mean age 83.7 years. Inclusion criteria: patients who had been in hospital for more than 3 months, requiring nursing care as a consequence of stroke disease, but without active medical problem.

Penn 1991 (*Continued*)

	Exclusion criteria: patients who were catheterised, or who had pressure sores, or who were receiving medication known to affect immune function.

Interventions	Participants were randomly assigned to receive:
	group 1: vitamin A 8000 IU, vitamin C 100 mg, and vitamin E 50 IU (n = 15);
	group 2: placebo (n = 15);
	for 28 days.

Outcomes	The primary outcome measures were: nutritional status and cell-mediated immune function.
Notes	Compliance with treatment is not described.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

PHS 1996Low

Methods	Physicians Health Study (PHS). Randomised, double-blind, placebo-controlled trial with two-by-two factorial design. Generation of the allocation sequence: adequate, by computer in blocks. Allocation concealment: adequate, the shipping department sent out calendar packs (which were identical whether active or placebo) to individual participants depending on this code. All of the calendar packs were in coded boxes, supplied by the drug manufacturer, so that the shippers did not know which drug they were shipping. Blinding: adequate, identical placebo capsules. Follow-up: adequate. By December 31, 1995, the scheduled end of the trial, less than 1% of the participants were lost to follow up. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: United States of America. Number of participants randomised: 22071 US male physicians at age 40 to 84 years, mean age 53 years. Inclusion criteria: US male physicians willing to take part in this trial. Exclusion criteria: chronic liver disease or evidence of abnormal liver function, severe renal disease or evidence of impaired renal function, inflammatory muscle disease or evidence of muscle problems (creatine kinase > 750 IU/L); concurrent treatment with cyclosporin, fibrates, or high-dose niacin; child-bearing potential; severe heart failure; some life-threatening condition other than vascular disease or diabetes (eg, severe chronic airways disease or any cancer other than non-melanoma skin cancer); or conditions that might limit long-term compliance (eg, severely disabling stroke, dementia, or psychiatric disorder).

PHS 1996Low (*Continued*)

Interventions	Physicians were randomly assigned to one of the four groups including: group 1: active aspirin 325 mg on alternate days plus beta-carotene placebo; group 2: active beta-carotene 50 mg on alternate days plus aspirin placebo; group 3: both active agents; or group 4: both placebos. The randomised aspirin component of the study was terminated early, on 25 January 1988. The beta-carotene component continued uninterrupted until its scheduled end in December 1995. A total of 11036 physicians were assigned at random to receive beta-carotene and 11035 to receive beta-carotene placebo. Time from randomisation to the end of study averaged 12 years, and time of follow-up 12.9 years.
Outcomes	The primary outcome measures were: overall and within subgroups, incidence of malignant neoplasms (except non melanoma skin cancer), incidence of cardiovascular disease, and overall mortality.
Notes	Compliance with treatment was checked by random serum assessments obtained at unannounced visits to trial participants. Compliance with treatment excellent, the average per cent of pills taken was 97% in both the active and placebo groups. There was 85% compliance with beta-carotene treatment after five years and 78% after 12 years. The use of vitamin A supplements was reported by only 6% of the placebo group even by the end of trial. Active trial packs and matching placebos were provided by: aspirin (Bufferin) by Bristol Meyers; beta-carotene (Lurotin), BASF corporation. Additional information received through personal communication with the authors. Data were extracted from the article: Cook et al. Effects of beta-carotene supplementation on cancer incidence by baseline characteristics in the Physicians' Health Study (United States). Cancer Causes and Control 2000; 11: 617-26, with extended follow-up of 12.9 years.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Pike 1995Low

Methods	Randomised, double-blind, placebo-controlled trial with parallel group design. Generation of the allocation sequence: adequate, blocks of computer generated random numbers. Allocation concealment: adequate, sealed envelopes. Blinding: adequate, identical placebo tablets. Follow-up: adequate. Five participants in the placebo group and 7 in the supplemented group did not complete the trial. Intention-to-treat analysis: yes. Sample size calculations: no.

Pike 1995Low (*Continued*)

Participants	Country: United States of America. Number of participants randomised: 47; 13 men and 34 women at age 61 to 79, mean age 69 years. Inclusion criteria: healthy, noninstitutionalised elderly participants with no known chronic or serious medical illness (eg, cancer, end stage renal disease, chronic liver disease). Exclusion criteria: taking nutritional supplements 3 months before the trial start.
Interventions	Participants were randomly assigned to receive: group 1: micronutrient supplement (Multivitol R) containing vitamin A (retinol acetate) 800 retinol equivalents (RE); vitamin D2 (ergocalciferol) 5.0 µg; vitamin E (alpha-tocopherol acetate) 45 mg; vitamin B1 (thiamin mononitrate) 2.18 mg; vitamin B2 (riboflavin) 2.6 mg; vitamin B6 (pyridoxin hydrochloride) 3.65 mg; vitamin B12 (cyanocobalamin) 9 µg; nicotinamide 30 mg; folic acid 0.4 mg; vitamin C (ascorbic acid) 90 mg; calcium (calcium hydrogen phosphate 2H2O 695 mg) 162 mg; magnesium (magnesium oxyde 165.78 mg) 100 mg; iron (iron (II) fumarate 82.14 mg) 27 mg; copper (copper (II) oxyde 1.87 mg) 1.5 mg; zinc (zinc oxide 28 mg) 22.5 mg; iodine (potassium iodide 0.294 mg) 0.225 mg); (n = 24); group 2: placebo: (n = 23); one tablet daily for a period of one year.
Outcomes	The primary outcome measure was: immune indices in healthy elderly.
Notes	Compliance was verified by interview with the patient during trimonthly visits to the center and through morbidity forms, phone calls, and checking supplement containers when brought back to the center. Trial agents were provided by Hermes Arzneimittel GmbH.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

PPP 2001

Methods	The Primary Prevention Project (PPP) Randomised controlled clinical trial with two-by-two factorial design. Generation of the allocation sequence: adequate, computer generated randomisation table produced in random permuted blocks of 12, allowing stratification. Allocation concealment: adequate, centrally assigned treatments on telephone verification of the correctness of inclusion criteria. Blinding: inadequate. There is no intervention in the control arm. Follow-up: adequate. At the end of the trial, 4150 (92.3%) patients had clinical follow-up. For 314 (7.0%) participants, information on vital status was obtained through census offices. Overall, vital status information was obtained for 99,3% of the population enrolled. Fourteen participants assigned to vitamin group and 17 assigned to control group were lost to follow-up. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: Italy. Number of participants randomised: 4495; 1912 males and 2583 females, mean age 64.4 years. Inclusion criteria: old age (> 65 years); hypertension (systolic blood pressure > 160 mmHg or diastolic blood pressure > 95 mm Hg on at least three separate occasions); hypercholesterolaemia (total blood cholesterol > 6.4 mmol/L on at least two separate occasions); diabetes mellitus (fasting venous plasma glucose concentration > 7.8 mmol/L on at least two separate occasions (chronic drug treatment for any of the three latter conditions was also a criterion for inclusion); obesity (body mass index > 30 kg/m2); and family history of myocardial infarction before 55 years of age in at least one parent or sibling. Exclusion criteria: treatment with antiplatelet drugs (history of vascular events or diseases); chronic use of anti-inflammatory agents or anticoagulants; contraindications to aspirin; diseases with predictable poor short-term prognosis; and predictable psychological or logistical difficulties affecting compliance with the trial requirements.
Interventions	Patients were randomly assigned to receive: group 1: aspirin, 100 mg (enteric-coated aspirin a day) (n = 2226); or group 2: no aspirin (n = 2269); and group 3: vitamin E (one capsule of 300 mg synthetic alpha-tocopherol a day), (n = 2231) or; group 4: no vitamin E (n = 2264), following a two-by-two factorial design. The mean follow-up was 3.6 years.
Outcomes	The primary outcome measure was: the cumulative rate of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. Predefined analyses included cardiovascular deaths, total deaths, total cardiovascular events (cardiovascular death, nonfatal myocardial infarction, non-fatal stroke, angina pectoris, transient ischaemic attacks, peripheral artery disease, and revascularisation procedures).
Notes	At the beginning, and repeatedly during the trial, all patients received advice on compliance with background treatments. Compliance with treatments: at year 1 and at the end of the study 19.2% and 19.3% of the patients randomised to aspirin and 13.1% and 13.6% of those randomised to vitamin E had stopped taking the treatment. Side effects were the reason for discontinuation for 7.9% of the patients in the aspirin group and 1.1% in the vitamin E group. At the end of the trial, 7.2% of the patients not randomised to aspirin were taking aspirin and 0.2% of those not randomised to vitamin E were taking vitamin E.

PPP 2001 (*Continued*)

	Bayer supplied the aspirin preparation, and vitamin E capsules were provided by Bracco SpA.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

PPS 1994Low

Methods	The Polyp Prevention Study (PPS). Randomised, double-blind, placebo-controlled trial with two-by-two factorial design. Generation of the allocation sequence: adequate, by computer. Allocation concealment: adequate, only pharmacy and safety and data monitoring committee had access to the treatment assignments. Blinding: adequate, identical placebo capsules provided by a sponsor. Follow-up: adequate. Of 864 patients randomised, 751 (87%) underwent follow-up colonoscopic examinations and provided all subsequent data. Overall, 69 participants were lost to follow-up; 56 in 3 active intervention groups and 13 in placebo group. Intention-to-treat analysis: no. Sample size calculations: yes.
Participants	Country: United States of America. Number of participants randomised: 864; 751 participants completed the study, 592 males and 159 females, mean age 61 years. Inclusion criteria: at least one adenoma diagnosed within the previous three months, patients have undergone colonoscopy with the entire large bowel seen and judged to be free of further polyps, good health, age less than 80 years. Exclusion criteria: familial polyposis, a history of invasive colorectal cancer, malabsorption syndromes, or any condition (such as a history of renal calculi or thrombophlebitis) that might be worsened by dietary supplementation with vitamin C or E. Participants agreed not to take supplemental vitamin C or E or beta carotene outside the trial. The trial protocol called for two follow-up colonoscopic examinations, the first approximately one year after the colonoscopy that qualified the patient for study (year 1), and second 36 months after the first (year 4). A colonoscopy was considered to be satisfactory for study purposes if cecum was reached, the entire mucosa was seen, and all polyps were removed. The endoscopist recorded the size and location of all raised mucosal lesions.

Interventions	Patients were randomly assigned to receive:
	group 1: beta carotene 25 mg, vitamin C 1000 mg, vitamin E (dl-alpha-tocopherol) 400 mg (n = 208);
	group 2: vitamin C 1000 mg, vitamin E 400 mg, and placebo (n = 225);
	group 3: beta carotene 25 mg plus placebo (n = 217);
	group 4: placebo (n = 214);
	daily for 4 years.

PPS 1994Low (*Continued*)

	The study agents were provided in the form of soft gelatine capsules (containing placebo, beta carotene alone, vitamin E alone, or beta carotene plus vitamin E) and tablets (containing placebo or vitamin C) packaged in calendar packs, with each day's blister containing one capsule and one pill.
Outcomes	The primary trial outcome was: the occurrence of new adenomas between the colonoscopic examinations conducted at year 1 and year 4.
Notes	Compliance was checked by random serum assessments. Compliance with treatment was good, 82% of all patients reported taking the study agents at least six days per week, and further 5% took them three to five days per week. Only five patients stopped taking the medications because of their presumed toxicity. Trial agents were provided at no cost by BASF of of Wiandotte, Michigan. Additional information received through personal communication with the authors.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Prince 2003Low

Methods	Randomised, double-blind, placebo-controlled cross-over trial. Generation of the allocation sequence: adequate, computer-generated. Allocation concealment: adequate, therapy was randomly allocated using computer-generated tables by an independent pharmacist (central randomisation). Blinding: adequate, identical looking capsules. Follow-up: adequate, 44 (72%) patients completed the trial per protocol. One patient died from previously undiagnosed ischaemic heart disease during the first (active) treatment period. Eight further patients (5 from the active group) withdrew from the trial during the first treatment period and 8 (4 from the active group) withdrew during the second treatment period. Intention-to-treat analysis: no. Sample size calculations: yes.
Participants	Country: United Kingdom. Number of participants randomised: 61 patient with primary biliary cirrhosis, 92% women, mean age 58 years. Inclusion criteria: primary biliary cirrhosis and self-reported fatigue. Exclusion criteria: change in disease (or symptom) altering medication in the 3 months prior to randomisation (e.g. ursodeoxycholic acid, colestyramine, rifampicin), current use or use within the last 3 months of nutritional supplements containing antioxidants, inability to complete symptom severity assessment documents, life-threatening intercurrent disease; presence of other uncontrolled disease with fatigue forming part of its clinical spectrum (eg, hypothyroidism, anaemia, renal failure, depression); drug dependency or addiction; women of child-bearing potential who were not practising effective contraception.

Prince 2003Low (*Continued*)

Interventions	Participants received 12 weeks each of placebo and antioxidant supplementation (vitamins A, C and E, selenium, methionine and ubiquinone) in random order, separated by a four-week washout period. Active medication consisted of four gelatine-covered capsules daily containing selenium (l-selenomethionine) 75 µg, beta-carotene 3 mg, vitamin E (d-alpha-tocopherol acetate) 50 mg, vitamin C 150 mg, l-methionine 375 mg, and ubiquinone (coenzyme Q10) 25 mg. Placebo consisted of identical-looking capsules containing inactive carrier. Participants were requested not to start any other nutrient supplements or complementary therapies during the trial. Forty-three (70%) patients were co-prescribed ursodeoxycholic acid. The median dose (interquartile range) prescribed was 9.6 mg/kg (8.5-11.3 mg/kg). Fifteen (25%) patients were taking thyroxine for pre-existing hypothyroidism. All patients had normal thyroid stimulating hormone levels and had been on stable thyroxine doses for at least 3 months prior to enrolment. Two patients were taking long-term beta-adrenergic blocking medication (one each propranolol and sotalol). Three patients were long-term users of benzodiazepines.
Outcomes	The primary outcome measure for this study was: the change in patient fatigue. Fatigue was assessed using the Fisk fatigue severity score (FFSS). The FFSS assesses the impact of fatigue-associated impairment in three domains (physical, cognitive and psychosocial) that can be summed to give a total score. Higher scores relate to increased fatigue severity.
Notes	Trial medications were provided by Bioquantox, Pharma Nord, Morpeth, UK. Additional information received through personal communication with the authors.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Rayman 2006Low

Methods	Prevention of Cancer by Intervention with Selenium Pilot Study (PRECISEp). Randomised, double-blind, placebo-controlled trial with parallel group design. Generation of the allocation sequence: adequate, computer-generated permuted blocks. Allocation concealment: adequate, research nurses telephoned the independent randomisation service to obtain an anonymous code for each volunteer, and then gave the volunteer their corresponding pre-coded tablets. Blinding: adequate, identical intervention and placebo yeast. Follow-up: adequate, 34 participants (7%) withdrew from treatment within the first 6 months. There was no significant difference in treatment withdrawals between groups (7, 10, 5, and 12 in the placebo and 100, 200, and 300 µg groups respectively. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: United Kingdom. Number of participants randomised: 501, 53% men at age 60 to 74 years, mean age 67 years. Inclusion criteria: volunteers from four general practices. Exclusion criteria: incapable of carrying out light housework or office work, active liver or kidney disease, prior diagnosis of cancer (excluding nonmelanoma skin cancer), diagnosed HIV infection, immunosuppressive therapy, diminished mental capacity, taking > 50 µg/day of selenium supplements in the previous six months (by patient report).

Interventions	Participants were randomly assigned to receive:
	group 1: placebo (n = 121);
	group 2: selenium 100 µg (n = 127);
	group 3: selenium 200 (n = 127);
	group 4: selenium 300 µg (n = 126);
	in the form of high-selenium yeast, Seleno PreciseTM per day for two years.

Outcomes	The primary outcome measures were: mood, quality of life, and plasma selenium level.
Notes	Compliance with randomised treatment was determined by pill count, with participants considered compliant if they took at least 80% of their allocated tablets. Reasons for participant withdrawal were noted. Four hundred fifty three of the 467 participants (97%) who completed six months were compliant according to pill count. Trial agents were provided by Pharma Nord, Vejle, Denmark.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

REACT 2002Low

Methods	The Roche European American Cataract Trial (REACT). Randomised, double blind, placebo-controlled, trial with parallel groups design. Generation of the allocation sequence: adequate, by Efron's biased coin method. Allocation concealment: adequate, the generator of the assignment (the individual who generated, using a bias-free method, the listing that identified the intervention assignment for every participant) was located in Munich, Germany. The executor of the assignment (the individual who, having determined a participant's eligibility, consulted the assignment system for that participant's intervention designation) was also located in Munich, Germany. The persons who prepared the randomisation scheme were not involved in determining eligibility, administering intervention, or assessing outcomes. Blinding: adequate, identical placebo capsules contained corn oil as the major constituent provided by a sponsor. Follow-up: adequate, the pattern of drop-outs was similar in the groups, and drop-outs created no imbalances between the placebo and treatment groups. There were no differences noted between the vitamin and placebo groups regardless of the length of follow-up. Overall 59 participants in the vitamin group and 68 participants in the placebo group were lost to follow-up. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: United States and United Kingdom Number of patients randomised: 297, mean age 68 years, 59 % females. Inclusion criteria: at least one eye met the following ocular criteria: cataract extraction unlikely within two years, immature idiopathic 'senile' cataract present in one or both eyes, (U.S. patients) presence of minimal cataract by Lens Opacities Classification System (U.K. patients) presence of cataract of minimal Oxford grade: cortical and posterior subcapsular grades: grade I; nuclear brunescence: grade II; and white nuclear scatter: grade II. If both eyes met the inclusion criteria, and cataracts were of different types, the cataract type in the eye with the worse visual acuity determined the group for randomisation. If an eye had more than one type of cataract, the morphological type that in the clinicians opinion was the more destructive to visual acuity determined the group for randomisation, no visually significant fundus pathology, no clinical signs of glaucoma and intraocular pressure, no history of amblyopia, eye surgery, argon or YAG laser eye treatment, or major eye trauma, no history of iritis, retinal crystalline deposits, or optic nerve disease, no extended (daily for >3 months) use of ocular corticosteroid or glaucoma therapy, no participation in another clinical trial investigating an anticataract formulation within the last year. Exclusion criteria: pregnancy, insulin dependent diabetes mellitus, severe renal failure or kidney stones, fat malabsorption syndrome, history of major intestinal surgery, chronic diarrhoea, alcoholism, extended use (daily for > 3 months) of systemic corticosteroid treatment, use of anticoagulants, or regular use of any vitamin supplement.

Interventions	Patients were randomly assigned to receive:
	group 1: 600 mg vitamin E (all-rac alpha-tocopherol acetate), vitamin C 750 mg, and beta-carotene 18 mg (n = 149);
	group 2: placebo (n = 148);
	The actual supplementation period ranged from 2 to 51 months, 231 patients were followed for at least two years, 158 patients for at least three years and 36 patients for at least four years. Patients remained in the study for 34 months.

REACT 2002Low (*Continued*)

Outcomes	The primary outcome was: the measure of area, 'increase % pixels opaque' cataract severity documented with serial digital retroillumination imagery of the lens; progression was quantified by image analysis assessing increased area of opacity.
Notes	Compliance with treatment was checked by serum assessments. The plasma concentrations of vitamin C, vitamin E, and beta-carotene in the treated and placebo groups were maintained at consistent levels throughout the trial indicating excellent compliance with instructions about the use of the trial medication. There appeared to be little if any supplementation of placebo with other vitamins or failure to take the vitamin capsules. The work was supported by grants from F. Hoffmann-La Roche, Ltd., Basel, Switzerland, and Roche Vitamins, Inc., Parsippany, NJ.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Sasazuki 2003

Methods	Randomised, double-blind placebo-controlled trial with three-by-three, then two-by-two factorial design and then parallel group design. Generation of the allocation sequence: unclear, not reported. Allocation concealment: adequate, the capsules were allocated to each participant in a central control centre. Blinding: adequate, identical looking capsules. Follow-up: inadequate, losses to follow-up were high due to modification of the protocol. Out of 439 participants randomised, 134 has dropped out before the trial was altered. Of the 397 remaining participants, 305 (77%) consented to take part in a modified trial and 244 completed the trial. Overall, 98 participants, assigned to receive 500 mg vitamin C and 97 participants, assigned to receive 50 mg vitamin C were lost to follow-up. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: Japan. Number of participants randomised: 439, 35% men and 65% women, aged 40 to 69 years, mean age 57 years. Inclusion criteria: men and women living in four municipalities (3 towns and one village of Yokote Public Health Centre District in Akita prefecture, participated in annual screening programmes for circulatory diseases with chronic atrophic gastritis (determined by serum pepsinogen (PG) levels (PG I < 70 ng/ml and PG I/PG II ration < 3.0). Exclusion criteria: past history of gastric cancer or surgery, liver cancer or cirrhosis, and other cancers within 5 years; abnormal liver function (AST > 100 IU/L, ALT > 100 IU/L, or ALP > 800 IU/L), use of supplements containing beta-carotene or vitamin C, unable to follow-up for at least one year.

Sasazuki 2003 (*Continued*)

Interventions	Participants were randomly assigned to receive:
	group 1: vitamin C 50 mg and beta-carotene placebo;
	group 2: vitamin C 500 mg and beta-carotene placebo;
	group 3: vitamin C 50 mg and beta-carotene 15 mg;
	group 4: vitamin C 500 mg and beta-carotene 15 mg.
	217 participants (low-dose group) were assigned to receive 50 mg of vitamin C and 0/15 mg of beta-carotene;
	222 participants were assigned to receive 500 mg of vitamin C and 0/15 mg of beta-carotene.
	daily for 5 years.
	Out of 439 persons initially participating in the study, 134 participants dropped before and on modification of the study protocol based on a National Cancer Institute report that indicated that 2 beta-carotene trials had shown no benefit or potential harm from the supplement. Of the 305 remaining participants, 244 completed this study.
	Participants were supplemented with beta-carotene from September 1995 to March 1996, (three to six months). After that study was continued with parallel group design.
	Participants were randomly assigned to receive:
	group 1: vitamin C 50 mg (n = 144);
	group 2: vitamin C 500 mg (n = 161);
	for five years.

Outcomes	The primary outcome measure was: the 10-year cumulative incidence of gastric cancer. The secondary outcome measure was: 5-year change in serum levels of pepsinogens. After the modification of the protocol the primary outcome measure was 5-year change in serum levels of pepsinogens and other biomarkers.
Notes	Compliance with treatment was constantly encouraged and monitored by nurses, who interviewed the participants and recorded pill counts every 3 months (compliance rate, 80%). Compliance with treatment was checked by serum assessments. Blood samples were drawn and stored three times (at baseline, and after the first, and the fifth year) in order to measure serum level of ascorbic acid. Compliance in taking the vitamin capsules was 92.9% in men and 95.4% in women. Additional information about all-cause mortality obtained through personal communication with authors. These data, which are extremely positive, are not published.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

SCPS 1990Low

Methods	Skin Cancer Prevention Study (SCPS). Randomised, double-blind placebo-controlled trial with parallel group design. Generation of the allocation sequence: adequate, on a computer in block of 16 without stratification. Allocation concealment: adequate, central independent unit. Blinding: adequate, identical looking capsules. Follow-up: adequate. Of the 1805 patients who have been randomised, 89% completed at least three years of observation, 79% four years, and 46% five years. The patterns of follow-up were similar in the two treatment groups. Intention-to-treat analysis: no. Sample size calculations: no.
Participants	Country: United States of America. Number of participants randomised: 1805, 1251 (70%) men and 554 (30%) women. Inclusion criteria: < 85 years old, at least one biopsy-proved basal-cell or squamous-cell carcinoma, could not become pregnant, agreement not to take vitamin supplements containing vitamin A or betacarotene, not a vegan vegetarian (one who eats no animal products, including milk or eggs). Exclusion criteria: xeroderma pigmentosum, basal-cell nevus syndrome, an active nonskin cancer, known exposure to arsenic, or any other major medical problem that would limit their ability to participate in the planned five years of study.

Interventions	Patients were randomly assigned to receive:
	group 1: beta-carotene 50 mg (n = 913);
	group 2: placebo (n = 892);
	one capsule daily for five years.
	Duration of follow-up was five years.

Outcomes	The primary outcome measures were: the first occurrence of basal-cell or squamous-cell skin cancer.
Notes	Compliance with the study medication was determined by interviewing the patients and by measurement of plasma beta-carotene levels. At four months interval patients were asked to complete questionnaires concerning compliance in taking the capsules. Reported adherence to treatment did not differ appreciably between the placebo and beta-carotene groups, and during each of the first four years at least 80% of the patients reported taking half or more of their capsules. Plasma beta-carotene levels showed more than eight-fold increase in the group that received beta-carotene and almost no-change in the placebo group. The trial agents were provided by BASF, Wyendotte, Michigen. Though a study with a longer follow-up on this same trial was published in JAMA (Mortality associated with low plasma concentration of beta carotene and the effect of oral supplementation. JAMA 1996;275(9):699-703.), we could not use the mortality data from the latter because it does not report on the 85 excluded patients. However, replacing the number of deaths from Greenberg 1990 with the mortality data given in the JAMA publication (146 vs 139 (placebo) does not change the result noticeably.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

SIT 2001

Methods	Shandong Intervention Trial Randomised, double-blind, placebo controlled, primary prevention trial with stratified, factorial design 2x2x2 versus 2x2. Generation of the allocation sequence: unclear, not reported. Allocation concealment: adequate, treatments were randomly assigned at Westat, Inc. and this assignment is used to distribute coded bottles of capsules from the pharmacy in the city of Weifang in Shandong Province. Blinding: adequate, using identical placebo capsules. Follow-up: adequate, overall 15 participants from placebo and 19 participants from active intervention group were lost to follow-up. Intention-to-treat analysis: no. Sample size calculations: yes.
Participants	Country: China (Linqu County, Shandong Province). Number of participants randomised: 3411, 1753 men and 1658 women aged 35 to 64 years. Inclusion criteria: participants aged 35 to 64 years willing to participate in 42-month study, baseline gastroscopy with biopsies, known Helicobacter pylori status. Exclusion criteria: illness, bleeding disorders, cancers (except nonmelanoma skin cancer), heart failure, emphysema, renal or liver diseases, other life-threatening illnesses, allergy to penicillin or related antibiotics.

Interventions	Participants were first divided on the basis of whether they showed serologic evidence of Helicobacter pylori infection at baseline (2285) or not (1126). Participants with serologic evidence of Helicobacter Pylori at baseline were eligible to receive amoxicillin (1 g twice a day) and omeprazole (20 mg twice a day) in three capsules (two 500 mg amoxicillin and one 20 mg omeprazole) to be taken twice daily (before breakfast and dinner) for 2 weeks. Look-alike placebo capsules containing lactose and starch for amoxicillin and sucrose and starch for omeprazole were given to serologically positive controls and to all seronegative participants. Approximately 3 months after initial treatment for Helicobacter Pylori, supplementation with 100 IU alpha-tocopherol, 250 mg vitamin C, and 37.5 µg selenium twice a day began its 39-month course. Participants receive this mixture in one capsule, to be taken twice daily before or after breakfast and dinner. From December 1995 to May 1996, this mixture also contained beta-carotene (7.5 mg twice a day). Look-alike placebo capsules contained cellulose, lactose, and magnesium stearate.
	In the garlic group, participants take two capsules twice a day before or after breakfast and dinner. Each capsule contains 200 mg Kyolic aged garlic extract and 1 mg steam-distilled garlic oil. To prepare the extract, the manufacturer slices garlic cloves and soaks them in aqueous ethanol (about 20%) for over 18 months at room temperature. The extract is then filtered, concentrated, and dried. The look-alike placebo capsules contain cellulose, granulated sugar, caramel, and magnesium stearate. Bottles holding placebo capsules contained minute quantities of garlic oil so they would smell like garlic.
	HP-seropositive at baseline (2258) entered 2x2x2 factorial of antibiotics, vitamins, and garlic. HP-seronegative at baseline (1126) entered 2x2 factorial trial of vitamins, and garlic.
	Participants were randomised in 12 groups:
	group 1: amoxicillin and omeprazole, garlic, vitamin and selenium (n=286);
	group 2: amoxicillin and omeprazole, garlic, vitamin and selenium placebo (n=285);
	group 3: amoxicillin and omeprazole, garlic placebo, vitamin and selenium (n=286);
	group 4: amoxicillin and omeprazole, garlic placebo, vitamin and selenium placebo (n=285);
	group 5: amoxicillin and omeprazole placebo, garlic, vitamin and selenium (n=285);
	group 6: amoxicillin and omeprazole placebo, garlic, vitamin and selenium placebo (n=286);
	group 7: amoxicillin and omeprazole placebo, garlic placebo, vitamin and selenium (n=286);

SIT 2001 (*Continued*)

	group 8: amoxicillin and omeprazole placebo, garlic placebo, vitamin and selenium placebo (n=286); group 9: amoxicillin and omeprazole placebo, garlic; vitamin and selenium (n=282); group 10: amoxicillin and omeprazole placebo, garlic, vitamin and selenium placebo (n=281); group 11: amoxicillin and omeprazole placebo, garlic placebo, vitamin and selenium (n=281); group 12: amoxicillin and omeprazole placebo, garlic placebo, vitamin and selenium placebo (n=282);
Outcomes	The primary outcome measures were: prevalence of dysplasia or gastric cancer, prevalence of severe chronic atrophic gastritis, intestinal metaplasia, dysplasia or gastric cancer, and average severity score. Secondary outcome measures were: rates of transition from baseline to final histopathologic states and the effects of treatments on these rates of transition; evidence of the effectiveness of amoxicillin and omeprazole in eradicating Helicobacter pylori, based on 13C-urea breath tests 3 months following treatment, on annual serology, and on a final pathologic examination of biopsies to look for Helicobacter pylori; and blood pressure at the time of the final examination.
Notes	Compliance with treatment was checked by measuring the plasma vitamin levels in randomly selected participants every 3 months and counting of the pills. Compliance with treatment was good. The average monthly proportion of participants taking all pills was 92.3%. Serum samples obtained from randomly selected participants demonstrate higher levels of vitamins C and E in participants assigned to vitamins 2 and higher levels of S-allylcysteine in those assigned to garlic preparation. (Wakunaga of America, Co., Ltd, Mission Viejo, CA) provided the garlic preparation, Astra (East Asia Region) provided axomicillin and omeprazole; and Sino-American Shanghai-Squibb Pharmaceuticals, Ltd. provided vitamin and mineral supplement.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

SKICAP AK 1997Low

Methods	Skin Cancer Prevention Study - actinic keratoses (SKICAP-AK). Randomised, double-blind placebo-controlled trial with parallel group design. Generation of the allocation sequence: adequate, on a computer in permuted blocks of size 4. Allocation concealment: adequate, numbered coded bottles. Blinding: adequate, identical looking capsules. Follow-up: adequate. Overall, 99 participants from the intervention group and 88 from the placebo group were lost to follow-up. Intention-to-treat analysis: no. Sample size calculations: yes.

SKICAP AK 1997Low (*Continued*)

Participants	Country: United States. Number of participants randomised: 2297, 679 (30%) women and 1618 (70%) men, aged 21 to 84 years, median age 63 years, with a history of more than 10 actinic keratoses and at most 2 squamous cell carcinoma (SCC) or basal cell carcinoma (BCC) skin cancers. Inclusion criteria: free living participants aged 21 to 84 years, ambulatory and capable of self care, with no diagnosis of life threatening diseases, an intended continual resident of Arizona for at least five years, willing to return during the five years for semi-annual follow-up clinic visits, and willing to limit non-study vitamin A supplementation to no more than 10,000 IU per day, clinical laboratory values within the 95% normal range for total cholesterol, liver function (AST and ALT), WBC count, haemoglobin and platelet count, and history of more than 10 actinic keratoses and at most 2 squamous cell carcinoma (SCC) or basal cell carcinoma (BCC) skin cancers. Exclusion criteria: cancer diagnosis or treatment within the year preceding the trial other than BCC or SCC, history of xeroderma pigmentosum or basal-cell nevus syndrome.

Interventions	Patients were randomly assigned to receive:
	group 1: vitamin A (retinol) 25,000 IU (n = 1157);
	group 2: placebo (n = 1140);
	one capsule daily for a period of 5 years (median follow-up time of 3.8 years.

Outcomes	The primary outcome measures were: the time to first new occurrence of SCC and time to first new occurrence of BCC pathologically confirmed by the study pathologist.
Notes	Compliance with the study medication was determined by counting capsules in the returned medication bottles and by measurement of plasma vitamin A levels. Participants were scheduled for a return clinic visit one month after randomisation and then every six months. They were interviewed to evaluate adherence, motivated to adhere and provided with a six-month supply of capsules. Participants were telephoned and mailed postcards between clinic visits for symptom assessment and adherence monitoring and motivation. Vitamin intake was reported by 73% of the participants, and 30% of participants reported dietary intake near or below the recommended. Calculated adherence to the intervention was almost identical between the placebo and retinol groups. During the 5-year intervention period, at least 85% of participants reported taking at least three-quarters of their capsules, and at least 95% reported taking at least half of their capsules. The results show very similar baseline retinyl palmitate levels and approximately an 8-fold increase in the median serum retynil palmitate level in the group assigned to receive retinol. Hoffmann-LaRoche provided intervention capsules.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

SPACE 2000Low

Methods	Secondary prevention with antioxidants of cardiovascular disease in end stage renal disease (SPACE). Randomised, double blind, placebo-controlled, secondary prevention intervention trial with parallel group design. Generation of the allocation sequence: adequate, computer generated coin toss within each stratum. Allocation concealment: adequate, central independent unit. Randomisation done by an individual not directly involved in the study. Blinding: adequate, identical placebo capsules provided by a sponsor. Follow-up: adequate. There were no losses to follow-up. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: Israel. Number of patients randomised: 196; 135 males and 61 females, aged 40 to 75 years, mean age 64.6 years. Inclusion criteria: stable haemodialysis patients between the ages of 40 and 75 years inclusive at baseline with a documented medical history of cardiovascular disease (including hospital records, appropriate electrocardiographic and biochemical supporting indices). Exclusion criteria: anticoagulant therapy with warfarin sodium; known history of malignant disease (except non-melanoma skin cancer); active liver disease; treatment with hypolipaemic agents for less than eight weeks before the study started; pregnant or planning to become pregnant during duration of the study; any condition the treating physician deemed to preclude the patient on grounds of safety or study evaluation.

Interventions	Patients were randomly assigned to receive:
	group 1: vitamin E 800 IU/day (n = 97);
	group 2: matching placebo (n = 99);
	Vitamin E was provided as two capsules of 400 IU each. Patients were instructed to take two capsules nightly.
	Median follow-up time was 519 (range 10 to 763) days.

Outcomes	The primary outcome measure was: a composite variable consisting of: acute myocardial infarction (fatal and nonfatal); ischaemic stroke; peripheral vascular disease (excluding the arterio-venous fistula) in a limb not previously affected; and unstable angina. Secondary outcome measures were: fatal and non-fatal myocardial infarction, cardiovascular disease mortality (fatal myocardial infarction, ischaemic stroke or sudden death), total mortality, ischaemic stroke, peripheral vascular disease, and unstable angina.
Notes	Compliance with treatment was evaluated by measuring serum vitamin E concentrations. Throughout the study, patients continued to receive regular monthly follow-up by their unit dieticians, who instructed them to comply with dietary recommendations for maintenance haemodialysis patients. Additional vitamin supplementation was similar in the two treatment conditions. Folate (5 to 10 mg/day), vitamin B6 (10 to 250 mg/day), and vitamin B12 (250 μg/day) were prescribed to 57 (57.5%) patients in the placebo group and 55 (56.7%) patients in the vitamin E group. Only one patient (in the vitamin E group) received vitamin B12 as a monthly intramuscular injection. Vitamin C (100 to 500 mg/day) was prescribed to 42 (42.5%) of the placebo group and 42 (43.3%) of the vitamin E group. Vitamin E and placebos were provided by Solgar, Inc, New York, USA, during the first year and Henkel Corp, La Grange, IL, USA, during the second year.

SPACE 2000Low (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Stevic 2001

Methods	Randomised, double-blind, placebo-controlled trial with parallel group design. Generation of the allocation sequence: unclear, not reported. Allocation concealment: unclear, not reported. Blinding: adequate, identical placebo pills. Follow-up: adequate. There were no losses to follow-up. Intention-to-treat analysis: no. Sample-size calculation: no.
Participants	Country: Yugoslavia. Number of participants randomised: 28, 75% men and 25% women, aged 20 to 70 years, mean age 57 years. Inclusion criteria: probable or definite ALS by El Escorial criteria, age 20 to 70 years, disease duration < 3 years, ambulatory. Exclusion criteria: significant compromise of bulbar or respiratory function, conduction block, M protein, significant imaging abnormality, dementia, and concurrent systemic disease.

Interventions	Participants were randomly assigned to receive:
	group 1: alsemet-L-methionine (2 g), vitamin E (400 IU), selenium (3 x 10-5g) three times daily (n = 16);
	group 2: placebo (n = 12);
	for a period of one year.

Outcomes	The primary outcome measures were: survival and rate of disease progression as expressed by decline in limb-function, bulbar-function and muscle-testing scores. Secondary outcome measures were: activity of antioxidative components, and level of vitamin E in blood.
Notes	Compliance with treatment is not reported.

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

SUVIMAX 2004Low

Methods	The SUpplementation en VItamines et Mine´ raux AntioXydants (SU.VI.MAX) Study. Randomised, double-blind, placebo-controlled, primary-prevention trial with parallel group design. Generation of the allocation sequence: adequate, random treatment allocation was performed by block-sequence generation stratified by sex and age group by computer. Allocation concealment: adequate, capsule boxes were labelled with the participant's number, using partitioned organisation to ensure total security of the blind study. Blinding: adequate, identical placebo capsules. Follow-up: adequate. Losses to follow-up; 5.4 % in the intervention group and 6.2% in the placebo group. Overall, 739 participants in the active and 828 participants in the placebo group were lost to follow-up. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: France. Number of participants randomised: 13017 French adults, 5141 men and 7876 women, aged from 35 to 60 years, mean age 48.95 years. Inclusion criteria: lack of disease likely to hinder active participation or threatened 5-year survival; acceptance of possibility to be given placebo and acceptance of the constraints of participation; lack of previous regular supplementation with any of the vitamins and minerals in the supplement provided and absence of extreme beliefs or behaviour regarding diet. Exclusion criteria: none stated.
Interventions	Participants were randomly assigned to receive: group 1: beta carotene 6 mg; vitamin C 120 mg; vitamin E 30 mg; selenium 100 µg; zinc 20 mg (n = 6481); group 2: placebo (n = 6536). All participants took a single daily capsule. Median follow-up time was 7.5 years.
Outcomes	The primary outcome measures were: major fatal and nonfatal ishaemic cardiovascular events and cancer of any kind, except for the basal cell carcinoma of the skin. The secondary outcome measure was: all cause mortality.
Notes	Compliance for the intervention group was confirmed by measuring the biochemical markers of supplementation after 2 years and after 7 years for beta-carotene, vitamin C and selenium. At the end of follow-up, 74% of participants reported having taken at least two thirds of the capsules. There were no differences between the groups mean percentage of capsules taken, ie, 79% in each group). Sponsors of the trial: Fruit d'Or Recherche, Candia, Lipton, Kellogg's, Centre d'Information sur Canderel, Orangina, Este e Lauder, Cereal, Grands Moulins de Paris, CERIN, L'Ore al, Peugeot, Jet Service, RP Scherer, Sodexho, France Telecom, Santogen, Becton Dickinson, Fould Springer, Boehringer Diagnostic, Seppic Givaudan Lavirotte, Le Grand Canal.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Takagi 2003

Methods	Randomised, clinical trial with parallel group design. Generation of the allocation sequence: unclear, not reported. Allocation concealment: unclear, not reported. Blinding: inadequate, no intervention in the control arm. Follow-up: adequate. Seven patients in the vitamin E group and 3 patients from the control group dropped out from the trial. Intention-to-treat analysis: no. Sample size calculations: no.
Participants	Country: Japan. Number of patients randomised: 93, 45% males and 55% females, mean age 62.5 years. Inclusion criteria: liver cirrhosis caused by hepatitis C infection. Exclusion criteria: none stated.

Interventions	Patients were randomly assigned to receive:
	group 1: vitamin E (600 mg) (n = 51);
	group 2: no treatment (n = 42);
	for a period of 5 years.

Outcomes	The primary outcome measures were: tumor-free survival and cumulative survival rate.
Notes	Compliance was not reported.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Takamatsu 1995

Methods	Randomised, double-blind, placebo-controlled trial with parallel group design. Generation of the allocation sequence: unclear, not reported. Allocation concealment: adequate, centrally by pharmacy. Capsules required by each participant for a 6-month period were placed in identical bottles labelled with the personal numbers of the volunteers. Blinding: adequate, capsules identical in size, shape, weight and colour. Follow-up: adequate. Losses to follow-up were 4 participants (6.75%) in the active treatment group and 10 participants (13.69%) in the placebo group during the trial. Intention-to-treat analysis: no. Sample-size calculation: no.
Participants	Country: Japan. Number of participants randomised: 161, 64 men and 97 women, aged 39 to 56 years. Inclusion criteria: healthy Japanese adults free of acute and chronic illness, including hypertension.

Takamatsu 1995 (*Continued*)

	Exclusion criteria: taking oral contraceptives, vitamins or mineral supplements, pregnant or lactating women.

Interventions	Participants were randomly assigned to receive:
	group 1: vitamin E (d-alpha-tocopheryl acetate) 100 mg (n = 82);
	group 2: placebo (vitamin E 3 mg), (n = 79);
	for a period of 6 years.

Outcomes	The primary outcome measure was: any illness.
Notes	Medication compliance during the trial period was 89.6% in vitamin E group and 91.3% in the placebo group. Vitamin E (d-alpha tocopheryl acetate capsules) were provided by Eisai Co. Ltd (Tokyo, Japan).

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Tam 2005Low

Methods	Randomised, double-blind, placebo-controlled trial with parallel group design. Generation of the allocation sequence: adequate, by computer. Allocation concealment: adequate, by a central independent unit (the school of pharmacy). Blinding: adequate, identical placebo tablets. Follow-up: adequate. There were no losses to follow-up. Intention-to-treat analysis: no. Sample size calculations: no.
Participants	Country: Hong Kong. Number of patient's randomised: 39 females, mean age 46. Inclusion criteria: female patients with systemic lupus erythematosus. Exclusion criteria: flare of systemic lupus erythematosus requiring increase in immunosuppressive agents.
Interventions	Patients were randomly assigned to receive: group 1: vitamin C 500 mg, vitamin E (D-alpha tocopheryl succinate) 800 IU n=20; group 2: placebo, n=19; daily, 12 weeks. Patients were followed 2.67 years.
Outcomes	The primary outcome measures were: effects on markers of oxidative stress, antioxidant defence, and endothelial function.
Notes	Compliance was assessed by tablet counting, and patients with less than 70% compliance were excluded from the analyses. Overall compliance by pill count was 95%.

Tam 2005Low (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

ter Riet 1995

Methods	Randomised, double-blind, placebo-controlled trial with two-by-two factorial design. Generation of the allocation sequence: adequate, by computer. Allocation concealment: unclear, not reported. Blinding: adequate, identical placebo tablets. The 'placebo' tablet was in fact containing 20 mg vitamin C. The dosis could eradicate vitamin C deficiency in the control arm. Accordingly, the 'placebo' control of the trial can be discussed. Follow-up: adequate, during the course of the study three participants withdrew. Overall 1 participant withdrew from the intervention group and 2 withdrew from the control group. Intention-to-treat analysis: yes. Sample size calculations: no.
Participants	Country: The Netherlands. Number of participants randomised: 88. Inclusion criteria: patients with pressure ulcers (partial thickness skin loss or worse). Exclusion criteria: difficulties with swallowing or frequent vomiting, osteomyelitis in the ulcer area, idiopathic haemochromatosis, thalassaemia major, sideroblastic anaemia, Cushing's syndrome or disease, pregnancy, radiotherapy in the ulcer area, and the use of antineoplastic agents or systemic glucocorticosteroids, high probability to drop out within the 12 week follow-up period (terminally ill patients, patients for whom surgical treatment of the ulcer-other than debridement), taking vitamin C supplements in excess of 50 mg/day.
Interventions	Participants were randomly assigned in four groups to receive: group 1: vitamin C 1000 mg and ultrasound; group 2: vitamin C 1000 mg and sham ultrasound; group 3: vitamin C 20 mg and ultrasound; group 4: vitamin C 20 mg and sham ultrasound; daily for 12 weeks. Overall 43 participants were supplemented with 1000 mg of vitamin C, while 45 participants were in 'placebo' group supplemented with 20 mg of vitamin C.
Outcomes	The primary outcome measures were: wound survival, healing rates of wound surfaces, and clinimetric changes.
Notes	Compliance with prevention is not reported. The trial used 20 mg vitamin C in the placebo pills. Removing this trial from our analyses does not noticeably change our results. Hoffmann-La Roche & Co., Ltd., Basel supplied vitamin C tablets.

ter Riet 1995 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

VEAPS 2002Low

Methods	The Vitamin E Atherosclerosis Prevention Study (VEAPS). Randomised, double-blind, placebo-controlled, primary-prevention trial with parallel group design. Generation of the allocation sequence: adequate, computer-generated random numbers. Allocation concealment: adequate, central independent unit. Participants, clinical staff, imaging specialists, data monitor, and statistical analysts were blinded to treatment assignment. Blinding: adequate, identical placebo capsules. Follow-up: adequate, 90% of the randomised participants completed the 2-year treatment. Overall, 15 participants in the active group and 6 participants in the placebo group were lost to follow-up. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: United States of America. Number of participants randomised: 353 men and women, aged from 40 to 82 years, mean age 56 years. Inclusion criteria: age > 40 years, with LDL cholesterol (LDL-C) > 3.37 mmol/L (130 mg/dL) and no clinical signs or symptoms of cardiovascular disease (CVD). Exclusion criteria: fasting triglycerides > 5.64 mmol/L, diabetes mellitus or fasting serum glucose > 3.62 mmol/L, regular vitamin E supplement intake > 1 year, lipid standardised plasma vitamin E > 35 µmol/L, diastolic blood pressure > 100 mm Hg, untreated thyroid disease, serum creatinine > 0.065 mmol/L, life-threatening disease with prognosis < 5 years, or alcohol intake > 5 drinks daily.

Interventions	Participants were randomly assigned to receive:
	group 1: vitamin E (DL-alpha-tocopherol) 400 IU (n = 177);
	group 2: placebo (n = 176);
	daily for a period of three years.
	Participants were instructed to take trial pills with their greatest fat-containing meal of the day.
	The initial trial design called for a 2-year treatment period. Based on evolving null results from other antioxidant clinical trials, the External Data and Safety Monitoring Board recommended after 2 years of initiation of the study that the treatment period be extended to 3 years. Participants were offered the opportunity to continue another year of their randomised and blinded treatment assignment. The 81% of 2-year completers, 73% of randomised elected to continue for a 3-year treatment period.

Outcomes	The primary trial outcome was: rate of change in the right distal common carotid artery intima-media thickness in computer image-processed B-mode ultrasonograms.

VEAPS 2002Low (*Continued*)

Notes	Compliance with treatment was assessed by counting unused pills and measuring plasma vitamin levels. Mean pill compliance was 92% in the placebo-treated group and 91% in the vitamin E group. Pill compliance for the placebo-treated versus the active vitamin E participants was maintained throughout the trial, as follows: 89% versus 87%, 90% versus 89%, 92% versus 92%, 91% versus 93%, 94% versus 91%, and 93% versus 93% at 6, 12, 24, 30, and 36 months, respectively. There was an appropriate rise in the mean plasma vitamin E level in the active vitamin E group from a baseline level. The trial was supported by Hoffmann-La Roche, Inc.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

VECAT 2004Low

Methods	itamin E, Cataract and Age-Related Maculopathy Trial (VECAT). Randomised, double blind, placebo-controlled trial with parallel group design. Generation of the allocation sequence: adequate, the randomisation schedule was prepared by a biostatistician using a permuted block allocation scheme. Allocation concealment: adequate, central, independent unit. The allocation list was stored at a remote site. Identification of which patients received vitamin E or placebo was concealed from the outcome assessors and data analysts until the analysis was finalised. Blinding: adequate, the medications were dispensed in identical containers so that neither the trial staff nor the participants were aware of the intervention in any specific patient. Follow-up: adequate. Overall, 60 participants from the placebo group and 58 participants from the vitamin group withdrew from the trial. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: Australia. Number of participants randomised: 1193, 44% men and 56% women, aged 55 to 80, mean age 65.7 years. Inclusion criteria: good general health, early or no cataract. Exclusion criteria: prior cataract surgery, advanced cataract in both eyes, glaucoma, known sensitivity to vitamin E, and long-term treatment with steroids or anticoagulants.
Interventions	Participants were randomly assigned to receive: group 1: vitamin E (natural vitamin E in soybean oil) 500 IU (n = 595). group 2: placebo (n = 598); for four years.
Outcomes	The primary outcome measures were: major age-related types of cataract: nuclear, cortical cuneiform, and posterior subcapsular.

VECAT 2004Low (*Continued*)

Notes	Compliance with the trial medication was determined by counting capsules in the returned medication bottles and by measurement of plasma vitamin E levels in a random sample of participants. Overall, 77% of the actively treated group and 79% of those participants randomised to placebo were estimated to have consumed 80% or more of their capsules. After 4 years of follow-up, 74% of the vitamin E group and 76% of the placebo group remained on their assigned medication and participated in the annual reviews. Among the remaining 25% of the participants, 12% in each group ceased taking the assigned medication but continued participating to have their eye examined. The trial was funded by Smith and Nphew, Australia, Henkel, Australia.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

WAVE 2002Low

Methods	Women's Angiographic Vitamin and Estrogen Trial (WAVE). Randomised, double blind, placebo-controlled trial with two-by-two factorial design. Generation of the allocation sequence: adequate, centrally by computer. Randomisation lists were produced for each stratum using a permuted block design with block sizes of two and four being randomly selected. Allocation concealment: adequate, the clinical centres nurse co-ordinators randomised women by calling the dedicated randomisation computer at the study co-ordinating centre. Blinding: adequate, identical placebo tablets. Follow-up: adequate. Twenty-three participants from the placebo group and 29 from the HRT group, 38 from the vitamins, and 27 from the HRT and vitamin group withdrew from the trial. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: United States of America and Canada. Number of participants randomised: 423 women mean age 65 years. Inclusion criteria: postmenopausal women as defined by any one of the following criteria: (bilateral oophorectomy at any age or age 45 to 55 with FSH 40 mIU/ml or older than 55 years. Protocol angiogram within four months performed while haemodynamically stable demonstrating at least one vessel segment free of intervention, with 15 to 75% stenosis. If the angiogram was performed within two weeks of a myocardial infarction, the qualifying segment may not be the infarct segment. Exclusion criteria: oestrogen replacement therapy within the past three months. Estrogen vaginal cream permitted if used no more than 25% of the time. Concurrent use of vitamins C and E exceeding the recommended dietary allowance, history of breast cancer or mammogram suggestive of cancer without subsequent negative biopsy, history of endometrial carcinoma without subsequent hysterectomy, any abnormal uterine bleeding or endometrial hyperplasia at baseline, pap smear with dysplasia of cervical intraepithelial neoplasia grade I or greater, uncontrolled diabetes or hypertension, myocardial infarction less than four weeks prior to randomisation, planned or prior coronary artery bypass grafting, fasting triglycerides 500 mg/dl within four months of randomisation, creatinine 2.0 mg/dl, symptomatic gallstones, New York Heart association class IV congestive heart failure or known ejection fraction 25%, history

WAVE 2002Low (*Continued*)

	of haemorrhagic stroke or bleeding diathesis, history of pulmonary embolism or idiopathic deep venous thrombosis, history of osteoporosis unless treated with nonhormonal therapy, anticipated survival three years, concurrent participation in other masked clinical trial, participation in an interventional device trial or short-term postangioplasty antithrombotic trial was permitted so long as follow-up angiography was not a requirement of that trial.

Interventions	The participants were randomly assigned to receive:
	group 1: vitamins (vitamin E 400 IU and vitamin C 500 mg) and hormone replacement therapy (HRT) placebo (n = 105);
	group 2: HRT (women with a prior hysterectomy took one tablet containing conjugated equine estrogens (0.625 mg of Premarin, while the women who had not had a hysterectomy took one tablet containing conjugated equine estrogens and medroxyprogesterone acetate (0.625 mg/2.5 mg of Prempro) and vitamins placebo daily (n = 103);
	group 3: vitamins C and E and HRT (n = 107);
	group 4: vitamin placebo and HRT placebo (n = 108);
	twice daily for a median of three years.

Outcomes	The primary outcome measure was: annualised mean change in minimum lumen diameter from baseline to concluding angiogram of all qualifying coronary lesions averaged for each patient. Patients with intercurrent death or myocardial infarction were imputed the worst rank of angiographic outcome.
Notes	Compliance with treatment was checked by serum assessments. Among the women with angiographic follow-up, those assigned to HRT took 67% of their prescribed medication according to pill counts, and those assigned to HRT placebo took 70%. The corresponding figures were both 84% for antioxidant vitamins and vitamin placebo. Nine women assigned to placebo estrogen crossed over to open-label estrogen, and one woman assigned to placebo vitamin supplements crossed over to open-label vitamins. Hormone replacement therapy drugs supplied by Wyeth Pharmaceuticals, Collegeville, Pa.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

White 2002Low

Methods	Randomised, double-blind, placebo-controlled trial with parallel group design. Generation of the allocation sequence: adequate, on random number basis. Allocation concealment: adequate, the randomisation allocation co-ordinated by a remote pharmacy, ie, central randomisation. The pharmacy kept all details until the samples had been analysed and the study was complete. Blinding: adequate, identical placebo pills. Follow-up: adequate. Seventeen participants failed to attend for endoscopy and 11 participants were not compliant with the trial medication, leaving 72 participants for final analyses. Overall, 14 participants in each group were lost to follow-up. Intention-to-treat analysis: no. Sample size calculations: no.
Participants	Country: United Kingdom. Number of participants randomised: 100, mean age 63, 58% males. Inclusion criteria: patients with Barrett's oesophagus on long-term (> 12 months) proton pump inhibitors (PPI) treatment attending for surveillance endoscopy. Exclusion criteria: pregnancy or lactation, previous gastric surgery, serious cardiovascular, respiratory, renal or neurological diseases, history of alcohol or drug abuse or use of non-steroidal antiinflammatory drugs.
Interventions	The participants were randomly assigned to receive: group 1: vitamin C 100 mg, vitamin E 200 mg, n = 50; group 2: placebo, n = 50. Participants were supplemented and followed 12 weeks.
Outcomes	The primary outcome measure was: changes in putative markers of DNA damage in gastric tissue following supplementation with vitamins C and E.
Notes	Plasma vitamin C and E were measured to assess patient compliance. Additional information about all-cause mortality obtained from the authors.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

WHS 2005Low

Methods	Women's Health Study (WHS). Randomised, double-blind, placebo-controlled trial with two-by-two-by-two factorial design in the beginning and than two-by-two. Generation of the allocation sequence: adequate, centrally by computer in batches of blocks of size 16. Allocation concealment: adequate, the randomisation allocation is coded. Shipping department sends out calendar packs (which are identical whether active or placebo) to individual participants depending on this code. All of the calendar packs are in coded boxes, supplied by the drug manufacturer, so that the shippers do not know which drug they are shipping. Blinding: adequate, identical placebo capsules. Follow-up: adequate. Losses to follow-up; 0.01% in beta-carotene group and 0.005% in placebo group. Overall, 132 participants in the active group and 102 participants in the placebo group had unknown vital status. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: United States of America. Number of participants randomised: 39876 females aged 45 years or older, mean age 54.6 years. Inclusion criteria: female health professionals willing to take part in the trial. Age 45 years or older; no previous history of coronary heart disease, cerebrovascular disease, cancer (except nonmelanoma skin cancer), or other major chronic illnesses; no history of adverse effects from aspirin; no use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) more than once a week, or willingness to forgo their use; no use of anticoagulants or corticosteroids; and no use of individual supplements of vitamin A, E, or beta carotene for more than once a week. Exclusion criteria: history of cancer (except non-melanoma skin cancer), coronary heart disease, or cerebrovascular disease.
Interventions	Participants were randomly assigned to one of the eight treatment groups. The active agents were 100 mg of aspirin, given on alternate days; 600 IU of vitamin E, given on alternate days; and 50 mg of beta-carotene, given on alternate days. group 1: aspirin 100 mg, beta carotene 50 mg, vitamin E 600 IU; group 2: aspirin 100 mg, beta carotene 50 mg, vitamin E placebo; group 3: aspirin 100 mg, beta carotene 50 mg placebo, vitamin E 600 IU; group 4: aspirin 100 mg, beta carotene placebo, vitamin E placebo; group 5: aspirin placebo, beta carotene 50 mg, vitamin E 600 IU; group 6: aspirin placebo, beta carotene 50 mg, vitamin E placebo; group 7: aspirin placebo, beta carotene placebo, vitamin E 600 IU; group 8: aspirin placebo, beta carotene placebo, vitamin E placebo; A total of 19939 women were assigned at random to receive beta-carotene and 19937 to receive placebo in the beginning of April 1993. A total of 19937 women were assigned at random to receive vitamin E and 19939 to receive placebo. The beta-carotene component of the trial was terminated early, on January 18, 1996. The aspirin and vitamin E components of the trial continued uninterrupted. The time from randomisation to the end of beta-carotene component of the study averaged 2.1 years. Authors published results of the beta-carotene component of the trial on February 6, 1998, after a median total follow-up of 4.1 years (2.1 years treatment plus 2.0 years follow-up). From that time trials proceeded as two-arm (vitamin E and placebo). Follow-up and validation of reported end points were completed in February 2005. The average duration of follow-up from randomization to the end of the trial was 10.1 years (range, 8.2-10.9 years).
Outcomes	The primary outcome measures were: incidence of invasive cancer (except non-melanoma skin cancer), myocardial infarction, and stroke. The secondary outcome measures were: non-fatal myocardial infarction, non-fatal stroke, death from cardiovascular causes, and death from any cause.
Notes	Compliance with treatment was checked by random serum assessments. Compliance with treatment was excellent. At the time of termination of the beta-carotene component, 87% of the active group have taken at least two thirds of the study capsules, while 9.9% of the women in the placebo group have taken beta-carotene or vitamin A supplements outside the trial. The active agents were provided as follows: aspirin by

WHS 2005Low (*Continued*)

	Bayer AG, Leverkusen, Germany; vitamin E by Natural Source Vitamin E Association, Washington DC; and beta-carotene by Lurotin, BASF Corporation, Wiandotte, MI. Data were extracted from the primary publication, but additional information was received through personal communication with the authors.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Witte 2005Low

Methods	Randomised, double-blind, placebo-controlled trial with parallel group design. Generation of the allocation sequence: adequate, random numbers generated by computer. Allocation concealment: adequate, the randomisation allocation co-ordinated by a remote pharmacy with which the investigators had no contact during the study (ie, central randomisation). Blinding: adequate, identical placebo capsules. Follow-up: adequate. Losses to follow-up; 1 patient in each arm. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: United States of America. Number of participants randomised: 32, aged > 70 years. Inclusion criteria: stable chronic heart failure due to ischaemic heart disease. Exclusion criteria: neurological or inflammatory conditions or other significant chronic morbidity affecting quality of life (eg, severe rheumatoid arthritis) or requiring long-term systemic steroid or non-steroidal anti-inflammatory drugs therapy (except low-dose aspirin). Patients in persistent atrial fibrillation were also excluded in order to optimise the reproducibility of the estimation of left ventricular function.
Interventions	Participants were randomly assigned to receive: group 1: calcium 250 mg; magnesium 150 mg; zinc 15 mg; copper 1.2 mg; selenium 50 µg; vitamin A 800 mg; thiamine 200 mg; riboflavin 2 mg; vitamin B6; 200 mg; folate 5 mg; vitamin B12 200 µg; vitamin C 500 mg; vitamin E 400 mg; vitamin D 10 µg; Co-enzyme Q10 150 mg, (n = 16); group 2: placebo (n = 16) (cellulose); four capsules per day for a period of 9 months. Patients were followed for an average of 295 days. Patients were on otherwise optimal therapy including diuretics, angiotensin-converting enzyme inhibitors, and beta-blockers if tolerated.
Outcomes	The primary outcome measures were: left ventricular function, levels of pro-inflammatory cytokines, and quality-of-life in elderly patients with chronic heart failure.
Notes	Authors did not measure blood levels of all the micronutrients to assess compliance, although the changes in the ferritin, vitamin B12, and folate levels in the patients, randomised to the micronutrient combination suggest that they took them.

Witte 2005Low (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Wluka 2002Low

Methods	Randomised, double-blind, placebo-controlled trial with parallel group design. Generation of the allocation sequence: adequate, computer generating block randomisation program. Allocation concealment: adequate, medications were dispensed by the centralised hospital pharmacy in coded bottles. Blinding: adequate, identical placebo tablets. Follow-up: adequate. Losses to follow-up; 5 patients in the active and 4 in the placebo group. Intention-to-treat analysis: yes. Sample size calculations: yes.
Participants	Country: Australia. Number of patients randomised: 136, 44,5% men and 55.5% women, mean age 64 years. Inclusion criteria: men and women aged 40 years and more fulfilling American College of Rheumatology clinical and radiographic criteria for osteoarthritis knee (all had osteophytes), have pain more than half the days of the previous month and at least one pain dimension of the Western Ontario and McMaster University osteoarthritis index (WOMAC) pain score above 20%. Pain that was at least mild in severity (no compromise of daily activities, frequent but tolerable pain that is worsened by unusual activity and patient may take a pain reliever occasionally). Exclusion criteria: known sensitivity to vitamin E, current anticoagulation therapy, previous stroke or history of poorly controlled hypertension, major morbidities such as a cancer or life threatening illnesses, inability to co-operate with study requirements and give informed consent, dementia, other forms of arthritis, inability to walk 50 feet without the use of assistive devices, hemiparesis of either lower limb, those awaiting knee replacement, grade IV knee osteoarthritis, and any contraindication to magnetic resonance imaging (MRI) (eg, pacemaker, cerebral aneurism clip, cochlear implant, presence of shrapnel/metal in strategic locations such as in the orbit, and claustrophobia).
Interventions	Patients were randomly assigned to receive: group 1: vitamin E 500 IU (n = 67); group 2: placebo (soybean); for a period of 2 years.
Outcomes	The primary outcome measure was: change in cartilage volume in patients with knee osteoarthritis.
Notes	Compliance was assessed by returned pill counts at each visit. Average compliance, assessed on the basis of residual capsule counts, was similar in the two groups; 95.7% in the vitamin E group and 97.0% in the placebo group. No side effects were attributed to vitamin E.

Wluka 2002Low (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

ADCS: Alzheimer's Disease Cooperative Study
AMDS: Age Related Macular Degeneration Study
AREDS: Age Related Eye Disease Study
ASAP: The Antioxidant Supplementation in Atherosclerosis Prevention Study
ATBC: Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study
CARET: The Beta-Carotene and Retinol Efficacy Trial
CHAOS: Cambridge Heart Antioxidant Study
DATATOP: The Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism
DATOR: D Alpha Tocopherol atORvastatin
GISSI: Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico
HATS: The HDL-Atherosclerosis Treatment Study
HOPE: The Heart Outcomes Prevention Evaluation Study
HOPE TOO: The Heart Outcomes Prevention Evaluation Study The Ongoing Outcomes
HPS: Heart Protection Study
LAST: Lutein Antioxidant Supplementation Trial
MAVIS: Mineral And Vitamin Intervention Study
MINVITAOX: The Geriatrie/MINéraux, VITamines, et AntiOXydants Network
NIT: Nutrition Intervention Trial
NPCT: Nutritional Prevention of Cancer Trial
NSCPT: Nambour Skin Cancer Prevention Trial
PHS: Physicians Health Study
PPP: The Primary Prevention Project
PPS: The Polyp Prevention Study
REACT: The Roche European American Cataract Trial
SCPS: Skin Cancer Prevention Study
SKICAP-AK: Skin Cancer Prevention Study - Actinic Keratoses
SPACE: Secondary Prevention with Antioxidants of Cardiovascular disease in End stage renal disease
SUVIMAX: The SUpplementation en VItamines et Mine´ raux AntioXydants
VEAPS: The Vitamin E Atherosclerosis Prevention Study
VECAT: Vitamin E, Cataract and Age-Related Maculopathy Trial
WAVE: Women's Angiographic Vitamin and Estrogen Trial
WHS: Women's Health Study
BCC: basal cell skin cancers
SCC: squamous cell skin cancer
RDA: recommended daily allowance
HBsAg: hepatitis B surface antigen
AFP: alpha fetoprotein
US: United States
AST: aspartate aminotransferase
ALT: alanine aminotransferase
WBC: white blood cells
QoL: quality of life

ARMD: age-related macular degeneration

Characteristics of excluded studies *[ordered by study ID]*

Abbey 1993	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Adler 1993	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Aghdassi 1999	Randomised clinical trial. There were no deaths during the follow-up period. Additional information obtained through personal communication with authors.
Aghdassi 2003	Randomised clinical trial where stable, but oxidatively stressed Crohn's disease participants (n = 57) were supplemented with vitamins E (800 IU) and C (1000 mg), or their placebo for 4 wk. Oxidative stress measured by breath pentane and ethane output, plasma lipid peroxides, and F2-isoprostane was assessed at baseline and at 4 wk. Disease activity was also monitored by measuring Crohn's disease (CD) activity index and plasma orosomucoid. Authors did not report any deaths during the trial.
Aguilo 2004	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Akova 2001	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Al-Taie 2003	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Albanes 1992	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Alberts 2004	Randomised, double-blind, placebo-controlled trial to evaluate dose escalation of vitamin A in skin cancer chemoprevention. One hundred and twenty-nine participants with severely sun-damaged skin on their lateral forearms were randomised to receive placebo or 25000, 50000, or 75000 IU/day vitamin A for 12 months. The primary outcome was the clinical and laboratory safety of vitamin A, and the secondary outcomes included quantitative, karyometric image analysis, and assessment of retinoid and rexinoid receptors in sun-damaged skin. Authors did not report any deaths during the trial.
Allard 1994	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Allard 1997	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Anah 1980	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Anderson 1974	Randomised double-blind clinical trial of daily dosage of 3200 IU of vitamin E in patients with angina pectoris during 9 weeks. Authors did not report any deaths during the follow-up period.
Anderson 1975	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Anderson 1997	Randomised clinical trial. The authors did not report any deaths during the follow-up period.

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Anderson 1999	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Andreone 2001	Randomised, double-blind, placebo-controlled trial to evaluate vitamin E supplementation as therapy for chronic hepatitis B in a pilot study including 32 patients. Patients were randomly allocated to receive vitamin E at the dose of 300 mg twice daily for 3 months (15 patients) or no treatment (17 patients). This trial did not meat our inclusion criteria.
Angstwurm 1999	Randomised open-label pilot trial comparing patients with and without selenium replacement. The aim was to determine the effect of selenium replacement on morbidity and mortality in patients with systemic inflammatory response syndrome. Three patients in active treatment group and two patients in placebo group had cancer at the time of randomisation. This trial did not meet our inclusion criteria.
Arad 2005	A double-blind, placebo-controlled randomised clinical trial of atorvastatin 20 mg daily, vitamin C 1 g daily, and vitamin E (alpha-tocopherol) 1,000 U daily versus matching placebos in 1,005 asymptomatic, apparently healthy men and women age 50 to 70 years with coronary calcium scores at or above the 80th percentile for age and gender. All trial participants also received aspirin 81 mg daily. Mean duration of treatment was 4.3 years. The aim of the trial was to determine whether lipid-lowering therapy and antioxidants retard the progression of coronary calcification and prevent atherosclerotic cardiovascular disease (ASCVD) events. One patient died, but it is not known in which arm. Authors did not respond to our request for further information.
Arvilommi 1983	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Astley 1999	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Avery 2003	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Bacic Vrca 2004	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Backman 1990	This is not a randomised trial.
Bailey 2001	Randomised clinical trial. There were no deaths during the follow-up period. Additional information obtained through personal communication with authors.
Baines 1988	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Barany 2001	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Barbagallo 1999	Randomised clinical trial. There were no deaths during the follow-up period. Additional information obtained through personal communication with authors.
Barbarich 2004	Randomised clinical trial. The authors did not report any deaths during the follow-up period.

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Barringer 2003	Randomised, double-blind, placebo-controlled trial to assess the effect of a multivitamin and mineral supplement on infection and quality of life. Twenty-eight persons did not complete the trial. There were no deaths during the follow-up period. Additional information obtained through personal communication with authors.
Basnayake 1983	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Bassenge 1998	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Bates 1998	This is not a randomised clinical trial. A cross-sectional analysis of survey data to characterize relationships among blood pressure, pulse rate, vitamin C status, and other protective and risk factors for older British people.
Beaton 2002	Randomised clinical trial. There were no deaths during the follow-up period. Additional information obtained through personal communication with authors.
Beckman 2003	Randomised clinical trial. There were no deaths during the follow-up period. Additional information obtained through personal communication with authors.
Benton 1991	Randomised clinical trial. The possibility that a subclinical deficiency of the trace element selenium might exist in a sample of the British population was examined by giving a selenium supplement for 5 weeks. Using a double-blind cross-over design, 50 participants received either a placebo or 100 mcg selenium on a daily basis. On three occasions they filled in the Profile of Moods States. A food frequency questionnaire was used to estimate the intake of selenium in the diet. Authors did not report any deaths during the trial.
Berger 1998	This randomised, placebo-controlled trial studied clinical and immune effects of trace element supplements. Twenty patients, aged 40 +/- 16 y (mean +/- SD), burned on 48 +/- 17% of their body surfaces, were studied for 30 d after injury. They consumed standard trace element intakes plus supplements (40.4 micromol Cu, 2.9 micromol Se, and 406 micromol Zn; group TE) or standard trace element intakes plus placebo (20 micromol Cu, 0.4 micromol Se, and 100 micromol Zn; group C) for 8 days. Demographic data were similar for both groups. This trial did not fulfil our inclusion criteria.
Bernard 2003	Randomised clinical trial. There were no deaths during the follow-up period. Additional information obtained through personal communication with authors.
Berson 1993	Randomised, clinical, double-masked trial with 2 x 2 factorial design and duration of 4 to 6 years to determine whether supplements of vitamin A or vitamin E alone or in combination affect the course of retinitis pigmentosa. Six-hundred-and-one patients aged 18 through 49 years with retinitis pigmentosa met preset eligibility criteria. Ninety-five per cent of the patients completed the trial (29/601). Four of 29 patients died and 25 decline to continue participation, most after the fourth year. We were not able to extract relevant data about the mortality in each arm from the published article. Authors were not able to provide these data too.

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Bespalov 2004	A randomised double blind placebo-controlled trial of the drug karinat was carried out in patients with chronic multifocal atrophic gastritis. Karinat contains beta-carotene 2.5 mg, alpha-tocopherol 5 mg, ascorbic acid 30 mg, and garlic powder 150 mg per tablet. Out of 66 patients, 34 received karinat, 32 placebo. There were no participants with gastrointestinal cancers at the end of the trial. Authors did not report any deaths during the trial.
Bierenbaum 1985	This is not a randomised clinical trial. The results of two experiments evaluating the effects of dietary supplementation with vitamin E are reported.
Bjorneboe 1988	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Blackhall 2005	A randomised placebo-controlled single-blind cross-over trial was conducted in 10 renal transplant recipients taking cyclosporin A (CsA) as part of their immunosuppressive therapy. Each phase of the trial lasted 6 months, with a 6 month wash-out period in between. During one of the phases, patients consumed a tablet twice per day, which delivered 400 IU/day of vitamin E, 500 mg/day of vitamin C, and 6 mg/day of beta-carotene. Authors did not report any deaths during the trial.
Block 2004	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Bloomer 2004	Randomised clinical trial. There were no deaths during the follow-up period. Additional information obtained through personal communication with authors.
Boardley 2000	Randomised, double-blind, placebo-controlled trial to determine if a daily micronutrient supplement could attenuate the decline in immune indexes during the autumn months in a group of elderly women supplemented for a period of 10 weeks. There were no deaths during the follow-up period. Additional information obtained through personal communication with authors.
Bogden 1990	This is not randomised clinical trial. The objective of this study was to determine the effects of a year of Zn supplementation on Zn concentrations in circulating cells and on cellular immune functions in the elderly. Participants, aged 60 to 89, were given a placebo, 15 mg Zn, or 100 mg Zn daily for 12 months. All participants also received a multivitamin/mineral supplement that contained no additional Zn. Blood samples were drawn and immune functions assessed prior to and at 3, 6, 12, and 16 months after beginning Zn supplementation. Participant diets were also assessed at each visit.
Bogden 1994	A placebo-controlled double-blind trial of the effects of daily micronutrient supplements on circulating vitamin and trace metal concentrations and delayed-hypersensitivity skin test. Participants aged 59 to 85 years, were randomly assigned to placebo (n = 27) or micronutrient (n = 29) treatment groups. Delayed-hypersensitivity skin test and circulating concentrations of nine micronutrients were measured before and after 6 and 12 months of micronutrient ingestion. Authors reported that one patient died after 1 month of enrolling the study, but did not report in which arm. Letter to the author was sent. Answer was not received.
Booth 2004	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Boshtam 2002	Randomised clinical trial. The authors did not report any deaths during the follow-up period.

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Boshtam 2005	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Bostom 1995	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Brand 2001	A six month, double blind, randomised, placebo controlled study of vitamin E 500 IU/day was carried out. Primary outcome measures were pain, stiffness, and function. Of seventy-seven participants, 5 withdrew before the end of study. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Broome 2004	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Brouwers 2002	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Brown 1994	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Brown 1998	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Brown 2000	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Brude 1997	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Bucca 1989	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Buchman 1999	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Bugianesi 2005	Randomised, double-blind, placebo-controlled trial to compare the usefulness of metformin versus prescriptive diet or vitamin E in the treatment of nonalcoholic fatty liver disease. Nondiabetic nonalcoholic fatty liver disease patients were given metformin (2 g/day; n = 55) for 12 months. The control cases were given either vitamin E (800 IU/day; n = 28) or were treated by a prescriptive, weight-reducing diet (n = 27). There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Bukin 1993	This is not a randomised trial. Increase of ornithine decarboxylase (ODC) activity is known to be associated with cell proliferation and, very likely, with tumour promotion. This prompted us to study the activity of ODC in gastric mucosa of patients with chronic atrophic gastritis that has been considered as a precursor of stomach cancer.
Bukin 1995	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Bukin 1997	Randomised clinical trial. The authors did not report any deaths during the follow-up period.

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Bunker 1994	This is not a randomised clinical trial. In this study a balanced nutritional supplement consisting of several macro- and micro-nutrients was administered daily to 27 housebound elderly (aged 70 to 85 years) for 12 weeks. Thirty-one matched participants served as a control group.
Bunout 2000	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Bursell 1999	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Bussey 1982	Randomised, double-blind trial of 49 patients with polyposis coli. Among the 49 patients, 36 were evaluable. During the trial two participants died, but authors did not report in which group they were. Letter to the author was sent.
Butcher 1993	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Cadenas 1996	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Cafolla 2002	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Calabrese 1987	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Calzada 1997	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Candan 1997	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Carpenter 2003	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Carty 2000	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Cases 2005	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Ceriello 1991	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Chan 2005	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Chandra 2001	Randomised, double-blind, placebo-controlled trial to assess cognitive function in apparently healthy, elderly participants. Author reported two deaths during the trial, but not in which arm of the study. The publication on the trial is retracted in 2005. Conflict of interest: Chandra failed to declare that he holds a patent on the tested supplement formula and has a financial stake in it because the supplement was licensed to Javaan Corporation, a company founded by his daughter, that sells the supplement. Letter to the author was sent.

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Chandra 2002	Randomised, double-blind placebo-controlled trial to examine the effect of multinutrient supplement on immune responses and infection-related illness in 50 to 65 year old individuals. Authors did not report any deaths during the follow-up period. Letter to the author was sent.
Chavance 1993	Randomised, double-blind placebo-controlled trial to assess the efficacy of a multivitamin supplement for the prevention of common infections in healthy elderly subjects. The treatment or placebo tablets were to be taken daily for four months. In each group seven participants (6.5%) withdrew from the trial before its end. There were no deaths reported during the trial.
Chesney 2000	The Arterial Disease Multiple Intervention Trial (ADMIT) was designed to determine the efficacy, safety, and compliance of an multifactorial therapy on selected atherosclerotic disease risk factors in patients with peripheral arterial disease. By a 2 x 2 x 2 factorial design, eligible participants (N = 468) were randomly assigned to low-dose warfarin, antioxidant vitamins, and niacin or its corresponding placebo, and followed up for 1 year. All participants were encouraged to use aspirin. Pravastatin was added to the drug regimen for those who needed to reduce LDL cholesterol to recommended levels. Authors did not report any deaths during the trial. Letter to the author was sent.
Cheung 2001	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Chuang 2002	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Clarke 2003	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Clausen 1989	Randomised clinical trial. Ninety-seven geriatric patients from two Danish homes for old people accepted to participate in a blinded experiment designed to counteract ageing phenomena. The participants were split into two groups, ie, the verum and the placebo group. The verum group received daily for one year an antioxidative cocktail consisting of: 300 micrograms selenium as L-selenomethionine, 45 mg zinc, 270 mg vitamin C, 2.7 mg vitamin A, 6 mg vitamin B-6, and 465 mg vitamin E (d-alfatocopherol). Furthermore, in order to enhance exchange in polyenoic acids, each participant received daily 250 mg gamma-linolenic acid. The placebo groups received similar looking pills and capsules without the active components. Authors did not report any deaths during the trial.
Colette 1988	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Corridan 2001	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Cox 1975	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Crary 1987	Randomised clinical trial. 102 patients with macular degeneration have been supplemented with vitamin C 500 mg, vitamin E 400 IU, beta-carotene 10,000 units and selenium (sodium selenite) 250 microg, and followed 7 to12 years. 176 patients with diabetes mellitus and diabetic macular edema have also been followed for 7 to 12 years. Authors did not report any deaths during the trial.

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Crimi 2004	Randomised, double-blind placebo-controlled trial to examine the effect of antioxidant supplementation in enteral feeding in critically ill patients. Baseline characteristics of patients were reason for exclusion. Eighteen patients in antioxidant group and 16 patients in placebo group had malignancy. This trial did not meet our inclusion criteria.
Crogan 2005	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Dabiri 1994	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Daga 2003	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Dakhale 2005	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Darko 2002	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Davison 2005	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Dawson 1999	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
De las Heras 2000	This is not a randomised clinical trial. The purpose of this report is to analyse the results of a 1-year clinical study of antioxidant therapy in the treatment of pain and recurrent inflammatory episodes in patients with chronic and acute recurrent pancreatitis, using a prospective, descriptive, pre-post, open design. The studied patients were with acute recurrent or chronic pancreatitis who had suffered from pain or acute inflammatory episodes the year before the beginning of treatment with a complex containing L-methionine, beta-carotene, vitamin C, vitamin E and organic selenium.
de Sanjose 1996	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
de Vet 1991	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
de Waart 1997	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
DeCosse 1989	Over a 4-year period in a chemoprevention randomised, double-blind, placebo-controlled trial on large bowel neoplasia, patients with familial adenomatous polyposis were treated with 4 g of ascorbic acid (vitamin C)/day plus 400 mg of alpha-tocopherol (vitamin E)/day alone or with a grain fiber supplement (22.5 g/day). Of the 62 randomly assigned patients, 58 were assessable. Four patients withdrew from the study. Authors did not report any deaths during the trial.
DeMaio 1992	Randomised, double-blind placebo-controlled trial to test whether alpha-tocopherol prevents restenosis following percutaneous transluminal coronary angioplasty (PTCA). Patients were randomised after successful PTCA to receive vitamin E in the form of dl-alpha-tocopherol, 1200 IU/day, orally versus an inactive placebo for 4 months. Fifteen participants withdrew from the trial before its end. Authors did not report any deaths during the trial. This trial did not meet our inclusion criteria.

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Desideri 2002	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Desideri 2002a	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Devaraj 1997	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Dieber-Roth 1991	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Diepeveen 2005	Randomised, double-blind placebo-controlled trial to examine the effects of treatment with atorvastatin, alpha-tocopherol and the combination of both, on lipoproteins and oxidative stress in dialysis patients. A total of 44 clinically stable, non-diabetic patients on dialysis therapy (23 on haemo- and 21 on peritoneal-dialysis) without manifest cardiovascular disease were included in this study. They were randomised for treatment during a period of 12 weeks with 40 mg atorvastatin + placebo alpha-tocopherol (group 1) once daily, 800 IU alpha-tocopherol + placebo atorvastatin once daily (group 2), 40 mg atorvastatin + 800 IU alpha-tocopherol once daily (group 3), or placebo atorvastatin + placebo alpha-tocopherol once daily (group 4). Assessment of lipid profile and oxidative stress was performed at the start of the study and after 12 weeks of treatment. Authors did not report any deaths during the trial.
Dietrich 2002	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Dietrich 2003	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Dorfman-Etrog 1999	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Duffy 1999	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Duffy 2001	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Duthie 1996	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Earnest 2003	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Economides 2005	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Edmonds 1997	This double blind and randomised trial used a broad spectrum of clinical and laboratory parameters to investigate whether there was any additional anti-inflammatory or analgesic effects, or both, of orally administered alpha-tocopherol in rheumatoid arthritis patients who were already receiving anti-rheumatic drugs. Forty two patients were enrolled and treated with alpha-tocopherol (n = 20) at a dose of 600 mg twice a day (2 x 2 capsules) or with placebo (n = 22) for 12 weeks. The following parameters were measured: (1) Three clinical indices of inflammation - the Ritchie articular index, the duration of morning stiffness,

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	and the number of swollen joints; (2) three measures of pain--pain in the morning, pain in the evening, and pain after chosen activity; (3) haematological and biochemical measures of inflammatory activity; (4) assays for the oxidative modification of proteins and lipids. There were no deaths during the follow-up period. Additional information obtained through personal communication with authors.
Egan 1992	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Eiselt 2001	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
El-Bayoumy 2002	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Elkashef 1990	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Ernster 1985	Randomised, double-blind placebo-controlled trial of the effect of vitamin E on clinically palpable benign breast findings. Women were supplemented mean two months. Eleven participants did not complete the trial. Authors did not report any deaths during the trial.
Everett 2002	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Fairley 1996	A randomised double-blind placebo controlled trial was designed for 117 women with abnormal cervical morphology. Thirty milligrams of oral beta carotene were administered daily for 12 months. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Fairris 1989	Since reduced concentrations of selenium in whole blood, plasma and white cells had previously been observed in psoriasis, 69 patients were supplemented daily with either 600 micrograms of selenium-enriched yeast, 600 micrograms of selenium-enriched yeast plus 600 IU of vitamin E, or a placebo for 12 weeks. Before supplementation, the patients' mean concentrations of selenium in whole blood and plasma were reduced compared with those of matched healthy controls, but their red cell glutathione peroxidase (GSH-Px) activity was normal. During the study, 4 patients were excluded. Authors did not report any deaths during the trial.
Falsini 2003	Non-randomised, comparative clinical study to evaluate the influence of short-term antioxidant supplementation on retinal function in age-related maculopathy (ARM) patients by recording focal electroretinograms.
Fang 2002	Randomised, double-blind, placebo-controlled trial to examine the effect of vitamins C and E on progression of transplant-associated arteriosclerosis. This trial did not meet our inclusion criteria.
Farvid 2005	In a randomised, double-blind, placebo-controlled clinical trial, 69 type 2 diabetic patients were randomly divided into four groups; each group received one of the following daily supplement for 3 months: group M (n = 16), 200 mg Mg and 30 mg Zn; group V (n = 18), 200 mg vitamin C and 100 IU vitamin E; group MV (n = 17), minerals plus vitamins; and group P (n = 18), placebo. The aim of the trial was to assess the effect of magnesium plus zinc, vitamins C plus E, and a combination of these micronutrients on nephropathy

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	indexes in type 2 diabetic patients. Urinary albumin excretion and N-acetyl-beta-d-glucosaminidase activity (NAG) in urine were determined at the beginning and at the end of the trial. Treatment effects were analysed by general linear modeling. Authors did not report any deaths during the trial.
Faure 2004	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Fawzi 2004	Randomised, double-blind, placebo-controlled trial in Dar es Salaam, Tanzania, to examine the effects of daily supplements of vitamin A (preformed vitamin A and beta carotene), multivitamins (vitamins B, C, and E), or both on progression of HIV disease, using survival models. Authors reported that A total of 343 women died during follow-up. Of these deaths, 243 were deemed to be due or related to AIDS: 82 were due to AIDS, 61 to pulmonary tuberculosis, 3 to extrapulmonary tuberculosis, 10 to anemia, 14 to meningitis, 5 to stroke, 23 to pneumonia, 21 to diarrhea, and 24 to fever. Only data about the mortality related to AIDS (243 women) were reported. This trial did not meet our inclusion criteria.
Fenech 1997	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Finley 1998	This is not a randomised clinical trial. Thirty healthy young men were fed diets that provided either 32.6 or 226.5 mg of selenium (Se)/day for 105 days.
Fischer 2004	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Florencio 1981	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Fogarty 2003	Randomised, double-blind, placebo-controlled trial to determine whether vitamin C or magnesium supplements improve the clinical control of asthma in primary care patients. Participants were supplemented with 1 g/day vitamin C, 450 mg/day magnesium chelate or matched placebo. Three hundred patients aged 18 to 60 years with physician-diagnosed asthma, controlled with at least one dose of an inhaled corticosteroid daily, were recruited from 24 primary care practices in Nottingham, United Kingdom. The main outcome measures were change in forced expiratory volume in 1 s, forced vital capacity, airway responsiveness to methacholine, mean morning and evening peak flow, symptom scores and bronchodilator use, both individually and as a combined summary statistic. There were no deaths during the follow-up period. Additional information obtained through personal communication with authors.
Fortes 1998	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Fotherby 2000	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Frank 2004	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Fuchs 1998	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Fuller 1996	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Fuller 2000	Randomised clinical trial. The authors did not report any deaths during the follow-up period.

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Fumeron 2005	This is a prospective, randomised, open-label trial to assess the effects of oral vitamin C supplementation (250 mg three times per week) for 2 months on well-defined oxidative and inflammatory markers in 33 chronic haemodialysis (HD) patients. Seven patients of 40 randomised withdrew from the trial. The authors did not report any deaths during the trial.
Gaede 2001	Randomised, double-blind, cross-over trial to examine the effect of vitamin C and E supplementation on albuminuria and glomerular hypertrophy in type 2 diabetic patients. The 29 patients were randomised and all of these completed the study. There were no deaths during the follow-up period.
Gal 1996	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Galley 1997	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Garewal 1999	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Garmyn 1995	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Gartner 2001	Mini review about the effect of a selenium supplementation on the outcome of patients with severe systemic inflammation, burn and trauma.
Gartner 2002	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Gazis 1999	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Gertz 1990	A study of vitamin E in patients with primary systemic amyloidosis. This is not a randomised clinical trial.
Gesch 2002	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Ghatak 1996	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Ghosh 1994	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Gianduzzo 2003	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Gokce 1999	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Goldfarb 2005	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Goldfarb 2005a	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Gollnick 2002	Randomised clinical trial. The authors did not report any deaths during the follow-up period.

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Gomez-Perez 1996	Randomised trial on antioxidant supplements. The aim of the study was to examine the effects of vitamin E on total serum protein glycation (fructosamine), haemoglobin glycation (HbA1c), and serum levels of glucose, total cholesterol, triglycerides, LDL-C, HDL-C, apolipoprotein A1, and apolipoprotein B. Sixty poorly controlled diabetic patients were randomly assigned to receive either 1200 mg/day of vitamin E or identical placebo capsules during a two month period following a double blind cross-over design with a four week wash-out period between regimens. Seven patients withdrew from the trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Goodman 1998	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Goudev 2000	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Green 1995	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Greul 2002	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Griesinger 2002	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Grievink 1998	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Grievink 1999	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Gueguen 2003	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Gupta 2001	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Hajjar 2002	Randomised, double-blind, placebo-controlled trial to examine the effect of vitamin C in the management of hypertension and lipids. No reported deaths during the eight months of follow-up.
Hamilton 2000	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Harman 1986	Randomised clinical trial to evaluate the effect of vitamin E on the immune response to influenza virus vaccine and the incidence of infectious disease in men. Patients were divided at random into three groups and were given daily for a period of six months either 0 mg (52 patients), 200 mg (26 patients), or 400 mg (25 patients) alpha-tocopherol acetate per day. One month after starting the vitamin E, the patients received polyvalent influenza virus vaccine. The incidence of infections was tabulated monthly throughout the trial. The authors did not report any deaths during the trial.
Harrison 2003	Prospective, double-blind, randomised, placebo-controlled trial with a total enrollment of 49 patients; 45 patients completed the study. All patients were randomised to receive either vitamins E and C (1000 IU and 1000 mg, respectively) or placebo daily for 6 months, based on their initial histologic diagnosis of non-alcoholic steato-hepatitis. Additionally, all patients were given standard weight-loss counseling and encouraged to follow a low fat diet (< 30 fat g/day). The pre- and posttreatment liver biopsies were reviewed

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	by a single pathologist, who was blinded to the patient's medication. Of 49 participants, 45 completed the trial. Authors did not report any deaths during the follow-up period.
Hasselmark 1993	Randomised clinical trial. The aim of this double-blind study was to investigate whether Se supplementation in asthmatic patients may increase GSH-Px activity and possibly bring about clinical improvement. Twenty-four patients suffering from intrinsic asthma were selected and randomised into two groups, and after a preintervention period of 4 weeks, one group received a daily supplement of 100 micrograms sodium selenite for 14 weeks, whereas the other group received placebo. Three participants drooped-out before the end of trial, one from selenium and two from placebo group. Authors did not report any deaths during the trial.
Hata 1992	This study was designed to prevent the patients already with cerebral infarction from recurrence of cerebrovascular accidents by administration of alpha-tocopheryl nicotinate. In this article authors described rationales for trial. No results of this study have been published later on.
Hawkes 1996	Randomised phase II clinical trial. The aim of the present double-blind trial was to investigate whether Se supplementation in asthmatic patients may increase GSH-Px activity and possibly bring about clinical improvement. Twenty-four patients suffering from intrinsic asthma were selected and randomised into two groups, and after a preintervention period of 4 weeks, one group received a daily supplement of 100 micrograms sodium selenite for 14 weeks, whereas the other group received placebo. Authors did not report any deaths during the trial.
Heinle 1997	Randomised clinical trial. There were no deaths during the follow-up period. Additional information obtained through personal communication with authors.
Heinrich 2003	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Heitzer 1999	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Hernandez 2005	Randomised clinical trial. The Prevention Research Veteran Affairs E-vitamin Nutrition Trial is a randomised, double-blind, placebo controlled trial designed to assess the effects of vitamin E supplementation on biomarkers associated with prostate cancer risk in peripheral blood and prostate tissue. A total of 44 patients with increased prostate specific antigen (PSA) and/or abnormal digital rectal examination on initial evaluation were randomised to receive 400 IU vitamin E (22) versus placebo (22). Serum vitamin E, PSA, dehydroepiandrosterone, testosterone, and insulin-like growth factor-1 (IGF-1) were measured in the 2 groups at baseline and then at 3-month intervals. Results are reported in 28 patients (placebo in 14 and vitamin E in 14) who completed the treatment as specified by the protocol. Three of the 44 randomised patients had biopsy proven prostate cancer at the time of enrollment. This trial did not meet our inclusion criteria.
Herraiz 1998	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Herrick 2000	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Hillert 2001	Randomised clinical trial. The authors did not report any deaths during the follow-up period.

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Hininger 2001	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Hodis 1995	A subgroup analysis of the on-trial antioxidant vitamin intake database acquired in the Cholesterol Lowering Atherosclerosis Study, a randomised, placebo-controlled, serial angiographic clinical trial evaluating the risk and benefit of colestipol-niacin on coronary artery disease progression.
Hoffman 1999	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Hofstad 1998	In a prospective intervention randomised trial of colorectal adenomas, and intermediary stage in colorectal carcinogenesis, 116 polyp-bearing patients received a placebo-controlled daily mixture of beta-carotene 15 mg, vitamin C 150 mg, vitamin E 75 mg, selenium 101 microg, and calcium (1.6 g daily) as carbonate for a period of 3 years with annual colonoscopic follow-up to test if the mixture was able to reduce polyp growth or recurrence. All polyps of < 10 mm at enrollment or follow-up were left unresected until the end of the study. Of 116 patients randomised, 93 were evaluable at the end of trial. Authors did not report any deaths during the trial.
Hornig 1998	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Huang 2005	Randomised, double-blind, placebo-controlled clinical trial to determine the effects of vitamin C supplementation for 2 months on serum uric acid concentrations. Ninety-two percent of participants completed the trial. The authors did not report any deaths during the trial.
Hughes 1997	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Huijuan 1989	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Iino 1977	A controlled double-blind randomised trial of effects of dl-alpha-tocopheryl nicotinate for relief of symptoms was performed in 94 participants with hypertension and cerebral arteriosclerosis. Treatment were given to all participants during 6 weeks and in 43 participants for 6 weeks. Of 94 participants 89 completed the study. There were 2 drop-out patients (4.5%) in the experimental treatment group and 3 in the placebo group, because of various individual reasons. There were no deaths reported during the trial.
Inagaki 1978	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Itoh 2000	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Iwanier 1995	This is not a randomised clinical trial. The objective of this study was to evaluate the effect of selenium (Se) supplementation on Se concentration and glutathione peroxidase (GSH-Px) activity in blood components and seminal fluid and on spermatozoal quality characteristics in subfertile men. Thirty-three men were supplemented for 12 weeks with 200 micrograms Se/day in the form of yeast-rich Se (group I, n = 16) or sodium selenite (group II, n = 17). Blood samples and sperm were collected at the start of the study and after 2, 4, 8, and 12 weeks following Se supplementation.

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Jacob 2003	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Jacques 1995	Randomised clinical trial.The authors did not report any deaths during the follow-up period.
Jain 2002	Randomised, double-blind, placebo-controlled clinical trial to test the influence of vitamins and trace-elements on the incidence of respiratory infection in the elderly. The authors did not report any deaths during the trial.
Jantti 1991	Randomised clinical trial. Twenty-eight patients suffering from rheumatoid arthritis were divided randomly into five groups, treated for eight weeks with either placebo, or capsules containing omega-3-fatty acids 3 g, selenium 150 microg, vitamin A 9000 IU, or vitamin E 600 mg daily. Clinical status was followed during the treatment and four weeks after that. The authors did not report any deaths during the trial.
Jaswal 2003	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Jeng 1996	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Jensen 2002	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Jessup 2003	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Jialal 1992	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Jialal 1993	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Jialal 1995	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Johnson 1995	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Kahler 1993	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Kaikkonen 1998	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Kaikkonen 2000	A phase II randomised, double-blind, placebo-controlled clinical trial to test separate effects and interaction between Q10 and vitamin E in the change of plasma concentrations and in the antioxidative efficiency in 40 participants with mild hypercholesterolemia undergoing statin treatment. Participants were randomly allocated to parallel groups to receive either Q10 (200 mg daily), d-alpha-tocopherol (700 mg daily), both antioxidants or placebo for 3 months. The authors did not report any deaths during the follow-up period.
Kaiser 1995	In this randomised, double-blind trail, 20 patients in an early stage of age-related macular degeneration were included. Over a period of 6 months, 9 patients were treated with visaline and 11 with a placebo. The authors did not report any deaths during the follow-up period.

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Kanter 1993	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Karlowski 1975	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Kawahara 2002	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Keefe 2001	A randomised, double-blind, placebo-controlled clinical trial to evaluate the effect of daily beta-carotene (30 mg) versus placebo over a 2-year period on cervical intraepithelial neoplasia grade 2 and 3 lesions. Women were randomised to beta-carotene or placebo, with cytology and colposcopy every 3 months. Twenty-five of 103 patients did not complete the trail. The authors did not report any deaths during the trial.
Keith 1982	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Keith 2001	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Keskes-Ammar 2003	This randomised and open trial aimed to test the effects of vitamin E and selenium supplementation on lipid peroxidation and on sperm parameters. The trial included 54 voluntary and infertile men who produced semen samples for spermiogram and for spectrophotometric measurement of a lipid peroxidation marker, the malondialdehyde (MDA), and produced blood samples for high-performance liquid chromatography assessment of serum vitamin E level. Twenty-eight men were supplemented daily by vitamin E (400 mg) and selenium (225 microg), during 3 months. The remaining 26 patients received vitamin B (4,5 g/day) for the same duration. Of 54 participants 20 completed the trial. The authors did not report any deaths during the trial.
Kessopoulou 1995	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Khajehdehi 2000	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Khajehdehi 2001	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Khassaf 2003	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Kim 2001	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
King 1997	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Kinlay 2004	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Kiremidjian-S 1994	Randomised clinical trial. The authors did not report any deaths during the follow-up period.

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Kitagawa 1989	Randomised clinical trial. A trial was conducted to investigate the effects of a megadosage of free RRR-alpha-tocopherol in healthy college student volunteers. Of 19 volunteers, 14 were given daily doses of 600 mg (900 IU) of RRR-alpha-tocopherol for 12 weeks, and the remaining 5 were given identical placebo capsules. The investigation was performed by the single-blind method. Alpha-tocopherol levels were measured in plasma, red blood cells (RBCs), platelets, leucocytes (WBCs), and buccal mucosal cells. The authors did not report any deaths during the trial.
Koh 1999	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Konen 2000	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Korpela 1989	Randomised clinical trial. The effect of selenium supplementation was evaluated in 81 patients with acute myocardial infarction in a double-blind, placebo-controlled trial. Patients were randomised into two treatment groups receiving either selenium-rich yeast (100 micrograms/day) or placebo in addition to conventional drug therapy for a 6-month period. During treatment the mean serum selenium concentration increased from 82 micrograms/l to 122 micrograms/l (P less than 0.001) in the selenium supplemented group and remained unaltered in the placebo group (83 micrograms/l). The trial did not meat our inclusion criteria. This is a tertiary prevention trial.
Kugiyama 1999	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
la Ruche 1991	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Li 2000	Randomised clinical trial. To study the preventive effects of selenium on primary liver cancer. After screening of blood samples in 18000 males from 20 to 65 years-old in Qidong, Jiangsu province (a high risk area for liver cancer), 2065 participants HBsAg positive, AFP negative and normal liver function (normal ALT values) were found. The participants were randomly divided into two groups, based on their residence areas; 1,112 people (experimental group) received one tablet of sodium selenite (0.5 mg Se) every day, and 953 people (control group) received one placebo tablet every day. The authors did not report any deaths during the trial.
Li 2004	A double-blind randomised trial was performed on the participants aged 35 to 74 years, who matched according to at least one of the following criteria: (1) a medical history of stomach disorder, (2) a family history of tumour, or (3) smoking and/or alcohol consumption. A total of 2526 and 2507 persons were randomly enrolled into intervention group and control group respectively from 288 natural villages of seven communities in Qixia County, Shandong Province, China. Each person of the intervention group orally took 200 mg synthetic allitridum every day and 100 microg selenium every other day for one month of each year during November 1989 to December 1991. At the same time, people in control group were given 2 placebo capsules containing corn oid with the identical appearance to that in the intervention group. Authors did not report any deaths during the trial.

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London 1983	In a double-blind, randomised dose-response trial, 75 women with benign breast disease were administered a written questionnaire in which they scored the severity of premenstrual syndrome (PMS) symptoms before and after two months of treatment with placebo or alpha-tocopherol (150, 300, or 600 IU/day). The authors did not report any deaths during the trial.
London 1985	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
London 1987	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
London 1991	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Loots 2004	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Lovat 1993	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Lykkesfeldt 2000	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Mackerras 1999	A double-blind, placebo-controlled, randomised, factorial trial using a daily oral administration of 30 mg beta-carotene and/or 500 mg vitamin C was conducted in 141 women with colposcopically and histologically confirmed minor squamous atypia or cervical intra-epithelial neoplasia (CIN) I. Over approximately 2 years of follow-up, 43 lesions regressed to normal and 13 progressed to CIN II. Of 147 women randomised, 6 did not return for follow-up. The authors did not report any deaths during the trial.
MacLennan 1995	Randomised partially double-blinded, placebo-controlled factorial trial. The aim was to assess the effects on the incidence of adenomas of reducing dietary fat to 25% of total calories and supplementing the diet with 25 g of wheat bran daily and a capsule of beta carotene (20 mg daily). Half the patients were assigned to each intervention, resulting in seven intervention groups and one control group. Eligibility criteria included histologic confirmation of at least one colorectal adenoma and confidence expressed by the colonoscopist that all polyps had been removed. Dietary changes were individually initiated and monitored by dietitians and research nurses. At surveillance colonoscopy, the size and location of all polyps were recorded, and their histology was later centrally reviewed. Among 424 patients who were randomly assigned in the trial, 13 were found to be ineligible upon histologic review. Among the remaining 411, complete outcome data were collected from 390 at 24 months and from 306 at 48 months. Eight participants died during the trial, but authors did not report in which arm they were. Letter to the author sent. We did not receive the answer.
MacPherson 1995	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Mader 1988	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Makinson 1948	Randomised clinical trial examining the influence of vitamin E on angina pectoris. Participants were supplemented over a period of 3 weeks. The authors did not report any deaths during the follow-up period.
Malo 1986	Randomised clinical trial. The authors did not report any deaths during the follow-up period.

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Mann 1987	A randomised, prospective, placebo-controlled trial of daily multivitamin supplementation in 101 noninstitutionalized ambulatory elderly persons (median age, 64 years). Vitamin levels were assayed at baseline, and at two and four months of supplementation. The authors did not report any deaths during the follow-up period.
Manzella 2001	A double-blind randomised controlled trial; 50 patients with type 2 diabetes were assigned to treatment with vitamin E (600 mg/d) or placebo for 4 months. The possible effects of vitamin E on the cardiac autonomic nervous system, as assessed by analysis of heart rate variability, in patients with type 2 diabetes and cardiac autonomic neuropathy were investigated.
Margaritis 2003	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Marotta 2003	The aim of this randomised clinical trial was to test the effect of antioxidants on enzymatic abnormalities and free radicals-modified DNA adducts associated with pre-malignant changes in HP-negative chronic atrophic gastritis patients. Sixty patients with and intestinal metaplasia underwent a GI endoscopy with biopsy samples for histology and for: alpha-tocopherol, malonyldialdehyde, xanthine oxidase, ornithine decarboxylase and 8-hydroxydeoxyguanosine. Patients were randomly allocated into three groups supplemented for 6 months with: vitamin E, 300 mg/day; multivitamin, 2 tablets/day, and a certified fermented papaya preparation 6 g/nocte (Immune-Age FPP, Osato Research Institute, Gifu, Japan). Ten dyspeptic patients without histological abnormalities served as control. Histological and biochemical parameters were blindly repeated at 3 and 6 months. The authors did not report any deaths during the follow-up period.
Martinez-Abun 2001	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Massey 2005	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Mastaloudis 2004	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Mathews-Roth 1972	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
McAuliffe 1998	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
McDowell 1994	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
McGavin 2001	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
McKay 2000	Randomised, double-blind, placebo-controlled trial to determine whether a daily multivitamin/mineral supplement can improve micronutrient status, plasma antioxidant capacity and cytokine production in healthy, free-living older adults already consuming a fortified diet. The authors did not report any deaths during the trial.

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Meagher 2001	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Meijer 2001	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Meltzer 1997	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Meydani 1990	Randomised double-blind, placebo-controlled trial. The effect of vitamin E supplementation on the immune response of healthy older adults was studied. Participants (n = 32) resided in a metabolic research unit and received placebo or vitamin E (800 mg dl-alpha-tocopheryl acetate) for 30 days. Alpha-tocopherol content of plasma and peripheral blood mononuclear cells, delayed-type hypersensitivity skin test, mitogen-stimulated lymphocyte proliferation, as well as interleukin (IL)-1, IL-2, prostaglandin E2, and serum lipid peroxides were evaluated before and after treatment. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Meydani 1994	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Meydani 1997	Randomised, double-blind, placebo-controlled trial to determine whether long-term supplementation with vitamin E enhances in vivo, clinically relevant measures of cell-mediated immunity in healthy elderly people. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Meyer 1990	A randomised, double-blind, placebo-controlled trial. To evaluate the efficacy of treatment by means of mammography as the objective and sensitive parameter, 105 women were randomly selected and entered into a double-blind, placebo-controlled crossover trial. All patients had mammographic evidence of benign breast disease. They received 600 mg of placebo and alpha-tocopherol acetate in 3-month treatment phases. Breast examinations and mammography were done, after each treatment, at approximately the same phase of the patients menstrual cycle. Of 105 women 83 completed the trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Micheletta 2004	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Micozzi 1992	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Miller 1997	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
MIVIT 2005	A randomised, double-blind, placebo-controlled trial to test the effects of antioxidant vitamins C and E on the clinical outcome of patients with acute myocardial infarction. Eight-hundred patients (mean age 62) were randomly allocated to receive, on top of routine medication, one of two treatments: vitamin C (1000 mg/12 h infusion) followed by 1200 mg/24 h orally and vitamin E (600 mg/24 h) or matching placebo for 30 days. The trial did not meet our inclusion criteria.
Mohsenin 1987	Randomised clinical trial. The authors did not report any deaths during the follow-up period.

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Moller 2004	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Mosca 1997	Randomised trial on antioxidant supplements to determine the effect of antioxidant supplementation on the susceptibility of low density lipoprotein to oxidation in patients with established cardiovascular disease. Patients with cardiovascular disease (n = 45) were randomised to (1) placebo control; (2) 400 IU of vitamin E, 500 mg of vitamin C, 12 mg of beta-carotene (mid-dose); or (3) 800 IU of vitamin E, 1,000 mg of vitamin C, 24 mg of beta-carotene (high dose) daily. Reduced susceptibility of low density lipoprotein to oxidation was estimated by an increase in lag phase (minutes). Baseline and 6- and 12-week measurements of lipoproteins and lag phase were obtained. Plasma levels of antioxidants were measured at baseline and 12 weeks. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Mottram 1999	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Mulholland 1993	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Mulholland 1996	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Mullan 2002	Randomised clinical trial. There were no deaths during the follow-up period. Additional information obtained through personal communication with authors.
Munoz 1985	A randomised double-blind intervention trial was carried out in Huixian, Henan Province, People's Republic of China, to determine whether combined treatment with retinol, riboflavine, and zinc could lower the prevalence of precancerous lesions of the oesophagus. Six-hundred and ten participants in the age group 35 to 64 were randomised to receive once a week the active treatment (15 mg [50 000 IU] retinol, 200 mg riboflavine, and 50 mg zinc) or placebo. Both at entry to the study and at the end of the treatment, 13.5 months later, the participants were examined, with an emphasis on signs of vitamin A and riboflavine deficiencies, and riboflavine, retinol, beta-carotene, and zinc levels were measured. Compliance was excellent. The final examination, on 567 (93%) participants, included oesophagoscopy and at least two biopsies. During the study, one person died, but the authors did not report in which arm did this happen, and additional information was not received.
Munoz 2001	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Mustad 2002	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Nelson 2003	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Nenseter 1995	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Neunteufl 2000	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.

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Nieman 1997	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Nieman 2002	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Nimmagadda 1998	This is an open-label study to assess the effect of short-term beta-carotene administration (180 mg/d with meals for 4 weeks) on the plasma human immunodeficiency virus (HIV) RNA levels and CD4+ lymphocyte counts in 21 HIV-infected patients. The trial did not meet our inclusion criteria.
Nyyssonen 1994	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
O'Byrne 2000	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Olmedilla 2002	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Olmedilla 2003	A randomised, double-blind, placebo-controlled trial investigated the effect of long-term antioxidant supplementation (lutein and alpha-tocopherol) on serum levels and visual performance in patients with cataracts. The authors did not report any deaths during the follow-up period.
Ono 1985	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Onofrj 2002	Randomised clinical trial testing the hypothesis that new cholinesterase inhibitors like donepezil (DPZ) may have an effect on the often abnormal P300 of patients with Alzheimer's Disease (AD), and, therefore, that P300 recordings might simplify the evaluation of responses to cholinesterase inhibitor in patients with mild and moderate-severe AD. It evaluated 60 patients with AD: 30 patients with 'mild' (Mini Mental State Examination 26-19) and 30 patients with 'moderate-severe' (Mini Mental State Examination 18-10), according to the National Institute of Neurological and Communicative Disorders and Alzheimer's Disease and Related Disorders Association criteria in comparison with 40 age-matched controls. All participants underwent P300 recordings and neuropsychologic examinations (Alzheimer's Disease Assessment Scale-Cognition and Wechsler Adult Intelligence Scale) during the 6-month follow-up. The participants were divided into four groups of 15 patients each: group I DPZ (10 mg/day) and group I vitamin E (2000 IU/day) with 'mild' AD; group II DPZ and group II vitamin E with 'moderate-severe' AD and same drug dosages. Seven of 67 patients dropped out. The authors did not report any deaths during the trial.
Orndahl 1994	A randomised, double-blind, placebo-controlled trial to study the effect of a combined selenium and vitamin E treatment in patients with myotonic dystrophy. Twenty-seven patients with myotonic dystrophy divided into an experimental (n = 13) and a control (n = 14) group. The experimental group was given increasing doses for 4 months up to a maximum of 1.6 mg selenium and 800 mg vitamin E daily and the control group a corresponding number of placebo tablets. The total treatment period was 2 years. Muscle strength (knee extension, knee flexion, hand-grip), maximal walking speed for 30 m, function in daily activities (disability), well-being and cognitive functioning. The authors did not report any deaths during the trial.
Osilesi 1991	Randomised clinical trial. The authors did not report any deaths during the follow-up period.

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Paganelli 1992	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Pallast 1999	A phase II, randomised, double-blind, placebo-controlled trial to study the effects of 6 month supplementation with 50 and 100 mg vitamin E on cellular immune responsiveness. The authors did not report any deaths during the trial.
Paolisso 1993	A phase II, randomised, double-blind, placebo-controlled trial to study the effects of 6 months supplementation with 50 and 100 mg vitamin E on cellular immune responsiveness. The authors did not report any deaths during the trial. Ten control (healthy) participants and 15 non-insulin-dependent diabetics underwent an oral glucose-tolerance test and a euglycemic hyperinsulinemic glucose clamp before and after vitamin E supplementation (900 mg/d for 4 mo). The authors did not report any deaths during the follow-up period.
Paolisso 1993a	A randomised, double-blind, placebo-controlled trial to study the effects of 6 months supplementation with 50 and 100 mg vitamin E. The authors did not report any deaths during the follow-up period.
Paolisso 1994	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Paolisso 1995	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Paolisso 1995a	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Paolisso 2000	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Park 2002	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Pasantes-Morale 2002	Randomised, double blind, placebo, trial assessing the effect of the formula taurine/diltiazem/vitamin E on the progression of visual field loss in retinitis pigmentosa in 62 patients: visual field threshold values were obtained in a Humphrey Field Analyzer from center (30 degrees) and periphery (30 to 60 degrees), every 4 months during 3-year follow-up. The authors did not report any deaths during the trial.
Patrignani 2000	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Pearson 2004	Randomised, double-blind, placebo-controlled trial to investigate the effect of supplementation with vitamin E for 6 weeks on bronchial hyperresponsiveness in atopic adults with asthma. Eight participants did not finish trial per protocol. The authors did not report any deaths during the trial.
Pellegrini 2004	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Peretz 2001	Double blind multi-centric placebo-controlled randomised trial assessing the effects of selenium supplementation in rheumatoid arthritis. Fifty-five patients with moderate rheumatoid arthritis received during 90 days either capsules containing selenium-enriched yeast (200 microg/d) or a placebo. A total of 7 patients did not complete the trial. The authors did not report any deaths during the trial.

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Peters 1993	Randomised clinical trial conducted to determine whether daily supplementation with 600 mg vitamin C would reduce the incidence of symptoms of upper-respiratory-tract (URT) infections after participation in a competitive ultramarathon race (> 42 km). Ultramarathon runners with age-matched controls were randomly divided into placebo and experimental (vitamin C-supplemented) groups. Symptoms of URT infections were monitored for 14 days after the race. Of the 92 runners, 84 complied with all the protocol requirements. The authors did not report any deaths during the follow-up period.
Peters 2001	Randomised clinical trial. There were no deaths during the follow-up period. Additional information obtained through personal communication with authors.
Petersen 2001	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Peyser 1995	A randomized, double-blind, placebo-controlled trial investigated the effect of high dose of vitamin E on slowing the progress of Huntingtons disease. Of 81 participants 74 completed one year follow-up. There were no deaths reported during the trial. Treatment with d-alpha-tocopherol had no effect on neurologic and neuropsychiatric symptoms in the treatment group overall. The authors did not report any deaths during the follow-up period.
Pfeiffer 1999	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Pinkney 1999	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Ponz-de-Leon 1997	Randomised clinical trial in which antioxidant vitamins or lactulose were used in an attempt to prevent the recurrence of colorectal polyps after their endoscopic removal. Authors did not report any deaths during the trial.
Porkkala-S 1998	A single-blind, placebo-controlled, randomised trial to examine the effect of 200 mg RRR-alpha-tocopheryl acetate/d on the oxidation resistance of atherogenic lipoproteins (VLDL+LDL including intermediate-density lipoproteins) in 40 smoking men. A part of a Multiple Antioxidant Supplementation Intervention Study. The authors did not report any deaths during the trial.
Preziosi 1998	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Prieme 1997	In a randomised placebo-controlled trial we investigated the effect of dietary supplementation with antioxidants on a biomarker of oxidative DNA damage with mechanistic relation to carcinogenesis. One hundred forty-two smoking men aged 35 to 65 years were randomly assigned to one of the following seven treatments for 2 mo: 100 mg D-alpha-tocopheryl acetate plus 250 mg slow-release ascorbic acid twice a day (n = 20), 100 mg D-alpha-tocopheryl acetate twice a day (n = 20), 250 mg ascorbic acid twice a day (n = 21), 250 mg slow-release ascorbic acid twice a day (n = 21), 30 mg coenzyme Q10 in oil three times a day (n = 20), 30 mg coenzyme Q10 as granulate three times a day (n = 20), or placebo twice a day (n = 20). The trial outcome was the urinary excretion rate of 8-oxo-7, 8-dihydro-2'-deoxyguanosine (8-oxodG)-a repair product of oxidative DNA damage. The authors did not report any deaths during the trial.

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Princen 1992	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Proteggente 2000	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Racek 2005	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Raitakari 2000	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Ramos 2005	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Range 2003	Randomised clinical trial of zinc and multi-micronutrient (MMN) supplementation in pulmonary TB patients in Tanzania. A total of 499 pulmonary TB patients were included in the trial after being confirmed sputum-positive by microscopy or culture. This study did not meet our inclusion criteria.
Rasool 2003	Randomised clinical trial aiming at establishing whether vitamin E improves arterial stiffness in post-menopausal women after 10 weeks of supplementation. Of 20 women, 3 withdrew before the end of trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Rayment 2003	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Reaven 1994	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Reaven 1995	Randomised clinical trial with an aim to evaluate the effect of vitamin E supplementation on the susceptibility of low-density lipoprotein (LDL) and LDL subfractions to oxidation and on protein glycation in non-insulin-dependent diabetes mellitus (NIDDM). Twenty-one men with NIDDM (HbA1c = 6-10%), ages 50-70, were randomly assigned to either 1,600 IU/day of vitamin E or placebo for 10 weeks after a 4-week placebo period. Of 21 participants, 20 completed the study. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Remans 2004	Randomised clinical trial with parallel group design to investigate the effects of a nutrient supplement, containing, among other ingredients, the omega-3 fatty acids eicosapentaenoic acid (1.4 g EPA), docosa-hexaenoic acid (0.211 g DHA), omega-6 fatty acid gamma-linolenic acid (0.5 g GLA), and micronutrients in patients with active rheumatoid arthritis (RA). RA patients were randomised to receive either daily liquid nutrient supplementation or placebo for 4 months. The primary end point was the change in tender joint count at 2 and 4 months. A total of 11 participants dropped out during the 4 months treatment period. The authors did not report any deaths during the trial.
Richards 1990	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.

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Rinzler 1950	Randomised clinical trial. Forty-one ambulatory patients with chronic chest pain and with arteriosclerotic and/or hypertensive heart disease were selected at random. Active group was supplemented with tocopherol acetate 300 mg by mouth daily for two or more months. Effects were compared to placebo group. Three patients withdrew from the study. The authors did not report any deaths during the trial.
Robinson 1997	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Robson 2003	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Rokitzki 1994	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Rokitzki 1994a	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Romieu 1998	A randomised trial using a double-blind cross-over design to evaluate whether acute effects of ozone on lung functions could be attenuated by antioxidant vitamin supplementation. Of 47 participants, 34 completed the trial. The authors did not report any deaths during the trial.
Romney 1997	Randomised clinical trial. Women with histopathologically confirmed cervical intraepithelial neoplasia (CIN) were followed at 3-month intervals in order to evaluate the efficacy of beta-carotene to cause regression of CIN. Of ninety-eight patients randomised, 69 had an outcome assessment. Authors did not report any deaths during the 9 months trial.
Roncucci 1993	Randomised clinical trial evaluating the effect of antioxidant vitamins or lactulose on the recurrence rate of adenomatous polyps. After polypectomy, 255 individuals were randomised into three groups. Group 1 was given vitamin A (30,000 IU/day), vitamin C (1 g/day), and vitamin E (70 mg/day); group 2 was given lactulose (20 g/day); group 3 received no treatment. Forty-six participants had to be excluded because the histologic diagnosis was not consistent with adenoma. The remaining 209 individuals were included in the analysis according to the 'intention to treat' criterion, though 34 did not adhere to the scheduled treatment, or were lost during the follow-up. The participants were followed at regular intervals for an average of 18 months. Polyps recurring before one year from index colonoscopy were considered missed by the endoscopist. Two people died during the trial, but the authors did not report in which arm they were.
Roodenburg 2000	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Rossig 2001	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Sacheck 2003	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Salonen 1991	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Samet 2001	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.

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Samman 1997	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Sampson 2001	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Sankaranarayana 1997	Randomised clinical trial evaluating the chemopreventive potential of either vitamin A alone or beta carotene alone in people with oral leukoplakia in Kerala, India. The 160 fishermen and women with oral precancerous lesions were randomised to receive oral vitamin A (retinyl acetate 300,000 IU/week x 12 months, n = 50), or beta carotene (360 mg/week x 12 months, n = 55), or placebo (n = 55). Blood, saliva and urine samples were collected at baseline and at exit to study serum micronutrients and mutagenicity assays. Biopsies of the mucosal lesions at entry were performed for histopathological exclusion of malignancy. The patients were examined once every 2 months to establish clinical response of lesions and toxicity, if any. The results are based on 43 complaint participants on placebo, 42 on vitamin A and 46 on beta carotene. The authors did not report any deaths during the trial.
Schachter 1982	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Schlebusch 2000	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Schneider 2003	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Schorah 1981	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Schroder 2001	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Schutte 2004	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Scott 1998	Randomised clinical trial trying to determine whether the decline in selenium intake and selenium status in men in the West of Scotland might be a contributory factor to male subfertility. Two semen samples were collected from patients attending a subfertility clinic, and those patients with samples showing reduced motility were invited to participate in an ethically approved double-blind clinically controlled trial with informed consent. Sixty-nine patients were recruited and received either placebo, selenium alone, or selenium plus vitamins A, C and E daily for 3 months. A further semen sample was collected at the end of the trial. Plasma selenium status was determined at the beginning and end of the trial period, as was total sperm density and motility. Sixty-four of sixty-nine participants completed the study. The authors did not report any deaths during the trial.
Scott 2005	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
SECURE 2001	Randomised clinical trial with a prospective, double-blind, 3x2 factorial design trial. The Study to Evaluate Carotid Ultrasound changes in patients treated with ramipril and vitamin E (SECURE) was a substudy of the Heart Outcomes Prevention Evaluation (HOPE) trial, that evaluated the effects of long-term treatment

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	with the angiotensin-converting enzyme inhibitor ramipril and vitamin E on atherosclerosis progression in high-risk patients.
Seppanen 2000	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Serwin 2003	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Shafat 2004	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Shahar 2004	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Shriqui 1992	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Simon-Schnass 1990	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Simone 2002	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Simons 1996	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Simons 1999	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Singh 1992	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Singh 2002	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Sisto 1995	Randomised clinical trial. Eighty-one patients with coronary artery disease were randomised into four study groups: group 1 (n = 20) patients had stable disease and received oral vitamin E for 4 weeks, and vitamin C and allopurinol 2 days before and 1 day after coronary artery bypass grafting. Group 2 (n = 25) consisted of their controls. Group 3 patients (n = 17) had more unstable disease and received the same medications as group 1, except that vitamin E was given only 2 days before the operation. Group 4 (n = 19) was their controls. This trial did not meet our inclusion criteria.
SKICAP S/B 1997	Randomised clinical trial to examine the effect of retinol and isotretinoin on the incidence of non-melanoma skin cancer in high-risk participants. Participants were randomly assigned to receive oral retinol (25,000 units), isotretinoin (5 mg to 10 mg), or placebo supplementation daily for 3 years. There were no deaths during the trial. Additional information was obtained through personal communication with authors.
Skyrme-Jones 2000	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Spiller 1985	Randomised clinical trial. The authors did not report any deaths during the follow-up period.

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Stampfer 1988	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Stark 1985	Observational study in attempt to prevent the senile degeneration of the macula treatment with cosaldon A+E.
Steck-Scott 2004	Randomised clinical trial. Authors did not report any deaths during the follow-up period.
Steinberg 1998	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Steiner 1995	Randomised clinical trial with 100 patients with transient ischaemic attacks, minor strokes, or residual ischaemic neurologic deficits and comparing the effects of aspirin plus vitamin E [0.4 g (400 IU)/d; n = 52] with aspirin alone (325 mg; n = 48). The patients received the trial medication for 2 years or until they reached a termination point. The authors did not report any deaths during the trial.
Stich 1986	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Stich 1988	Randomised clinical trial. A short-term intervention trial of vitamin A therapy. Participants were randomly distributed into two groups; one receiving 200,000 IU vitamin A per week (0.14 mg/kg body wt/per day) for 6 months, and the other receiving placebo capsules. There were deaths, but in which arm it is not reported. The authors did not answer to our requests for additional information.
Stone 2005	In a randomised clinical trial, 300 patients with stable coronary disease, a positive exercise treadmill test, 48-hour ambulatory ECG with > or =1 episode of ischemia, and fasting total cholesterol of 180 to 250 mg/dL were assigned to 1-year treatment with intensive atorvastatin to reduce LDL to < 80 mg/dL (n=96), intensive atorvastatin to reduce LDL to <80 mg/dL plus antioxidant vitamins C (1000 mg/d) and E (800 mg/d) (n = 101), or diet and low-dose lovastatin, if needed, to reduce LDL to <130 mg/dL (n = 103; control group). Ischemia end points, including ambulatory ECG monitoring and exercise treadmill testing, and endothelial assessment using brachial artery flow-mediated dilation were obtained at baseline, and at 6 and 12 months. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Studinger 2004	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Subakir 2000	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Subudhi 2004	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Sumida 1997	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Sureda 2004	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Surmen-Gur 1999	Randomised clinical trial. The authors did not report any deaths during the follow-up period.

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Tahir 2005	Randomised clinical trial to determine the impact of the combination of vitamins C and E or vitamin C only on serum levels of cell adhesion molecules and C-reactive protein in patients with chronic degenerative AS, with or without concomitant coronary artery disease. One hundred patients with asymptomatic or mildly symptomatic moderate AS were randomised in 2:2:1 format in an open-label trial. Forty-one patients received vitamin E (400 IU) and vitamin C (1000 mg) daily, 39 patients received vitamin C (1000 mg) only, and 20 patients were followed as controls. The authors did not report any deaths during the trial.
Tardif 1997	Randomised clinical trial. One month before angioplasty, 317 patients were randomly assigned to receive one of four treatments: placebo, probucol (500 mg), multivitamins (30,000 IU of beta carotene, 500 mg of vitamin C, and 700 IU of vitamin E), or both probucol and multivitamins-all given twice daily. Patients were treated for four weeks before and six months after angioplasty. The patients received an extra 1000 mg of probucol, 2000 IU of vitamin E, both probucol and vitamin E, or placebo 12 hours before angioplasty, according to their treatment assignments. Base-line and follow-up angiograms were interpreted by blinded investigators using a quantitative approach. This trial did not meet our inclusion criteria.
Tarng 2004	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Tarp 1985	Randomised clinical trial assessing a possible antirheumatic effect of selenium. Forty patients with active RA were included in a 6-month double-blind clinical study of selenium versus placebo. The patients in the selenium group were given daily supplements of 256 micrograms selenium in selenium-enriched yeast. Although concentrations of selenium in serum and erythrocytes increased considerably, no significant antirheumatic effect of selenium could be demonstrated. All patients completed the trial.
Tauler 2002	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Tessier 1995	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Thomson 1988	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Title 2000	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Tofler 2000	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Tolonen 1985	Randomised clinical trial. Sodium selenate (8 mg/d, organic selenium (50 microg/d) and d-alpha-tocopherol acetate (400 mg/d) were administered for 1 year to 15 geriatric patients. Fifteen comparable controls received placebo. The mean age of both groups was 76 years. There were no deaths during the follow-up period.
Tousoulis 2003	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Trebble 2003	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Trebble 2005	Randomised clinical trial. There were no deaths during the follow-up period. Additional information obtained through personal communication with authors.

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Trenga 2001	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Tsai 1978	Randomised clinical trial examining the effect of megavitamine supplementation in healthy college student volunteers. Two hundred-two participants were randomly assigned to either of the two treatment groups (vitamin E 600 IU and placebo) for a period of four weeks. The authors did not report any deaths during the trial.
Tutuncu 1998	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Uden 1990	Randomised clinical trial. In a 20-week double-blind double-dummy cross-over trial, active treatment was given as two types of tablets providing daily doses of 600 micrograms organic selenium, 9000 IU beta carotene, 0.54 g vitamin C, 270 IU vitamin E and 2 g methionine. Of 28 patients enrolled, 20 adhered to the full protocol (idiopathic chronic 8, alcoholic chronic 7, idiopathic acute 5). Of 28 patients, 23 completed the trial. The authors did not report any deaths during the trial.
Upritchard 2000	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Upritchard 2003	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
van Amsterdam 2005	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Van Gossum 1995	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Van Hoydonck 2004	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
van Poppel 1994	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
van Rhijn 1990	Randomised clinical trial to evaluate dietary supplementation with compounds containing zinc and selenium, as these elements are reduced in brain tissues in Alheimer's disease, and with fatty acids, as compensation for the putative reduction in antioxidant activity. Thirty-six participants with early dementia of Alzheimer's type were randomly allocated to evening primrose oil/zinc/selenium or olive oil treatment for 20 weeks, and 30 completed the trial. Four participants were excluded from the analysis. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Van Straten 2002	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
van Tits 2003	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Vannas 1958	This is not a randomised clinical trial. A clinico-pathological investigation; an attempt to cure the arteriosclerotic changes seen in the fundus and affecting vision, and to compare the results achieved by different methods of treatment inclusive of placebo.

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Vasankari 1997	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Vasankari 1998	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Vega-Lopez 2004	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Vela 2000	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Venn 2003	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Verret 2005	Randomised clinical trialamong 121 men and women chronically exposed to arsenic in drinking water was conducted in rural Bangladesh. Participants were randomised to one of four treatment arms: vitamin E, selenium, vitamin E and selenium (combination), or placebo and were treated for 6 months. The aim of the trial was to determine whether supplementation of vitamin E (alpha-tocopherol), selenium (L-selenomethionine), or their combination improves arsenical skin lesions. The authors did not report any deaths during the trial.
Vertrugno 2001	Randomised clinical trial to evaluate the effect of a high dose vitamin A and E supplementation on corneal re-epithelialisation time, visual acuity and haze following photorefractive keratectomy (PRK). Two groups of 20 patients who underwent myopic PRK were supplemented with either 25 000 IU retinol palmitate and 230 mg alpha tocopheryl nicotinate or a placebo. Clinical outcomes were evaluated up to 360 days. This trial did not meet our inclusion criteria.
Viscovich 2004	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Volkovova 2005	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
von Herbay 1997	Randomised clinical trial using a double-blind cross-over design to evaluate whether treatment of hepatitis C patients refractory to alpha-interferon therapy with high doses of vitamin E (2 x 400 IU RRR-alpha-tocopherol/day) for 12 weeks improves the aminotransferase status. This trial did not meet our inclusion criteria.
Wander 1996	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Watanabe 1997	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Watanabe 1998	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Watson 1991	Randomised clinical trial. The effects of various doses (0, 15, 30, 45, and 60 mg/day) of supplementary beta-carotene were evaluated. The percentage of lymphoid cells with surface markers for T-helper and natural killer (NK) cells and cells with interleukin 2 (IL-2) and transferrin receptors were significantly and substantially increased in peripheral blood mononuclear cells collected from older human adult volunteers after supplementation with greater than or equal to 30 mg beta-carotene/day for 2 months. There were no deaths during the trial.

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Welch 1999	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Wen 1997	Randomised clinical trial. The effect of 4 weeks pharmacological supplementation with vitamin C 1 g day on copper induced LDL oxidation and lipid peroxidation. Blood samples were obtained at baseline and at the end of 4 weeks supplementation from 11 healthy non-smokers and also from nine control subjects. The authors did not report any deaths during the trial.
Wen 1999	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Wenzel 1993	Quasi-randomised clinical study including 56 patients suffering from acute alcohol hepatitis. Patients were randimised using the date of birth. This study was originally included in our JAMA review but during assessment of the review we realized our mistake.
Werninghaus 1994	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Wesnes 2003	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Wijnen 2002	Randomised clinical trial to examine the effect of antioxidants on the activation and sequestration of white blood cells and muscle injury during intra-abdominal aortic aneurysm repair. Forty-two patients undergoing elective infrarenal aneurysm repair were randomised to either standard therapy (22 patients) or standard therapy with additional multiantioxidant supplementation (20 patients). Vitamin E and C, allopurinol, N-acetylcysteine, and mannitol was administered perioperatively. White blood cell count, serum creatine kinase, aspartateaminotransferase, lactate, and lipofuscine were measured. This trial did not meet our inclusion criteria.
Willett 1983	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Willett 1984	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Williams 2001	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Winkler 2005	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Wittenborg 1998	In a randomised clinical trial comparison the antiphlogistic and analgetic efficacy of high-dosed vitamin E (3 x 400 mg RRR-alpha-Tocopherolacetat/d) versus diclofenac-sodium has been investigated in hospitalized patients with established chronic rheumatoid arthritis. After 3 weeks of treatment, the vitamin E group (n = 42) as well as the diclofenac group (n = 43) showed a significant improvement of all assessed clinical parameters. There were no deaths during the trial.
Wolters 2005	Randomised clinical trial. The authors did not report any deaths during the follow-up period.

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Wood 1999	Randomised clinical trial evaluated immunological changes in free-living, healthy aged humans (57 to 84 years of age) given a placebo, beta-carotene (45 mg/day), and/or selenium (400 microg/day) supplement for 6 months and after 2 months of discontinuation. Peripheral blood lymphocytes were evaluated and subtyped using flowcytometry. Natural killer (NK) cell cytotoxicity was determined by a fluorescent method. Plasma diene conjugates were assessed to evaluate changes in oxidative stress. Of 45 participants, 10 withdrew from the trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Woodside 1999	Randomised clinical trial. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Wu 2004	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Wuyi 2001	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Xia 2005	Randomised clinical trial in a selenium-deficient population in China to assess the requirement for selenium as selenite and as selenomethionine. One-hundred-twenty participants with an average selenium intake of 10 mug/d were randomly assigned and administered tablets containing no selenium or amounts as high as 66 mug Se/d for 20 wk. Plasma was sampled before supplementation and at 4-wk intervals during supplementation and was assayed for the 2 plasma selenoproteins, glutathione peroxidase and selenoprotein P. There were no deaths during the follow-up period. Additional information was obtained through personal communication with authors.
Xu 1992	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Yu 1990	Randomised clinical trial. The authors did not report any deaths during the follow-up period.
Yu 1991	The purpose of this trial was to evaluate the effect of selenium (Se) in the prevention of human primary liver cancer. Three intervention trials were conducted among the residents at high risk to primary liver cancer (PLC) in Qidong county, Jiang-su province, the People's Republic of China. This area has the second highest rate of PLC in China. One trial was undertaken among the general population in a township with supplement of table salt fortified with 15 ppm anhydrous sodium selenite (Se-salt) for 5 y and the other four townships with similar PLC incidence rate served as the controls using normal table salt. The second trial was undertaken among hepatitis B virus surface antigen carriers (HBVsAg+) receiving supplement of 200 micrograms Se in form of selenized yeast (Se-yeast) daily vs placebo for 4 y. The third trial was carried out in members of families with high PLC incidence using Se-yeast (200 micrograms of Se daily) versus placebo for 2 years.
Yu 1997	An intervention trial was undertaken among the general population of 130,471. Individuals in five townships were involved for observation of the preventive effect of Se. The 8-year follow-up data showed reduced PLC incidence by 35.1% in selenized table salt supplemented versus the nonsupplemented population. On withdrawal of Se from the treated group, PLC incidence rate began to increase. However, the inhibitory response to HBV was sustained during the 3-year cessation of treatment. The clinical study among 226 hepatitis B surface antigen (HBsAg)-positive persons provided either 200 micrograms of Se in the form of selenized yeast tablet or an identical placebo of yeast tablet daily for 4 years.

(*Continued*)

Zaridze 1993	Randomised clinical trial. This intervention trial carried out in Uzbekistan (former USSR) in an area with a high incidence of oral and esophageal cancer involved random allocation of 532 men, 50 to 69 years old, with oral leukoplakia and/or chronic esophagitis to one of four arms in a double-blind, two-by-two factorial design, with active arms defined by the administration of (a) riboflavin; (b) a combination of retinol, beta-carotene, and vitamin E; or (c) both. Weekly doses were 100,000 IU of retinol, 80 mg of vitamin E, and 80 mg of riboflavin. The dose of beta-carotene was 40 mg/d. Men in the trial were followed for 20 months after randomisation. The aim of the trial was to determine whether treatment with these vitamins or their combination could affect the prevalence of oral leukoplakia and/or protect against progression of oral leukoplakia and esophagitis, conditions considered to be precursors of cancer of the mouth and esophagus. Among 519 men, 32 gave up taking supplements. The authors did not report any deaths during the trial.
Zhu 2002	Randomised, double-blind, placebo-controlled clinical trial with an aim to evaluate the roles of folic acid and beta-carotene in the chemoprevention of gastric and other gastrointestinal (GI) cancers. A total of 216 patients with atrophic gastritis were randomly assigned to one of the four groups: (1) folate (FA, 20 mg per day plus vitamin B(12) 1 mg, intramuscularly, per month for one year, then 20 mg two times a week plus 1 mg per three months for the next year); (2) natural beta-carotene (N-betaC, 30 mg per day for first year, then 30 mg two times a week for the next); (3) synthetic beta-carotene (S-betaC, administered as in N-betaC); and (4) placebo. Follow-ups continued from 1994 to 2001. The authors did not report any deaths during the trial.
Zielinski 1978	Not a randomised clinical trial. Cosaldon A+E (containing vitamin A and vitamin E) was applied in 61 patients, most of whom presented severe vascular degenerative retinochoroidal circulatory disorders and chronic glaucoma.
Zimmermann 1997	In this study the effect of antioxidant therapy with sodium selenite was investigated in patients with systemic inflammatory response syndrome and multiple organ failure. Forty patients were included and observed over a period of 28 days. This study did not meet our inclusion criteria.
Zollinger 1999	Randomised clinical trial. The authors did not report any deaths during the follow-up period.

PPT: Polyp Prevention Trial
wk = week

Characteristics of ongoing studies *[ordered by study ID]*

APPOSE 2001

Trial name or title	Australian Prostate Cancer Prevention Trial Using Selenium (APPOSE). Randomised double-blind, placebo-controlled trial with parallel group design.
Methods	

APPOSE 2001 (*Continued*)

Participants	Country: Australia. Number of participants randomised: 6000 men who are at increased risk because of a first-degree relative with prostate cancer.
Interventions	Participants will be supplemented with selenium.
Outcomes	The primary outcome measure is incidence of prostate cancer.
Starting date	2001
Contact information	Anthony J. Costello, MD, Level 1, 77 Victoria Parade, Fitzroy, Melbourne 3065, Australia
Notes	

PHS II 2000

Trial name or title	Physicians' Health Study II (PHS II). Randomised double-blind, placebo-controlled trial with two-by-two-by-two-by-two factorial design.
Methods	
Participants	Country: United States of America. Number of participants randomised: 15,000 US male physicians, aged 55 years and older. Inclusion criteria: willing and eligible physicians to take part in this trial, including all willing and eligible participants from Physician Health Study I.
Interventions	Physicians' Health Study II utilized a two-by-two-by-two-by-two factorial design to test alternate day beta-carotene, alternate day vitamin E, daily vitamin C, and a daily multivitamin. During the first half of 2003 the beta-carotene component of the ongoing Physicians' Healthy Study II has been terminated. It continues to examine a multivitamin, vitamin C, and vitamin E.
Outcomes	The primary outcome measures are the incidence of total and prostate cancer, cardiovascular and eye disease.
Starting date	1999
Contact information	Charles H. Hennekens MD 1415 W. Camino Real, Boca Raton, FL 33486, United States of America
Notes	

SELECT 2003

Trial name or title	The selenium and vitamin E cancer prevention trial, SELECT). Randomised double-blind, placebo-controlled trial with two-by-two factorial design.
Methods	
Participants	Country: United States of America. Number of participants randomised: 32,400 males, aged 50 years or older. Inclusion criteria: age > 55 years for Caucasians and > 50 years for African-Americans, digital rectal examination not suspicious for prostate cancer, total serum prostate specific antigen < 4.0 ng/ml, no prior history of prostate cancer or high-grade prostatic intraepithelial neoplasia, no anticoagulation therapy, except low-dose aspirin, normal blood pressure (systolic blood pressure < 150 mm Hg and diastolic blood pressure < 90 mm Hg), willing to restrict supplementation of selenium and vitamin E during participation.

Interventions	Participants were randomly assigned to receive either 200 µg of 1-selenomethionine, 400 mg of racaemic alpha-tocopherol, and an optional multivitamin containing no selenium or vitamin E. The racaemic mix of alpha-tocopherol will include both the d- and l-isomers. Participants will be divided in four group according to two-by-two factorial design:
	group 1: placebo (n = 8100);
	group 2: vitamin E (n = 8100);
	group 3: selenium (n = 8100);
	group 4: vitamin E and selenium (n = 8100).

Outcomes	The primary outcome measure is the clinical incidence of prostate cancer as determined by a clinical diagnostic work-up, including yearly digital rectal examination and serum prostate specific antigen level. Secondary outcome measures will include prostate cancer-free survival, all cause mortality, and the incidence and mortality of other cancers and diseases potentially impacted by the chronic use of selenium and vitamin E. Other trial objectives will include periodic quality of life assessments, assessment of serum micronutrient levels and prostate cancer risk, and studies of the evaluation of biological and genetic markers with the risk of prostate cancer.
Starting date	2001
Contact information	Eric A. Klein, Section of Urologic Oncology, Department of Urology, Cleveland Clinic Foundation, Cleveland, OH, USA Tel.: +1-216-444-5591; Fax: +1-216-445-3532, e-mail address: kleine@ccf.org.
Notes	

WACS 1995

Trial name or title	The Women's Antioxidant and Cardiovascular Study (WACS). Randomised double-blind, placebo-controlled secondary prevention trial.
Methods	
Participants	Country: United States of America Number of participants randomised: 8000 females, aged 40 years and older. Inclusion criteria: preexisting cardiovascular disease.
Interventions	The Women's Antioxidant and Cardiovascular Study utilized two-by-two-by-two factorial design. Participants were randomly assigned to receive: beta-carotene, 50 mg, (Lurotin, supplied by BASF) or placebo on alternate days; and/or natural vitamin E, 600 IU (alpha-tocopherol, supplied by Henkel Corporation), or placebo on alternate days; and/or vitamin C 500 mg, (supplied by BASF) or placebo daily.
Outcomes	The composite primary outcome measure is nonfatal myocardial infarction, nonfatal stroke, coronary revascularization procedures defined as coronary artery bypass or angioplasty, and cardiovascular disease mortality.
Starting date	1995
Contact information	JoAnn Manson, MD, DrPH, 900 Commonwealth Avenue East, Boston, MA 02215-1204, United States of America
Notes	

WACS: The Women's Antioxidant and Cardiovascular Study
PHS II: Physicians' Health Study II
SELECT: The selenium and vitamin E cancer prevention trial

DATA AND ANALYSES

Comparison 1. Antioxidants versus placebo/no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality in trials with a low or high risk of bias	67	232550	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.99, 1.06]
1.1 Trials with low risk of bias	47	180938	Risk Ratio (M-H, Random, 95% CI)	1.05 [1.02, 1.08]
1.2 Trials with high risk of bias	20	51612	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.85, 0.99]
2 Mortality in primary and secondary prevention trials with a low or high risk of bias	67	232550	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.99, 1.06]
2.1 Primary prevention trials with a low risk of bias	14	126407	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.98, 1.12]
2.2 Primary prevention trials with a high risk of bias	7	38032	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.85, 1.06]
2.3 Secondary prevention trials with a low risk of bias	33	54531	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.98, 1.08]
2.4 Secondary prevention trials with a high risk of bias	13	13580	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.80, 1.00]
3 Mortality after excluding trials administrating extra supplements in the antioxidant group	56	197509	Risk Ratio (M-H, Random, 95% CI)	1.03 [1.00, 1.07]
3.1 Trials with low risk of bias	39	175683	Risk Ratio (M-H, Random, 95% CI)	1.05 [1.02, 1.09]
3.2 Trials with high risk of bias	17	21826	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.82, 1.00]
4 Mortality after excluding trials with extra supplements for both intervention groups	58	229622	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.99, 1.06]
4.1 Trials with low risk of bias	43	179252	Risk Ratio (M-H, Random, 95% CI)	1.05 [1.01, 1.08]
4.2 Trials with high risk of bias	15	50370	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.86, 1.00]
5 Mortality after excluding factorial trials with potential confounding	47	55939	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.94, 1.09]
5.1 Low-bias risk trials	34	48369	Risk Ratio (M-H, Random, 95% CI)	1.11 [1.05, 1.17]
5.2 High-bias risk trials	13	7570	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.73, 0.98]
6 Mortality after excluding factorial trials with potential confounding and trials with extra supplements	33	49719	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.91, 1.12]
6.1 Low-bias risk trials	24	42960	Risk Ratio (M-H, Random, 95% CI)	1.12 [1.07, 1.19]
6.2 High-bias risk trials	9	6759	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.73, 0.98]
7 Mortality after excluding trials with any potential confounding	19	27889	Risk Ratio (M-H, Random, 95% CI)	1.16 [1.09, 1.23]

8 Mortality in beta-carotene trials with a low or high risk of bias	25	172826	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.97, 1.08]
8.1 Trials with a low risk of bias	20	150329	Risk Ratio (M-H, Random, 95% CI)	1.05 [1.00, 1.10]
8.2 Trials with a high risk of bias	5	22497	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.62, 1.07]
9 Mortality in vitamin A trials with a low or high risk of bias	15	44766	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.93, 1.19]
9.1 Trials with a low risk of bias	10	25740	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.93, 1.28]
9.2 Trials with a high risk of bias	5	19026	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.84, 1.08]
10 Mortality in vitamin C trials with a low or high risk of bias	33	70145	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.92, 1.06]
10.1 Trials with a low risk of bias	23	46935	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.93, 1.10]
10.2 Trials with a high risk of bias	10	23210	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.83, 1.05]
11 Mortality in vitamin E trials with a low or high risk of bias	54	163454	Risk Ratio (M-H, Random, 95% CI)	1.02 [1.00, 1.05]
11.1 Trials with a low risk of bias	37	123761	Risk Ratio (M-H, Random, 95% CI)	1.04 [1.01, 1.06]
11.2 Trials with a high risk of bias	17	39693	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.85, 0.99]
12 Mortality in selenium trials with a low or high risk of bias	20	43097	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.83, 0.98]
12.1 Trials with a low risk of bias	14	20707	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.80, 1.01]
12.2 Trials with a high risk of bias	6	22390	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.80, 1.01]
13 Mortality in low-bias risk beta-carotene trials without selenium	12	132610	Risk Ratio (M-H, Random, 95% CI)	1.07 [1.02, 1.11]
14 Mortality in low-bias risk vitamin A trials without selenium	5	21677	Risk Ratio (M-H, Random, 95% CI)	1.16 [1.10, 1.24]
15 Mortality in low-bias risk vitamin C trials without selenium	13	29275	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.94, 1.20]
16 Mortality in low-bias risk vitamin E trials without selenium	26	105065	Risk Ratio (M-H, Random, 95% CI)	1.04 [1.01, 1.07]

Analysis 1.1. Comparison 1 Antioxidants versus placebo/no intervention, Outcome 1 Mortality in trials with a low or high risk of bias.

Review: Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases

Comparison: 1 Antioxidants versus placebo/no intervention

Outcome: 1 Mortality in trials with a low or high risk of bias

Study or subgroup	Antioxidants n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Trials with low risk of bias					
Allsup 2004Low	4/81	4/83		0.1 %	1.02 [0.27, 3.96]
AMDS 1996Low	2/39	2/32		0.0 %	0.82 [0.12, 5.50]
AREDS 2001Low	251/2370	240/2387		3.5 %	1.05 [0.89, 1.25]
ASAP 2003Low	19/390	3/130		0.1 %	2.11 [0.63, 7.02]
ATBC 2003Low	8226/21846	2605/7287		16.1 %	1.05 [1.02, 1.09]
CARET 2004Low	1855/9420	1509/8894		12.0 %	1.16 [1.09, 1.23]
CHAOS 1996Low	68/1035	52/967		0.9 %	1.22 [0.86, 1.73]
Collins 2003Low	1/26	1/26		0.0 %	1.00 [0.07, 15.15]
Correa 2000Low	16/739	2/237		0.1 %	2.57 [0.59, 11.08]
DATATOP 2005Low	154/399	142/401		3.1 %	1.09 [0.91, 1.31]
DATOR 2004Low	1/12	0/12		0.0 %	3.00 [0.13, 67.06]
Desnuelle 2001Low	34/144	35/144		0.7 %	0.97 [0.64, 1.47]
Graat 2002Low	3/499	5/153		0.1 %	0.18 [0.04, 0.76]
Graf 2005Low	31/83	28/77		0.7 %	1.03 [0.68, 1.54]
HATS 2001Low	1/84	1/76		0.0 %	0.90 [0.06, 14.22]
HOPE TOO 2005Low	799/4761	801/4780		8.5 %	1.00 [0.92, 1.10]
HPS 2002Low	1446/10269	1389/10267		11.1 %	1.04 [0.97, 1.11]
Jacobson 2000Low	0/57	1/55		0.0 %	0.32 [0.01, 7.74]
LAST 2004Low	0/30	2/31		0.0 %	0.21 [0.01, 4.13]
Limburg 2005Low	1/180	0/180		0.0 %	3.00 [0.12, 73.16]
MAVIS 2005 Low	8/456	4/454		0.1 %	1.99 [0.60, 6.57]
Meydani 2004Low	39/311	44/306		0.7 %	0.87 [0.58, 1.30]
Mezey 2004Low	4/25	5/26		0.1 %	0.83 [0.25, 2.75]
MINVITAOX 1999Low	155/543	51/182		1.5 %	1.02 [0.78, 1.33]

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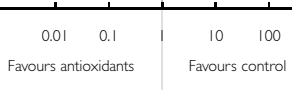
Study or subgroup	Antioxidants n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Mooney 2005Low	1/142	0/142		0.0 %	3.00 [0.12, 73.03]
Murphy 1992Low	4/53	2/56		0.0 %	2.11 [0.40, 11.06]
NIT2 1993Low	157/1657	167/1661		2.5 %	0.94 [0.77, 1.16]
NPCT 1996Low	108/653	129/659		2.0 %	0.84 [0.67, 1.07]
NSCPT 1999Low	15/820	22/801		0.3 %	0.67 [0.35, 1.27]
PHS 1996Low	979/11036	968/11035		9.0 %	1.01 [0.93, 1.10]
Pike 1995Low	1/24	0/23		0.0 %	2.88 [0.12, 67.29]
PPS 1994Low	30/650	14/214		0.3 %	0.71 [0.38, 1.31]
Prince 2003Low	1/29	0/32		0.0 %	3.30 [0.14, 77.95]
Rayman 2006Low	1/380	0/121		0.0 %	0.96 [0.04, 23.43]
REACT 2002Low	9/149	3/148		0.1 %	2.98 [0.82, 10.79]
SCPS 1990Low	79/913	72/892		1.2 %	1.07 [0.79, 1.46]
SKICAP AK 1997Low	62/1157	53/1140		0.9 %	1.15 [0.81, 1.65]
SPACE 2000Low	31/97	29/99		0.7 %	1.09 [0.72, 1.66]
SUVIMAX 2004Low	76/6481	98/6536		1.3 %	0.78 [0.58, 1.05]
Tam 2005Low	1/20	1/19		0.0 %	0.95 [0.06, 14.13]
VEAPS 2002Low	2/177	1/176		0.0 %	1.99 [0.18, 21.73]
VECAT 2004Low	20/595	11/598		0.2 %	1.83 [0.88, 3.78]
WAVE 2002Low	16/212	6/211		0.1 %	2.65 [1.06, 6.65]
White 2002Low	1/50	1/50		0.0 %	1.00 [0.06, 15.55]
WHS 2005Low	636/19937	615/19939		6.7 %	1.03 [0.93, 1.15]
Witte 2005Low	1/16	1/16		0.0 %	1.00 [0.07, 14.64]
Wluka 2002Low	1/67	0/69		0.0 %	3.09 [0.13, 74.50]
Subtotal (95% CI)	**99114**	**81824**		**84.9 %**	**1.05 [1.02, 1.08]**
Total events: 15350 (Antioxidants), 9119 (Control)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 49.73, df = 46 (P = 0.33); I^2 =8%					
Test for overall effect: Z = 2.98 (P = 0.0029)					
2 Trials with high risk of bias					
ADCS 1 1997	19/170	22/171		0.4 %	0.87 [0.49, 1.55]
ADCS 2 2005	5/257	5/259		0.1 %	1.01 [0.30, 3.44]
Bonelli 1998	1/147	0/157		0.0 %	3.20 [0.13, 78.00]
Chandra 1992	0/48	2/48		0.0 %	0.20 [0.01, 4.06]
de la Maza 1995	5/37	4/37		0.1 %	1.25 [0.36, 4.29]



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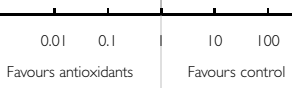
Study or subgroup	Antioxidants n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
de Waart 2001	0/109	1/109		0.0 %	0.33 [0.01, 8.09]
Gillilan 1977	2/26	2/26		0.0 %	1.00 [0.15, 6.57]
Girodon 1997	18/61	7/20		0.2 %	0.84 [0.41, 1.72]
GISSI 1999	488/5660	529/5664		6.0 %	0.92 [0.82, 1.04]
Hogarth 1996	7/54	6/52		0.1 %	1.12 [0.40, 3.12]
McKeown-Eyssen 1988	4/96	3/89		0.1 %	1.24 [0.28, 5.37]
NIT1 1993	1847/25886	280/3698		5.8 %	0.94 [0.84, 1.06]
Penn 1991	1/15	0/15		0.0 %	3.00 [0.13, 68.26]
PPP 2001	72/2231	68/2264		1.1 %	1.07 [0.78, 1.49]
Sasazuki 2003	6/222	18/217		0.1 %	0.33 [0.13, 0.81]
SIT 2001	38/1706	43/1705		0.6 %	0.88 [0.57, 1.36]
Stevic 2001	3/16	6/12		0.1 %	0.38 [0.12, 1.20]
Takagi 2003	10/51	16/42		0.3 %	0.51 [0.26, 1.01]
Takamatsu 1995	1/74	0/73		0.0 %	2.96 [0.12, 71.50]
ter Riet 1995	3/43	5/45		0.1 %	0.63 [0.16, 2.47]
Subtotal (95% CI)	**36909**	**14703**		**15.1 %**	**0.92 [0.85, 0.99]**
Total events: 2530 (Antioxidants), 1017 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 15.21$, df = 19 (P = 0.71); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.11 (P = 0.035)					
Total (95% CI)	**136023**	**96527**		**100.0 %**	**1.02 [0.99, 1.06]**
Total events: 17880 (Antioxidants), 10136 (Control)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 75.97$, df = 66 (P = 0.19); $I^2 = 13\%$					
Test for overall effect: Z = 1.35 (P = 0.18)					



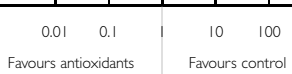
Analysis 1.2. Comparison 1 Antioxidants versus placebo/no intervention, Outcome 2 Mortality in primary and secondary prevention trials with a low or high risk of bias.

Review: Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases

Comparison: 1 Antioxidants versus placebo/no intervention

Outcome: 2 Mortality in primary and secondary prevention trials with a low or high risk of bias

Study or subgroup	Antioxidants n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Primary prevention trials with a low risk of bias					
ASAP 2003Low	19/390	3/130		0.1 %	2.11 [0.63, 7.02]
ATBC 2003Low	8226/21846	2605/7287		16.1 %	1.05 [1.02, 1.09]
CARET 2004Low	1855/9420	1509/8894		12.0 %	1.16 [1.09, 1.23]
Graat 2002Low	3/499	5/153		0.1 %	0.18 [0.04, 0.76]
Jacobson 2000Low	0/57	1/55		0.0 %	0.32 [0.01, 7.74]
MAVIS 2005 Low	8/456	4/454		0.1 %	1.99 [0.60, 6.57]
Meydani 2004Low	39/311	44/306		0.7 %	0.87 [0.58, 1.30]
Mooney 2005Low	1/142	0/142		0.0 %	3.00 [0.12, 73.03]
PHS 1996Low	979/11036	968/11035		9.0 %	1.01 [0.93, 1.10]
Pike 1995Low	1/24	0/23		0.0 %	2.88 [0.12, 67.29]
Rayman 2006Low	1/380	0/121		0.0 %	0.96 [0.04, 23.43]
SUVIMAX 2004Low	76/6481	98/6536		1.3 %	0.78 [0.58, 1.05]
VEAPS 2002Low	2/177	1/176		0.0 %	1.99 [0.18, 21.73]
WHS 2005Low	636/19937	615/19939		6.7 %	1.03 [0.93, 1.15]
Subtotal (95% CI)	**71156**	**55251**		**46.1 %**	**1.05 [0.98, 1.12]**
Total events: 11846 (Antioxidants), 5853 (Control)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 24.47$, df = 13 (P = 0.03); $I^2 = 47\%$					
Test for overall effect: Z = 1.33 (P = 0.18)					
2 Primary prevention trials with a high risk of bias					
Chandra 1992	0/48	2/48		0.0 %	0.20 [0.01, 4.06]
de Waart 2001	0/109	1/109		0.0 %	0.33 [0.01, 8.09]
Girodon 1997	18/61	7/20		0.2 %	0.84 [0.41, 1.72]
NIT1 1993	1847/25886	280/3698		5.8 %	0.94 [0.84, 1.06]
PPP 2001	72/2231	68/2264		1.1 %	1.07 [0.78, 1.49]
SIT 2001	38/1706	43/1705		0.6 %	0.88 [0.57, 1.36]
Takamatsu 1995	1/74	0/73		0.0 %	2.96 [0.12, 71.50]



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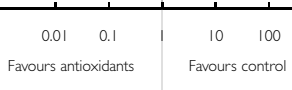
Study or subgroup	Antioxidants n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**30115**	**7917**		**7.8 %**	**0.95 [0.85, 1.06]**
Total events: 1976 (Antioxidants), 401 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.71, df = 6 (P = 0.84); I^2 =0.0%					
Test for overall effect: Z = 0.97 (P = 0.33)					
3 Secondary prevention trials with a low risk of bias					
Allsup 2004Low	4/81	4/83		0.1 %	1.02 [0.27, 3.96]
AMDS 1996Low	2/39	2/32		0.0 %	0.82 [0.12, 5.50]
AREDS 2001Low	251/2370	240/2387		3.5 %	1.05 [0.89, 1.25]
CHAOS 1996Low	68/1035	52/967		0.9 %	1.22 [0.86, 1.73]
Collins 2003Low	1/26	1/26		0.0 %	1.00 [0.07, 15.15]
Correa 2000Low	16/739	2/237		0.1 %	2.57 [0.59, 11.08]
DATATOP 2005Low	154/399	142/401		3.1 %	1.09 [0.91, 1.31]
DATOR 2004Low	1/12	0/12		0.0 %	3.00 [0.13, 67.06]
Desnuelle 2001Low	34/144	35/144		0.7 %	0.97 [0.64, 1.47]
Graf 2005Low	31/83	28/77		0.7 %	1.03 [0.68, 1.54]
HATS 2001Low	1/84	1/76		0.0 %	0.90 [0.06, 14.22]
HOPE TOO 2005Low	799/4761	801/4780		8.5 %	1.00 [0.92, 1.10]
HPS 2002Low	1446/10269	1389/10267		11.1 %	1.04 [0.97, 1.11]
LAST 2004Low	0/30	2/31		0.0 %	0.21 [0.01, 4.13]
Limburg 2005Low	1/180	0/180		0.0 %	3.00 [0.12, 73.16]
Mezey 2004Low	4/25	5/26		0.1 %	0.83 [0.25, 2.75]
MINVITAOX 1999Low	155/543	51/182		1.5 %	1.02 [0.78, 1.33]
Murphy 1992Low	4/53	2/56		0.0 %	2.11 [0.40, 11.06]
NIT2 1993Low	157/1657	167/1661		2.5 %	0.94 [0.77, 1.16]
NPCT 1996Low	108/653	129/659		2.0 %	0.84 [0.67, 1.07]
NSCPT 1999Low	15/820	22/801		0.3 %	0.67 [0.35, 1.27]
PPS 1994Low	30/650	14/214		0.3 %	0.71 [0.38, 1.31]
Prince 2003Low	1/29	0/32		0.0 %	3.30 [0.14, 77.95]
REACT 2002Low	9/149	3/148		0.1 %	2.98 [0.82, 10.79]
SCPS 1990Low	79/913	72/892		1.2 %	1.07 [0.79, 1.46]
SKICAP AK 1997Low	62/1157	53/1140		0.9 %	1.15 [0.81, 1.65]
SPACE 2000Low	31/97	29/99		0.7 %	1.09 [0.72, 1.66]
Tam 2005Low	1/20	1/19		0.0 %	0.95 [0.06, 14.13]



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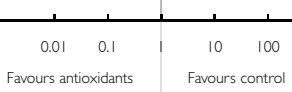
Study or subgroup	Antioxidants n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
VECAT 2004Low	20/595	11/598		0.2 %	1.83 [0.88, 3.78]
WAVE 2002Low	16/212	6/211		0.1 %	2.65 [1.06, 6.65]
White 2002Low	1/50	1/50		0.0 %	1.00 [0.06, 15.55]
Witte 2005Low	1/16	1/16		0.0 %	1.00 [0.07, 14.64]
Wluka 2002Low	1/67	0/69		0.0 %	3.09 [0.13, 74.50]
Subtotal (95% CI)	**27958**	**26573**		**38.8 %**	**1.03 [0.98, 1.08]**
Total events: 3504 (Antioxidants), 3266 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 23.60, df = 32 (P = 0.86); I^2 =0.0%					
Test for overall effect: Z = 1.27 (P = 0.20)					
4 Secondary prevention trials with a high risk of bias					
ADCS 1 1997	19/170	22/171		0.4 %	0.87 [0.49, 1.55]
ADCS 2 2005	5/257	5/259		0.1 %	1.01 [0.30, 3.44]
Bonelli 1998	1/147	0/157		0.0 %	3.20 [0.13, 78.00]
de la Maza 1995	5/37	4/37		0.1 %	1.25 [0.36, 4.29]
Gillilan 1977	2/26	2/26		0.0 %	1.00 [0.15, 6.57]
GISSI 1999	488/5660	529/5664		6.0 %	0.92 [0.82, 1.04]
Hogarth 1996	7/54	6/52		0.1 %	1.12 [0.40, 3.12]
McKeown-Eyssen 1988	4/96	3/89		0.1 %	1.24 [0.28, 5.37]
Penn 1991	1/15	0/15		0.0 %	3.00 [0.13, 68.26]
Sasazuki 2003	6/222	18/217		0.1 %	0.33 [0.13, 0.81]
Stevic 2001	3/16	6/12		0.1 %	0.38 [0.12, 1.20]
Takagi 2003	10/51	16/42		0.3 %	0.51 [0.26, 1.01]
ter Riet 1995	3/43	5/45		0.1 %	0.63 [0.16, 2.47]
Subtotal (95% CI)	**6794**	**6786**		**7.3 %**	**0.89 [0.80, 1.00]**
Total events: 554 (Antioxidants), 616 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 11.93, df = 12 (P = 0.45); I^2 =0.0%					
Test for overall effect: Z = 2.02 (P = 0.043)					
Total (95% CI)	**136023**	**96527**		**100.0 %**	**1.02 [0.99, 1.06]**
Total events: 17880 (Antioxidants), 10136 (Control)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 75.97, df = 66 (P = 0.19); I^2 =13%					
Test for overall effect: Z = 1.35 (P = 0.18)					



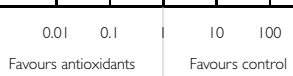
Analysis 1.3. Comparison 1 Antioxidants versus placebo/no intervention, Outcome 3 Mortality after excluding trials administrating extra supplements in the antioxidant group.

Review: Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases

Comparison: 1 Antioxidants versus placebo/no intervention

Outcome: 3 Mortality after excluding trials administrating extra supplements in the antioxidant group

Study or subgroup	Supplements n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Trials with low risk of bias					
AREDS 2001Low	251/2370	240/2387		3.6 %	1.05 [0.89, 1.25]
ASAP 2003Low	19/390	3/130		0.1 %	2.11 [0.63, 7.02]
ATBC 2003Low	8226/21846	2605/7287		19.1 %	1.05 [1.02, 1.09]
CARET 2004Low	1855/9420	1509/8894		13.6 %	1.16 [1.09, 1.23]
CHAOS 1996Low	68/1035	52/967		0.9 %	1.22 [0.86, 1.73]
Collins 2003Low	1/26	1/26		0.0 %	1.00 [0.07, 15.15]
Correa 2000Low	16/739	2/237		0.1 %	2.57 [0.59, 11.08]
DATATOP 2005Low	154/399	142/401		3.2 %	1.09 [0.91, 1.31]
DATOR 2004Low	1/12	0/12		0.0 %	3.00 [0.13, 67.06]
Desnuelle 2001Low	34/144	35/144		0.7 %	0.97 [0.64, 1.47]
Graf 2005Low	31/83	28/77		0.7 %	1.03 [0.68, 1.54]
HATS 2001Low	1/84	1/76		0.0 %	0.90 [0.06, 14.22]
HOPE TOO 2005Low	799/4761	801/4780		9.2 %	1.00 [0.92, 1.10]
HPS 2002Low	1446/10269	1389/10267		12.4 %	1.04 [0.97, 1.11]
Jacobson 2000Low	0/57	1/55		0.0 %	0.32 [0.01, 7.74]
Limburg 2005Low	1/180	0/180		0.0 %	3.00 [0.12, 73.16]
Meydani 2004Low	39/311	44/306		0.7 %	0.87 [0.58, 1.30]
Mezey 2004Low	4/25	5/26		0.1 %	0.83 [0.25, 2.75]
MINVITAOX 1999Low	155/543	51/182		1.6 %	1.02 [0.78, 1.33]
Mooney 2005Low	1/142	0/142		0.0 %	3.00 [0.12, 73.03]
Murphy 1992Low	4/53	2/56		0.0 %	2.11 [0.40, 11.06]
NPCT 1996Low	108/653	129/659		2.1 %	0.84 [0.67, 1.07]
NSCPT 1999Low	15/820	22/801		0.3 %	0.67 [0.35, 1.27]
PHS 1996Low	979/11036	968/11035		9.8 %	1.01 [0.93, 1.10]



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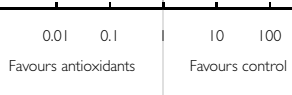
Study or subgroup	Supplements n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
PPS 1994Low	30/650	14/214		0.3 %	0.71 [0.38, 1.31]
Prince 2003Low	1/29	0/32		0.0 %	3.30 [0.14, 77.95]
Rayman 2006Low	1/380	0/121		0.0 %	0.96 [0.04, 23.43]
REACT 2002Low	9/149	3/148		0.1 %	2.98 [0.82, 10.79]
SCPS 1990Low	79/913	72/892		1.2 %	1.07 [0.79, 1.46]
SKICAP AK 1997Low	62/1157	53/1140		0.9 %	1.15 [0.81, 1.65]
SPACE 2000Low	31/97	29/99		0.7 %	1.09 [0.72, 1.66]
SUVIMAX 2004Low	76/6481	98/6536		1.3 %	0.78 [0.58, 1.05]
Tam 2005Low	1/20	1/19		0.0 %	0.95 [0.06, 14.13]
VEAPS 2002Low	2/177	1/176		0.0 %	1.99 [0.18, 21.73]
VECAT 2004Low	20/595	11/598		0.2 %	1.83 [0.88, 3.78]
WAVE 2002Low	16/212	6/211		0.1 %	2.65 [1.06, 6.65]
White 2002Low	1/50	1/50		0.0 %	1.00 [0.06, 15.55]
WHS 2005Low	636/19937	615/19939		7.1 %	1.03 [0.93, 1.15]
Wluka 2002Low	1/67	0/69		0.0 %	3.09 [0.13, 74.50]
Subtotal (95% CI)	**96312**	**79371**		**90.4 %**	**1.05 [1.02, 1.09]**
Total events: 15174 (Supplements), 8934 (Control)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 40.08$, df = 38 (P = 0.38); $I^2 = 5\%$					
Test for overall effect: Z = 3.53 (P = 0.00041)					
2 Trials with high risk of bias					
ADCS 1 1997	19/170	22/171		0.4 %	0.87 [0.49, 1.55]
ADCS 2 2005	5/257	5/259		0.1 %	1.01 [0.30, 3.44]
Bonelli 1998	1/147	0/157		0.0 %	3.20 [0.13, 78.00]
de la Maza 1995	5/37	4/37		0.1 %	1.25 [0.36, 4.29]
de Waart 2001	0/109	1/109		0.0 %	0.33 [0.01, 8.09]
Gillilan 1977	2/26	2/26		0.0 %	1.00 [0.15, 6.57]
Girodon 1997	18/61	7/20		0.2 %	0.84 [0.41, 1.72]
GISSI 1999	488/5660	529/5664		6.4 %	0.92 [0.82, 1.04]
McKeown-Eyssen 1988	4/96	3/89		0.1 %	1.24 [0.28, 5.37]
Penn 1991	1/15	0/15		0.0 %	3.00 [0.13, 68.26]
PPP 2001	72/2231	68/2264		1.1 %	1.07 [0.78, 1.49]
Sasazuki 2003	6/222	18/217		0.1 %	0.33 [0.13, 0.81]
SIT 2001	38/1706	43/1705		0.6 %	0.88 [0.57, 1.36]



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Study or subgroup	Supplements n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Stevic 2001	3/16	6/12		0.1 %	0.38 [0.12, 1.20]
Takagi 2003	10/51	16/42		0.3 %	0.51 [0.26, 1.01]
Takamatsu 1995	1/74	0/73		0.0 %	2.96 [0.12, 71.50]
ter Riet 1995	3/43	5/45		0.1 %	0.63 [0.16, 2.47]
Subtotal (95% CI)	**10921**	**10905**		**9.6 %**	**0.91 [0.82, 1.00]**
Total events: 676 (Supplements), 729 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 13.83, df = 16 (P = 0.61); I² =0.0%					
Test for overall effect: Z = 1.94 (P = 0.052)					
Total (95% CI)	**107233**	**90276**		**100.0 %**	**1.03 [1.00, 1.07]**
Total events: 15850 (Supplements), 9663 (Control)					
Heterogeneity: Tau² = 0.00; Chi² = 62.53, df = 55 (P = 0.23); I² =12%					
Test for overall effect: Z = 1.92 (P = 0.055)					

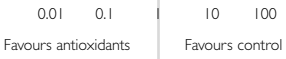
Analysis 1.4. Comparison 1 Antioxidants versus placebo/no intervention, Outcome 4 Mortality after excluding trials with extra supplements for both intervention groups.

Review: Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases

Comparison: 1 Antioxidants versus placebo/no intervention

Outcome: 4 Mortality after excluding trials with extra supplements for both intervention groups

Study or subgroup	Antioxidants n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Trials with low risk of bias					
Allsup 2004Low	4/81	4/83		0.1 %	1.02 [0.27, 3.96]
AMDS 1996Low	2/39	2/32		0.0 %	0.82 [0.12, 5.50]
AREDS 2001Low	251/2370	240/2387		3.7 %	1.05 [0.89, 1.25]
ASAP 2003Low	19/390	3/130		0.1 %	2.11 [0.63, 7.02]
ATBC 2003Low	8226/21846	2605/7287		16.6 %	1.05 [1.02, 1.09]
CARET 2004Low	1855/9420	1509/8894		12.5 %	1.16 [1.09, 1.23]
CHAOS 1996Low	68/1035	52/967		1.0 %	1.22 [0.86, 1.73]
Collins 2003Low	1/26	1/26		0.0 %	1.00 [0.07, 15.15]



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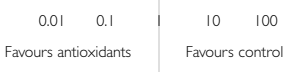
Study or subgroup	Antioxidants n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Correa 2000Low	16/739	2/237		0.1 %	2.57 [0.59, 11.08]
DATOR 2004Low	1/12	0/12		0.0 %	3.00 [0.13, 67.06]
Desnuelle 2001Low	34/144	35/144		0.7 %	0.97 [0.64, 1.47]
Graat 2002Low	3/499	5/153		0.1 %	0.18 [0.04, 0.76]
Graf 2005Low	31/83	28/77		0.7 %	1.03 [0.68, 1.54]
HOPE TOO 2005Low	799/4761	801/4780		8.9 %	1.00 [0.92, 1.10]
HPS 2002Low	1446/10269	1389/10267		11.5 %	1.04 [0.97, 1.11]
Jacobson 2000Low	0/57	1/55		0.0 %	0.32 [0.01, 7.74]
LAST 2004Low	0/30	2/31		0.0 %	0.21 [0.01, 4.13]
Limburg 2005Low	1/180	0/180		0.0 %	3.00 [0.12, 73.16]
MAVIS 2005 Low	8/456	4/454		0.1 %	1.99 [0.60, 6.57]
Mezey 2004Low	4/25	5/26		0.1 %	0.83 [0.25, 2.75]
MINVITAOX 1999Low	155/543	51/182		1.6 %	1.02 [0.78, 1.33]
Mooney 2005Low	1/142	0/142		0.0 %	3.00 [0.12, 73.03]
NIT2 1993Low	157/1657	167/1661		2.6 %	0.94 [0.77, 1.16]
NPCT 1996Low	108/653	129/659		2.1 %	0.84 [0.67, 1.07]
NSCPT 1999Low	15/820	22/801		0.3 %	0.67 [0.35, 1.27]
PHS 1996Low	979/11036	968/11035		9.4 %	1.01 [0.93, 1.10]
Pike 1995Low	1/24	0/23		0.0 %	2.88 [0.12, 67.29]
PPS 1994Low	30/650	14/214		0.3 %	0.71 [0.38, 1.31]
Prince 2003Low	1/29	0/32		0.0 %	3.30 [0.14, 77.95]
Rayman 2006Low	1/380	0/121		0.0 %	0.96 [0.04, 23.43]
REACT 2002Low	9/149	3/148		0.1 %	2.98 [0.82, 10.79]
SCPS 1990Low	79/913	72/892		1.3 %	1.07 [0.79, 1.46]
SKICAP AK 1997Low	62/1157	53/1140		1.0 %	1.15 [0.81, 1.65]
SPACE 2000Low	31/97	29/99		0.7 %	1.09 [0.72, 1.66]
SUVIMAX 2004Low	76/6481	98/6536		1.3 %	0.78 [0.58, 1.05]
Tam 2005Low	1/20	1/19		0.0 %	0.95 [0.06, 14.13]
VEAPS 2002Low	2/177	1/176		0.0 %	1.99 [0.18, 21.73]
VECAT 2004Low	20/595	11/598		0.2 %	1.83 [0.88, 3.78]
WAVE 2002Low	16/212	6/211		0.2 %	2.65 [1.06, 6.65]



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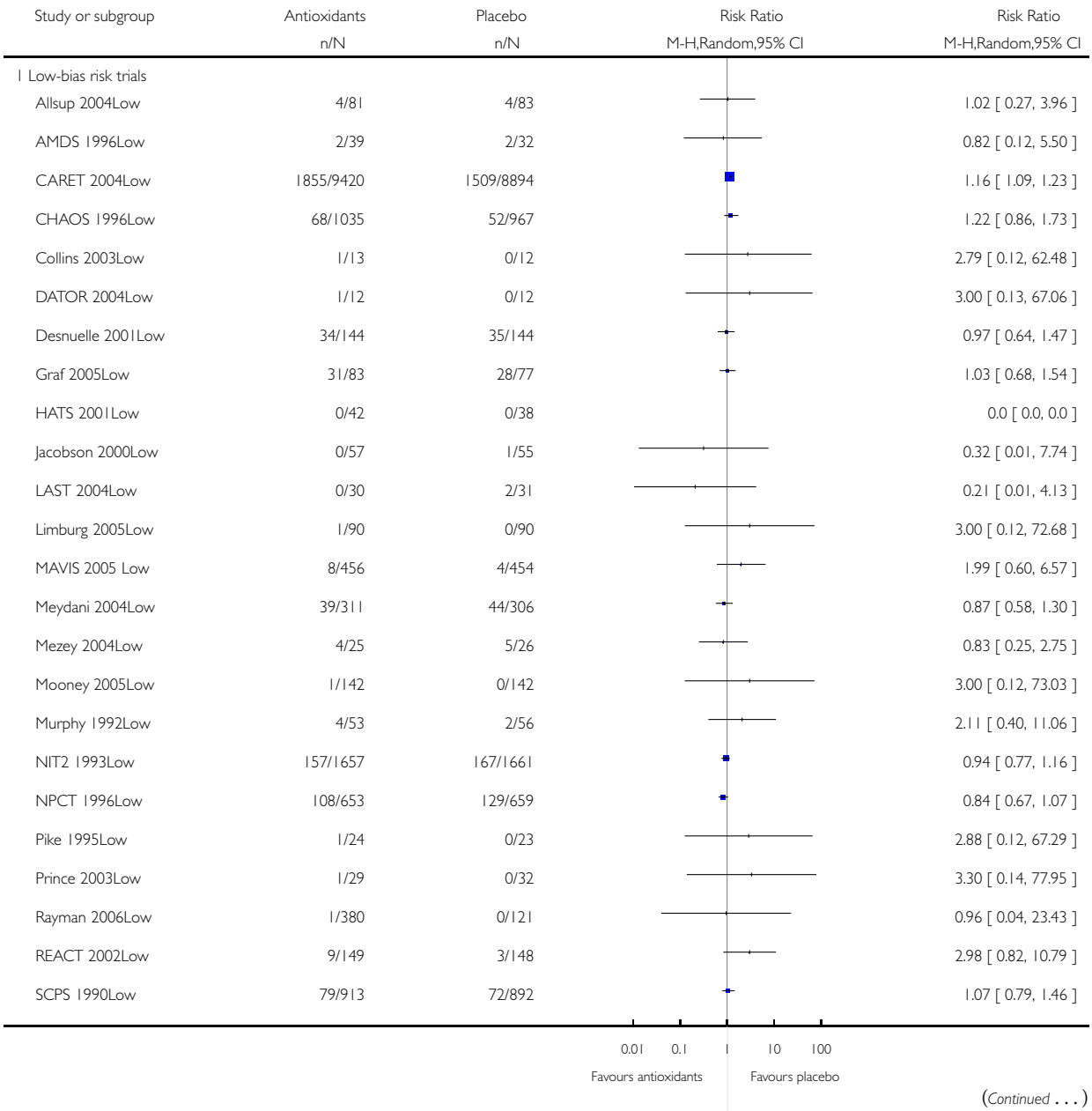
Study or subgroup	Antioxidants n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
White 2002Low	1/50	1/50		0.0 %	1.00 [0.06, 15.55]
WHS 2005Low	636/19937	615/19939		7.0 %	1.03 [0.93, 1.15]
Witte 2005Low	1/16	1/16		0.0 %	1.00 [0.07, 14.64]
Wluka 2002Low	1/67	0/69		0.0 %	3.09 [0.13, 74.50]
Subtotal (95% CI)	**98267**	**80985**		**84.5 %**	**1.05 [1.01, 1.08]**
Total events: 15152 (Antioxidants), 8930 (Control)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 48.06$, df = 42 (P = 0.24); $I^2 = 13\%$					
Test for overall effect: Z = 2.48 (P = 0.013)					
2 Trials with high risk of bias					
ADCS 1 1997	19/170	22/171		0.4 %	0.87 [0.49, 1.55]
Bonelli 1998	1/147	0/157		0.0 %	3.20 [0.13, 78.00]
Chandra 1992	0/48	2/48		0.0 %	0.20 [0.01, 4.06]
de la Maza 1995	5/37	4/37		0.1 %	1.25 [0.36, 4.29]
de Waart 2001	0/109	1/109		0.0 %	0.33 [0.01, 8.09]
Girodon 1997	18/61	7/20		0.2 %	0.84 [0.41, 1.72]
GISSI 1999	488/5660	529/5664		6.3 %	0.92 [0.82, 1.04]
Hogarth 1996	7/54	6/52		0.1 %	1.12 [0.40, 3.12]
McKeown-Eyssen 1988	4/96	3/89		0.1 %	1.24 [0.28, 5.37]
NIT1 1993	1847/25886	280/3698		6.1 %	0.94 [0.84, 1.06]
Penn 1991	1/15	0/15		0.0 %	3.00 [0.13, 68.26]
PPP 2001	72/2231	68/2264		1.1 %	1.07 [0.78, 1.49]
SIT 2001	38/1706	43/1705		0.7 %	0.88 [0.57, 1.36]
Stevic 2001	3/16	6/12		0.1 %	0.38 [0.12, 1.20]
Takagi 2003	10/51	16/42		0.3 %	0.51 [0.26, 1.01]
Subtotal (95% CI)	**36287**	**14083**		**15.5 %**	**0.93 [0.86, 1.00]**
Total events: 2513 (Antioxidants), 987 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 9.27$, df = 14 (P = 0.81); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.90 (P = 0.057)					
Total (95% CI)	**134554**	**95068**		**100.0 %**	**1.02 [0.99, 1.06]**
Total events: 17665 (Antioxidants), 9917 (Control)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 66.96$, df = 57 (P = 0.17); $I^2 = 15\%$					
Test for overall effect: Z = 1.35 (P = 0.18)					

Analysis 1.5. Comparison 1 Antioxidants versus placebo/no intervention, Outcome 5 Mortality after excluding factorial trials with potential confounding.

Review: Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases

Comparison: 1 Antioxidants versus placebo/no intervention

Outcome: 5 Mortality after excluding factorial trials with potential confounding



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Study or subgroup	Antioxidants n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
SKICAP AK 1997Low	62/1157	53/1140		1.15 [0.81, 1.65]
SPACE 2000Low	31/97	29/99		1.09 [0.72, 1.66]
SUVIMAX 2004Low	76/6481	98/6536		0.78 [0.58, 1.05]
Tam 2005Low	1/20	1/19		0.95 [0.06, 14.13]
VEAPS 2002Low	2/177	1/176		1.99 [0.18, 21.73]
VECAT 2004Low	20/595	11/598		1.83 [0.88, 3.78]
WAVE 2002Low	6/105	2/108		3.09 [0.64, 14.95]
White 2002Low	1/50	1/50		1.00 [0.06, 15.55]
Witte 2005Low	1/16	1/16		1.00 [0.07, 14.64]
Wluka 2002Low	1/67	0/69		3.09 [0.13, 74.50]
Subtotal (95% CI)	**24603**	**23766**		**1.11 [1.05, 1.17]**
Total events: 2610 (Antioxidants), 2256 (Placebo)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 29.65$, df = 32 (P = 0.59); $I^2 = 0.0\%$				
Test for overall effect: Z = 3.91 (P = 0.000091)				
2 High-bias risk trials				
ADCS 1 1997	12/85	12/84		0.99 [0.47, 2.07]
ADCS 2 2005	5/257	5/259		1.01 [0.30, 3.44]
Bonelli 1998	1/147	0/157		3.20 [0.13, 78.00]
Chandra 1992	0/48	2/48		0.20 [0.01, 4.06]
de la Maza 1995	5/37	4/37		1.25 [0.36, 4.29]
de Waart 2001	0/109	1/109		0.33 [0.01, 8.09]
Gillilan 1977	2/26	2/26		1.00 [0.15, 6.57]
GISSI 1999	252/2830	293/2828		0.86 [0.73, 1.01]
McKeown-Eyssen 1988	4/96	3/89		1.24 [0.28, 5.37]
Penn 1991	1/15	0/15		3.00 [0.13, 68.26]
Stevic 2001	3/16	6/12		0.38 [0.12, 1.20]
Takagi 2003	10/51	16/42		0.51 [0.26, 1.01]
Takamatsu 1995	1/74	0/73		2.96 [0.12, 71.50]
Subtotal (95% CI)	**3791**	**3779**		**0.84 [0.73, 0.98]**
Total events: 296 (Antioxidants), 344 (Placebo)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 8.01$, df = 12 (P = 0.78); $I^2 = 0.0\%$				
Test for overall effect: Z = 2.25 (P = 0.025)				
Total (95% CI)	**28394**	**27545**		**1.01 [0.94, 1.09]**
Total events: 2906 (Antioxidants), 2600 (Placebo)				
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 49.33$, df = 45 (P = 0.30); $I^2 = 9\%$				

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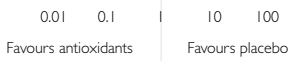
Study or subgroup	Antioxidants n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 0.31 (P = 0.75)				



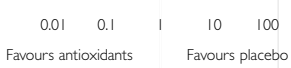
Analysis 1.6. Comparison 1 Antioxidants versus placebo/no intervention, Outcome 6 Mortality after excluding factorial trials with potential confounding and trials with extra supplements.

Review: Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases

Comparison: 1 Antioxidants versus placebo/no intervention

Outcome: 6 Mortality after excluding factorial trials with potential confounding and trials with extra supplements

Study or subgroup	Antioxidants n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low-bias risk trials					
CARET 2004Low	1855/9420	1509/8894		20.9 %	1.16 [1.09, 1.23]
CHAOS 1996Low	68/1035	52/967		6.3 %	1.22 [0.86, 1.73]
Collins 2003Low	1/13	0/12		0.1 %	2.79 [0.12, 62.48]
DATOR 2004Low	1/12	0/12		0.1 %	3.00 [0.13, 67.06]
Desnuelle 2001Low	34/144	35/144		4.9 %	0.97 [0.64, 1.47]
Graf 2005Low	31/83	28/77		5.1 %	1.03 [0.68, 1.54]
Jacobson 2000Low	0/57	1/55		0.1 %	0.32 [0.01, 7.74]
Limburg 2005Low	1/90	0/90		0.1 %	3.00 [0.12, 72.68]
Mezey 2004Low	4/25	5/26		0.7 %	0.83 [0.25, 2.75]
Mooney 2005Low	1/142	0/142		0.1 %	3.00 [0.12, 73.03]
NPCT 1996Low	108/653	129/659		10.6 %	0.84 [0.67, 1.07]
Prince 2003Low	1/29	0/32		0.1 %	3.30 [0.14, 77.95]
Rayman 2006Low	1/380	0/121		0.1 %	0.96 [0.04, 23.43]
REACT 2002Low	9/149	3/148		0.6 %	2.98 [0.82, 10.79]
SCPS 1990Low	79/913	72/892		7.6 %	1.07 [0.79, 1.46]
SKICAP AK 1997Low	62/1157	53/1140		6.1 %	1.15 [0.81, 1.65]



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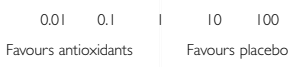
Study or subgroup	Antioxidants n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
SPACE 2000Low	31/97	29/99		4.8 %	1.09 [0.72, 1.66]
SUVIMAX 2004Low	76/6481	98/6536		7.9 %	0.78 [0.58, 1.05]
Tam 2005Low	1/20	1/19		0.1 %	0.95 [0.06, 14.13]
VEAPS 2002Low	2/177	1/176		0.2 %	1.99 [0.18, 21.73]
VECAT 2004Low	20/595	11/598		1.9 %	1.83 [0.88, 3.78]
WAVE 2002Low	6/105	2/108		0.4 %	3.09 [0.64, 14.95]
White 2002Low	1/50	1/50		0.1 %	1.00 [0.06, 15.55]
Wluka 2002Low	1/67	0/69		0.1 %	3.09 [0.13, 74.50]
Subtotal (95% CI)	**21894**	**21066**		**79.2 %**	**1.12 [1.07, 1.19]**
Total events: 2394 (Antioxidants), 2030 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 22.46$, df = 23 (P = 0.49); $I^2 = 0.0\%$					
Test for overall effect: Z = 4.26 (P = 0.000021)					
2 High-bias risk trials					
ADCS 1 1997	12/85	12/84		1.8 %	0.99 [0.47, 2.07]
Bonelli 1998	1/147	0/157		0.1 %	3.20 [0.13, 78.00]
de la Maza 1995	5/37	4/37		0.7 %	1.25 [0.36, 4.29]
de Waart 2001	0/109	1/109		0.1 %	0.33 [0.01, 8.09]
GISSI 1999	252/2830	293/2828		14.7 %	0.86 [0.73, 1.01]
McKeown-Eyssen 1988	4/96	3/89		0.5 %	1.24 [0.28, 5.37]
Penn 1991	1/15	0/15		0.1 %	3.00 [0.13, 68.26]
Stevic 2001	3/16	6/12		0.8 %	0.38 [0.12, 1.20]
Takagi 2003	10/51	16/42		2.1 %	0.51 [0.26, 1.01]
Subtotal (95% CI)	**3386**	**3373**		**20.8 %**	**0.84 [0.73, 0.98]**
Total events: 288 (Antioxidants), 335 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.42$, df = 8 (P = 0.60); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.26 (P = 0.024)					
Total (95% CI)	**25280**	**24439**		**100.0 %**	**1.01 [0.91, 1.12]**
Total events: 2682 (Antioxidants), 2365 (Placebo)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 41.64$, df = 32 (P = 0.12); $I^2 = 23\%$					
Test for overall effect: Z = 0.25 (P = 0.81)					



Analysis 1.7. Comparison 1 Antioxidants versus placebo/no intervention, Outcome 7 Mortality after excluding trials with any potential confounding.

Review: Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases

Comparison: 1 Antioxidants versus placebo/no intervention

Outcome: 7 Mortality after excluding trials with any potential confounding

Study or subgroup	Antioxidants n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
CARET 2004Low	1855/9420	1509/8894		84.4 %	1.16 [1.09, 1.23]
CHAOS 1996Low	68/1035	52/967		2.6 %	1.22 [0.86, 1.73]
Collins 2003Low	1/13	0/12		0.0 %	2.79 [0.12, 62.48]
DATOR 2004Low	1/12	0/12		0.0 %	3.00 [0.13, 67.06]
Desnuelle 2001Low	34/144	35/144		1.9 %	0.97 [0.64, 1.47]
Graf 2005Low	31/83	28/77		1.9 %	1.03 [0.68, 1.54]
Jacobson 2000Low	0/57	1/55		0.0 %	0.32 [0.01, 7.74]
Mezey 2004Low	4/25	5/26		0.2 %	0.83 [0.25, 2.75]
Mooney 2005Low	1/142	0/142		0.0 %	3.00 [0.12, 73.03]
REACT 2002Low	9/149	3/148		0.2 %	2.98 [0.82, 10.79]
SCPS 1990Low	79/913	72/892		3.4 %	1.07 [0.79, 1.46]
SKICAP AK 1997Low	62/1157	53/1140		2.5 %	1.15 [0.81, 1.65]
SPACE 2000Low	31/97	29/99		1.8 %	1.09 [0.72, 1.66]
Tam 2005Low	1/20	1/19		0.0 %	0.95 [0.06, 14.13]
VEAPS 2002Low	2/177	1/176		0.1 %	1.99 [0.18, 21.73]
VECAT 2004Low	20/595	11/598		0.6 %	1.83 [0.88, 3.78]
WAVE 2002Low	6/105	2/108		0.1 %	3.09 [0.64, 14.95]
White 2002Low	1/50	1/50		0.0 %	1.00 [0.06, 15.55]
Wluka 2002Low	1/67	0/69		0.0 %	3.09 [0.13, 74.50]
Total (95% CI)	**14261**	**13628**		**100.0 %**	**1.16 [1.09, 1.23]**

Total events: 2207 (Antioxidants), 1803 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 9.05$, df = 18 (P = 0.96); $I^2 = 0.0\%$

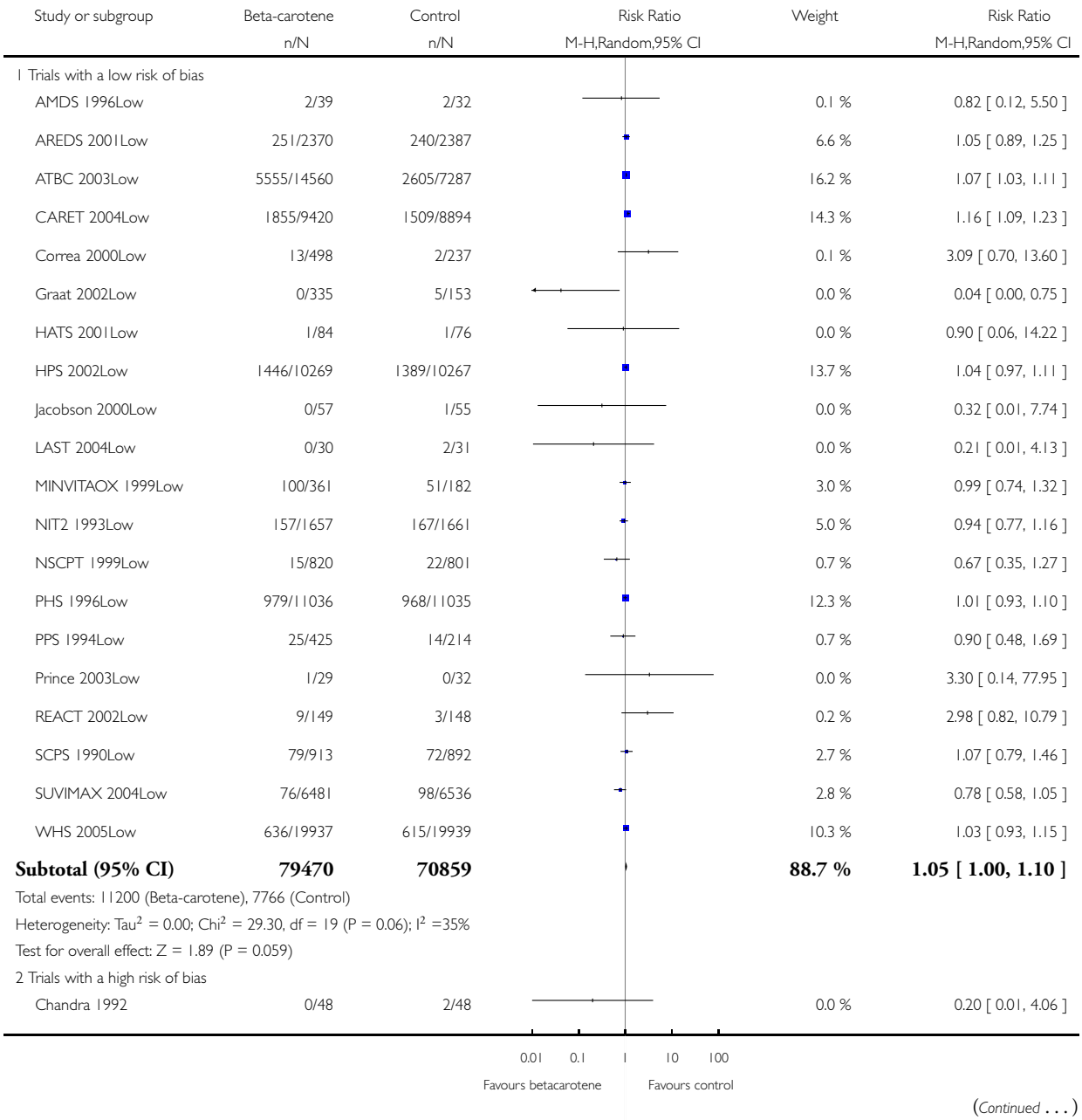
Test for overall effect: Z = 5.09 (P < 0.00001)

Analysis 1.8. Comparison 1 Antioxidants versus placebo/no intervention, Outcome 8 Mortality in beta-carotene trials with a low or high risk of bias.

Review: Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases

Comparison: 1 Antioxidants versus placebo/no intervention

Outcome: 8 Mortality in beta-carotene trials with a low or high risk of bias



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Study or subgroup	Beta-carotene n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Girodon 1997	12/41	7/20		0.5 %	0.84 [0.39, 1.79]
NIT1 1993	1018/14792	280/3698		8.9 %	0.91 [0.80, 1.03]
Sasazuki 2003	6/222	18/217		0.4 %	0.33 [0.13, 0.81]
SIT 2001	38/1706	43/1705		1.5 %	0.88 [0.57, 1.36]
Subtotal (95% CI)	**16809**	**5688**		**11.3 %**	**0.81 [0.62, 1.07]**
Total events: 1074 (Beta-carotene), 350 (Control)					
Heterogeneity: Tau² = 0.03; Chi² = 5.82, df = 4 (P = 0.21); I² =31%					
Test for overall effect: Z = 1.47 (P = 0.14)					
Total (95% CI)	**96279**	**76547**		**100.0 %**	**1.02 [0.97, 1.08]**
Total events: 12274 (Beta-carotene), 8116 (Control)					
Heterogeneity: Tau² = 0.00; Chi² = 43.87, df = 24 (P = 0.01); I² =45%					
Test for overall effect: Z = 0.71 (P = 0.48)					

Analysis 1.9. Comparison 1 Antioxidants versus placebo/no intervention, Outcome 9 Mortality in vitamin A trials with a low or high risk of bias.

Review: Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases

Comparison: 1 Antioxidants versus placebo/no intervention

Outcome: 9 Mortality in vitamin A trials with a low or high risk of bias

Study or subgroup	Vitamin A n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Trials with a low risk of bias					
Allsup 2004Low	4/81	4/83		0.9 %	1.02 [0.27, 3.96]
CARET 2004Low	1855/9420	1509/8894		36.9 %	1.16 [1.09, 1.23]
Graat 2002Low	0/335	5/153		0.2 %	0.04 [0.00, 0.75]
LAST 2004Low	0/30	2/31		0.2 %	0.21 [0.01, 4.13]
MAVIS 2005 Low	8/456	4/454		1.1 %	1.99 [0.60, 6.57]
Murphy 1992Low	4/53	2/56		0.6 %	2.11 [0.40, 11.06]
NIT2 1993Low	157/1657	167/1661		19.5 %	0.94 [0.77, 1.16]
Pike 1995Low	1/24	0/23		0.2 %	2.88 [0.12, 67.29]

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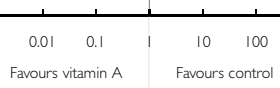
Study or subgroup	Vitamin A n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
SKICAP AK 1997Low	62/1157	53/1140		9.6 %	1.15 [0.81, 1.65]
Witte 2005Low	1/16	1/16		0.2 %	1.00 [0.07, 14.64]
Subtotal (95% CI)	**13229**	**12511**		**69.2 %**	**1.09 [0.93, 1.28]**
Total events: 2092 (Vitamin A), 1747 (Control)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 11.63$, df = 9 (P = 0.24); $I^2 = 23\%$					
Test for overall effect: Z = 1.11 (P = 0.27)					
2 Trials with a high risk of bias					
Bonelli 1998	1/147	0/157		0.2 %	3.20 [0.13, 78.00]
Chandra 1992	0/48	2/48		0.2 %	0.20 [0.01, 4.06]
Hogarth 1996	7/54	6/52		1.5 %	1.12 [0.40, 3.12]
NIT1 1993	1067/14792	280/3698		28.8 %	0.95 [0.84, 1.08]
Penn 1991	1/15	0/15		0.2 %	3.00 [0.13, 68.26]
Subtotal (95% CI)	**15056**	**3970**		**30.8 %**	**0.96 [0.84, 1.08]**
Total events: 1076 (Vitamin A), 288 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.20$, df = 4 (P = 0.70); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.70 (P = 0.48)					
Total (95% CI)	**28285**	**16481**		**100.0 %**	**1.05 [0.93, 1.19]**
Total events: 3168 (Vitamin A), 2035 (Control)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 20.21$, df = 14 (P = 0.12); $I^2 = 31\%$					
Test for overall effect: Z = 0.78 (P = 0.44)					



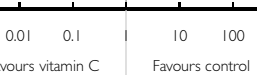
Analysis 1.10. Comparison 1 Antioxidants versus placebo/no intervention, Outcome 10 Mortality in vitamin C trials with a low or high risk of bias.

Review: Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases

Comparison: 1 Antioxidants versus placebo/no intervention

Outcome: 10 Mortality in vitamin C trials with a low or high risk of bias

Study or subgroup	Vitamin C n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Trials with a low risk of bias					
Allsup 2004Low	4/81	4/83		0.2 %	1.02 [0.27, 3.96]
AMDS 1996Low	2/39	2/32		0.1 %	0.82 [0.12, 5.50]
AREDS 2001Low	251/2370	240/2387		13.0 %	1.05 [0.89, 1.25]
ASAP 2003Low	2/260	1/130		0.1 %	1.00 [0.09, 10.93]
Correa 2000Low	3/241	2/237		0.1 %	1.48 [0.25, 8.75]
Graat 2002Low	0/335	5/153		0.1 %	0.04 [0.00, 0.75]
HATS 2001Low	1/84	1/76		0.1 %	0.90 [0.06, 14.22]
HPS 2002Low	1446/10269	1389/10267		40.2 %	1.04 [0.97, 1.11]
Jacobson 2000Low	0/57	1/55		0.0 %	0.32 [0.01, 7.74]
LAST 2004Low	0/30	2/31		0.1 %	0.21 [0.01, 4.13]
MAVIS 2005 Low	8/456	4/454		0.3 %	1.99 [0.60, 6.57]
MINVITAOX 1999Low	100/361	51/182		5.1 %	0.99 [0.74, 1.32]
Mooney 2005Low	1/142	0/142		0.0 %	3.00 [0.12, 73.03]
NIT2 1993Low	157/1657	167/1661		9.1 %	0.94 [0.77, 1.16]
Pike 1995Low	1/24	0/23		0.0 %	2.88 [0.12, 67.29]
PPS 1994Low	15/433	14/214		0.9 %	0.53 [0.26, 1.08]
Prince 2003Low	1/29	0/32		0.0 %	3.30 [0.14, 77.95]
REACT 2002Low	9/149	3/148		0.3 %	2.98 [0.82, 10.79]
SUVIMAX 2004Low	76/6481	98/6536		4.7 %	0.78 [0.58, 1.05]
Tam 2005Low	1/20	1/19		0.1 %	0.95 [0.06, 14.13]
WAVE 2002Low	16/212	6/211		0.5 %	2.65 [1.06, 6.65]
White 2002Low	1/50	1/50		0.1 %	1.00 [0.06, 15.55]
Witte 2005Low	1/16	1/16		0.1 %	1.00 [0.07, 14.64]
Subtotal (95% CI)	**23796**	**23139**		**75.3 %**	**1.01 [0.93, 1.10]**



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Study or subgroup	Vitamin C n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 2096 (Vitamin C), 1993 (Control)					
Heterogeneity: Tau² = 0.00; Chi² = 23.37, df = 22 (P = 0.38); I² =6%					
Test for overall effect: Z = 0.20 (P = 0.84)					
2 Trials with a high risk of bias					
Bonelli 1998	1/147	0/157		0.0 %	3.20 [0.13, 78.00]
Chandra 1992	0/48	2/48		0.0 %	0.20 [0.01, 4.06]
Girodon 1997	12/41	7/20		0.8 %	0.84 [0.39, 1.79]
Hogarth 1996	7/54	6/52		0.4 %	1.12 [0.40, 3.12]
McKeown-Eyssen 1988	4/96	3/89		0.2 %	1.24 [0.28, 5.37]
NIT1 1993	1069/14792	280/3698		20.0 %	0.95 [0.84, 1.08]
Penn 1991	1/15	0/15		0.0 %	3.00 [0.13, 68.26]
Sasazuki 2003	6/222	18/217		0.5 %	0.33 [0.13, 0.81]
SIT 2001	38/1706	43/1705		2.3 %	0.88 [0.57, 1.36]
ter Riet 1995	3/43	5/45		0.2 %	0.63 [0.16, 2.47]
Subtotal (95% CI)	**17164**	**6046**		**24.7 %**	**0.93 [0.83, 1.05]**
Total events: 1141 (Vitamin C), 364 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 8.17, df = 9 (P = 0.52); I² =0.0%					
Test for overall effect: Z = 1.20 (P = 0.23)					
Total (95% CI)	**40960**	**29185**		**100.0 %**	**0.99 [0.92, 1.06]**
Total events: 3237 (Vitamin C), 2357 (Control)					
Heterogeneity: Tau² = 0.00; Chi² = 33.56, df = 32 (P = 0.39); I² =5%					
Test for overall effect: Z = 0.32 (P = 0.75)					

Analysis 1.11. Comparison 1 Antioxidants versus placebo/no intervention, Outcome 11 Mortality in vitamin E trials with a low or high risk of bias.

Review: Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases

Comparison: 1 Antioxidants versus placebo/no intervention

Outcome: 11 Mortality in vitamin E trials with a low or high risk of bias

Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Trials with a low risk of bias					
Allsup 2004Low	4/81	4/83		0.0 %	1.02 [0.27, 3.96]
AMDS 1996Low	2/39	2/32		0.0 %	0.82 [0.12, 5.50]
AREDS 2001Low	251/2370	240/2387		2.4 %	1.05 [0.89, 1.25]
ASAP 2003Low	4/260	1/130		0.0 %	2.00 [0.23, 17.71]
ATBC 2003Low	5433/14564	2605/7287		49.4 %	1.04 [1.01, 1.08]
CHAOS 1996Low	68/1035	52/967		0.6 %	1.22 [0.86, 1.73]
Collins 2003Low	1/26	1/26		0.0 %	1.00 [0.07, 15.15]
DATATOP 2005Low	154/399	142/401		2.1 %	1.09 [0.91, 1.31]
DATOR 2004Low	1/12	0/12		0.0 %	3.00 [0.13, 67.06]
Desnuelle 2001Low	34/144	35/144		0.4 %	0.97 [0.64, 1.47]
Graat 2002Low	3/499	5/153		0.0 %	0.18 [0.04, 0.76]
Graf 2005Low	31/83	28/77		0.4 %	1.03 [0.68, 1.54]
HATS 2001Low	1/84	1/76		0.0 %	0.90 [0.06, 14.22]
HOPE TOO 2005Low	799/4761	801/4780		8.6 %	1.00 [0.92, 1.10]
HPS 2002Low	1446/10269	1389/10267		14.7 %	1.04 [0.97, 1.11]
Jacobson 2000Low	0/57	1/55		0.0 %	0.32 [0.01, 7.74]
LAST 2004Low	0/30	2/31		0.0 %	0.21 [0.01, 4.13]
MAVIS 2005 Low	8/456	4/454		0.0 %	1.99 [0.60, 6.57]
Meydani 2004Low	39/311	44/306		0.4 %	0.87 [0.58, 1.30]
Mezey 2004Low	4/25	5/26		0.0 %	0.83 [0.25, 2.75]
MINVITAOX 1999Low	100/361	51/182		0.8 %	0.99 [0.74, 1.32]
Mooney 2005Low	1/142	0/142		0.0 %	3.00 [0.12, 73.03]
NIT2 1993Low	157/1657	167/1661		1.6 %	0.94 [0.77, 1.16]
Pike 1995Low	1/24	0/23		0.0 %	2.88 [0.12, 67.29]

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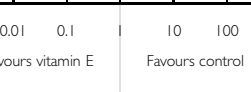
Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
PPS 1994Low	15/433	14/214		0.1 %	0.53 [0.26, 1.08]
Prince 2003Low	1/29	0/32		0.0 %	3.30 [0.14, 77.95]
REACT 2002Low	9/149	3/148		0.0 %	2.98 [0.82, 10.79]
SPACE 2000Low	31/97	29/99		0.4 %	1.09 [0.72, 1.66]
SUVIMAX 2004Low	76/6481	98/6536		0.8 %	0.78 [0.58, 1.05]
Tam 2005Low	1/20	1/19		0.0 %	0.95 [0.06, 14.13]
VEAPS 2002Low	2/177	1/176		0.0 %	1.99 [0.18, 21.73]
VECAT 2004Low	20/595	11/598		0.1 %	1.83 [0.88, 3.78]
WAVE 2002Low	16/212	6/211		0.1 %	2.65 [1.06, 6.65]
White 2002Low	1/50	1/50		0.0 %	1.00 [0.06, 15.55]
WHS 2005Low	636/19937	615/19939		5.8 %	1.03 [0.93, 1.15]
Witte 2005Low	1/16	1/16		0.0 %	1.00 [0.07, 14.64]
Wluka 2002Low	1/67	0/69		0.0 %	3.09 [0.13, 74.50]
Subtotal (95% CI)	**65952**	**57809**		**89.1 %**	**1.04 [1.01, 1.06]**
Total events: 9352 (Vitamin E), 6360 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 31.07$, df = 36 (P = 0.70); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.47 (P = 0.014)					
2 Trials with a high risk of bias					
ADCS 1 1997	12/85	12/84		0.1 %	0.99 [0.47, 2.07]
ADCS 2 2005	5/257	5/259		0.0 %	1.01 [0.30, 3.44]
Bonelli 1998	1/147	0/157		0.0 %	3.20 [0.13, 78.00]
Chandra 1992	0/48	2/48		0.0 %	0.20 [0.01, 4.06]
de la Maza 1995	5/37	4/37		0.0 %	1.25 [0.36, 4.29]
de Waart 2001	0/109	1/109		0.0 %	0.33 [0.01, 8.09]
Gillilan 1977	2/26	2/26		0.0 %	1.00 [0.15, 6.57]
Girodon 1997	12/41	7/20		0.1 %	0.84 [0.39, 1.79]
GISSI 1999	488/5660	529/5664		5.0 %	0.92 [0.82, 1.04]
McKeown-Eyssen 1988	4/96	3/89		0.0 %	1.24 [0.28, 5.37]
NIT1 1993	1018/14792	280/3698		4.2 %	0.91 [0.80, 1.03]
Penn 1991	1/15	0/15		0.0 %	3.00 [0.13, 68.26]
PPP 2001	72/2231	68/2264		0.6 %	1.07 [0.78, 1.49]
SIT 2001	38/1706	43/1705		0.4 %	0.88 [0.57, 1.36]
Stevic 2001	3/16	6/12		0.1 %	0.38 [0.12, 1.20]



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Study or subgroup	Vitamin E n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Takagi 2003	10/51	16/42		0.2 %	0.51 [0.26, 1.01]
Takamatsu 1995	1/74	0/73		0.0 %	2.96 [0.12, 71.50]
Subtotal (95% CI)	**25391**	**14302**		**10.9 %**	**0.92 [0.85, 0.99]**
Total events: 1672 (Vitamin E), 978 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 9.59, df = 16 (P = 0.89); I^2 =0.0%					
Test for overall effect: Z = 2.17 (P = 0.030)					
Total (95% CI)	**91343**	**72111**		**100.0 %**	**1.02 [1.00, 1.05]**
Total events: 11024 (Vitamin E), 7338 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 48.87, df = 53 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 1.62 (P = 0.11)					

Analysis 1.12. Comparison 1 Antioxidants versus placebo/no intervention, Outcome 12 Mortality in selenium trials with a low or high risk of bias.

Review: Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases

Comparison: 1 Antioxidants versus placebo/no intervention

Outcome: 12 Mortality in selenium trials with a low or high risk of bias

Study or subgroup	Selenium n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Trials with a low risk of bias					
Allsup 2004Low	4/81	4/83		0.4 %	1.02 [0.27, 3.96]
AMDS 1996Low	2/39	2/32		0.2 %	0.82 [0.12, 5.50]
Graat 2002Low	0/335	5/153		0.1 %	0.04 [0.00, 0.75]
HATS 2001Low	1/84	1/76		0.1 %	0.90 [0.06, 14.22]
LAST 2004Low	0/30	2/31		0.1 %	0.21 [0.01, 4.13]
Limburg 2005Low	1/180	0/180		0.1 %	3.00 [0.12, 73.16]
Meydani 2004Low	39/311	44/306		4.3 %	0.87 [0.58, 1.30]
MINVITAOX 1999Low	110/363	51/182		8.9 %	1.08 [0.82, 1.43]
NIT2 1993Low	157/1657	167/1661		16.2 %	0.94 [0.77, 1.16]
NPCT 1996Low	108/653	129/659		13.0 %	0.84 [0.67, 1.07]

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Study or subgroup	Selenium n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Prince 2003Low	1/29	0/32		0.1 %	3.30 [0.14, 77.95]
Rayman 2006Low	1/380	0/121		0.1 %	0.96 [0.04, 23.43]
SUVIMAX 2004Low	76/6481	98/6536		7.9 %	0.78 [0.58, 1.05]
Witte 2005Low	1/16	1/16		0.1 %	1.00 [0.07, 14.64]
Subtotal (95% CI)	**10639**	**10068**		**51.4 %**	**0.90 [0.80, 1.01]**
Total events: 501 (Selenium), 504 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 9.59, df = 13 (P = 0.73); I² =0.0%					
Test for overall effect: Z = 1.72 (P = 0.085)					
2 Trials with a high risk of bias					
Bonelli 1998	1/147	0/157		0.1 %	3.20 [0.13, 78.00]
Chandra 1992	0/48	2/48		0.1 %	0.20 [0.01, 4.06]
Girodon 1997	13/41	7/20		1.2 %	0.91 [0.43, 1.91]
NIT1 1993	1018/14792	280/3698		43.0 %	0.91 [0.80, 1.03]
SIT 2001	38/1706	43/1705		3.7 %	0.88 [0.57, 1.36]
Stevic 2001	3/16	6/12		0.5 %	0.38 [0.12, 1.20]
Subtotal (95% CI)	**16750**	**5640**		**48.6 %**	**0.90 [0.80, 1.01]**
Total events: 1073 (Selenium), 338 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 3.76, df = 5 (P = 0.58); I² =0.0%					
Test for overall effect: Z = 1.76 (P = 0.078)					
Total (95% CI)	**27389**	**15708**		**100.0 %**	**0.90 [0.83, 0.98]**
Total events: 1574 (Selenium), 842 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 13.32, df = 19 (P = 0.82); I² =0.0%					
Test for overall effect: Z = 2.46 (P = 0.014)					

Analysis 1.13. Comparison 1 Antioxidants versus placebo/no intervention, Outcome 13 Mortality in low-bias risk beta-carotene trials without selenium.

Review: Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases

Comparison: 1 Antioxidants versus placebo/no intervention

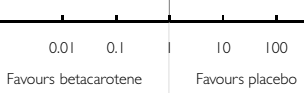
Outcome: 13 Mortality in low-bias risk beta-carotene trials without selenium

Study or subgroup	Beta-carotene n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
AREDS 2001Low	251/2370	240/2387		5.6 %	1.05 [0.89, 1.25]
ATBC 2003Low	5555/14560	2605/7287		27.1 %	1.07 [1.03, 1.11]
CARET 2004Low	1855/9420	1509/8894		20.2 %	1.16 [1.09, 1.23]
Correa 2000Low	13/498	2/237		0.1 %	3.09 [0.70, 13.60]
HPS 2002Low	1446/10269	1389/10267		18.4 %	1.04 [0.97, 1.11]
Jacobson 2000Low	0/57	1/55		0.0 %	0.32 [0.01, 7.74]
NSCPT 1999Low	15/820	22/801		0.4 %	0.67 [0.35, 1.27]
PHS 1996Low	979/11036	968/11035		14.8 %	1.01 [0.93, 1.10]
PPS 1994Low	25/425	14/214		0.5 %	0.90 [0.48, 1.69]
REACT 2002Low	9/149	3/148		0.1 %	2.98 [0.82, 10.79]
SCPS 1990Low	79/913	72/892		1.9 %	1.07 [0.79, 1.46]
WHS 2005Low	636/19937	615/19939		10.8 %	1.03 [0.93, 1.15]
Total (95% CI)	**70454**	**62156**		**100.0 %**	**1.07 [1.02, 1.11]**

Total events: 10863 (Beta-carotene), 7440 (Placebo)

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 16.77$, df = 11 (P = 0.11); $I^2 = 34\%$

Test for overall effect: Z = 2.90 (P = 0.0038)



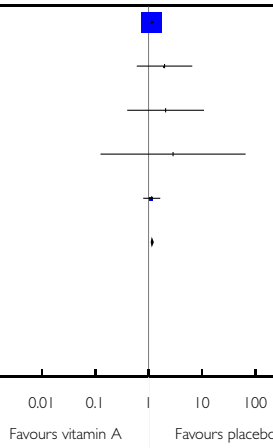
Analysis 1.14. Comparison 1 Antioxidants versus placebo/no intervention, Outcome 14 Mortality in low-bias risk vitamin A trials without selenium.

Review: Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases

Comparison: 1 Antioxidants versus placebo/no intervention

Outcome: 14 Mortality in low-bias risk vitamin A trials without selenium

Study or subgroup	Vitamin A n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
CARET 2004Low	1855/9420	1509/8894		96.7 %	1.16 [1.09, 1.23]
MAVIS 2005 Low	8/456	4/454		0.3 %	1.99 [0.60, 6.57]
Murphy 1992Low	4/53	2/56		0.1 %	2.11 [0.40, 11.06]
Pike 1995Low	1/24	0/23		0.0 %	2.88 [0.12, 67.29]
SKICAP AK 1997Low	62/1157	53/1140		2.9 %	1.15 [0.81, 1.65]
Total (95% CI)	**11110**	**10567**		**100.0 %**	**1.16 [1.10, 1.24]**
Total events: 1930 (Vitamin A), 1568 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.61$, df = 4 (P = 0.81); $I^2 = 0.0\%$					
Test for overall effect: Z = 4.91 (P < 0.00001)					



Analysis 1.15. Comparison 1 Antioxidants versus placebo/no intervention, Outcome 15 Mortality in low-bias risk vitamin C trials without selenium.

Review: Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases

Comparison: 1 Antioxidants versus placebo/no intervention

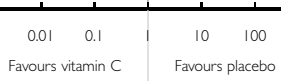
Outcome: 15 Mortality in low-bias risk vitamin C trials without selenium

Study or subgroup	Vitamin C n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
AREDS 2001Low	251/2370	240/2387		31.0 %	1.05 [0.89, 1.25]
ASAP 2003Low	2/260	1/130		0.3 %	1.00 [0.09, 10.93]
Correa 2000Low	9/496	2/237		0.6 %	2.15 [0.47, 9.87]
HPS 2002Low	1446/10269	1389/10267		60.9 %	1.04 [0.97, 1.11]
Jacobson 2000Low	0/57	1/55		0.1 %	0.32 [0.01, 7.74]
MAVIS 2005 Low	8/456	4/454		1.0 %	1.99 [0.60, 6.57]
Mooney 2005Low	1/142	0/142		0.1 %	3.00 [0.12, 73.03]
Pike 1995Low	1/24	0/23		0.1 %	2.88 [0.12, 67.29]
PPS 1994Low	15/433	14/214		2.8 %	0.53 [0.26, 1.08]
REACT 2002Low	9/149	3/148		0.9 %	2.98 [0.82, 10.79]
Tam 2005Low	1/20	1/19		0.2 %	0.95 [0.06, 14.13]
WAVE 2002Low	16/212	6/211		1.7 %	2.65 [1.06, 6.65]
White 2002Low	1/50	1/50		0.2 %	1.00 [0.06, 15.55]
Total (95% CI)	**14938**	**14337**		**100.0 %**	**1.06 [0.94, 1.20]**

Total events: 1760 (Vitamin C), 1662 (Placebo)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 13.38$, df = 12 (P = 0.34); $I^2 = 10\%$

Test for overall effect: Z = 1.00 (P = 0.32)



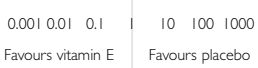
Analysis 1.16. Comparison 1 Antioxidants versus placebo/no intervention, Outcome 16 Mortality in low-bias risk vitamin E trials without selenium.

Review: Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases

Comparison: 1 Antioxidants versus placebo/no intervention

Outcome: 16 Mortality in low-bias risk vitamin E trials without selenium

Study or subgroup	Vitamin E n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
AREDS 2001Low	251/2370	240/2387		2.9 %	1.05 [0.89, 1.25]
ASAP 2003Low	4/260	1/130		0.0 %	2.00 [0.23, 17.71]
ATBC 2003Low	5433/14564	2605/7287		57.9 %	1.04 [1.01, 1.08]
CHAOS 1996Low	68/1035	52/967		0.7 %	1.22 [0.86, 1.73]
Collins 2003Low	1/26	1/26		0.0 %	1.00 [0.07, 15.15]
DATATOP 2005Low	154/399	142/401		2.5 %	1.09 [0.91, 1.31]
DATOR 2004Low	1/12	0/12		0.0 %	3.00 [0.13, 67.06]
Desnuelle 2001Low	34/144	35/144		0.5 %	0.97 [0.64, 1.47]
Graf 2005Low	31/83	28/77		0.5 %	1.03 [0.68, 1.54]
HOPE TOO 2005Low	799/4761	801/4780		10.1 %	1.00 [0.92, 1.10]
HPS 2002Low	1446/10269	1389/10267		17.2 %	1.04 [0.97, 1.11]
Jacobson 2000Low	0/57	1/55		0.0 %	0.32 [0.01, 7.74]
MAVIS 2005 Low	8/456	4/454		0.1 %	1.99 [0.60, 6.57]
Mezey 2004Low	4/25	5/26		0.1 %	0.83 [0.25, 2.75]
Mooney 2005Low	1/142	0/142		0.0 %	3.00 [0.12, 73.03]
Pike 1995Low	1/24	0/23		0.0 %	2.88 [0.12, 67.29]
PPS 1994Low	15/433	14/214		0.2 %	0.53 [0.26, 1.08]
REACT 2002Low	9/149	3/148		0.0 %	2.98 [0.82, 10.79]
SPACE 2000Low	31/97	29/99		0.5 %	1.09 [0.72, 1.66]
Tam 2005Low	1/20	1/19		0.0 %	0.95 [0.06, 14.13]
VEAPS 2002Low	2/177	1/176		0.0 %	1.99 [0.18, 21.73]
VECAT 2004Low	20/595	11/598		0.2 %	1.83 [0.88, 3.78]
WAVE 2002Low	16/212	6/211		0.1 %	2.65 [1.06, 6.65]
White 2002Low	1/50	1/50		0.0 %	1.00 [0.06, 15.55]
WHS 2005Low	636/19937	615/19939		6.8 %	1.03 [0.93, 1.15]



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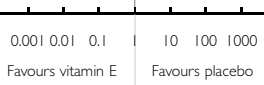
Study or subgroup	Vitamin E n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Wluka 2002Low	1/67	0/69		0.0 %	3.09 [0.13, 74.50]
Total (95% CI)	**56364**	**48701**		**100.0 %**	**1.04 [1.01, 1.07]**
Total events: 8968 (Vitamin E), 5985 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 18.46$, df = 25 (P = 0.82); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.86 (P = 0.0042)					



APPENDICES

Appendix 1. Search strategies

Database	Timespan	Search strategy	Number of references
Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library	Issue 3, 2005.	antioxidant* or vitamin* and supplement* not children	2548
MEDLINE	1966 to October 2005.	antioxidant* or vitamin* and supplement* not children Limits: Clinical Trial, Humans	2263
EMBASE	1985 to October 2005.	antioxidant* or vitamin* and supplement* not children	1572
Science Citation Index Expanded (http://portal.isiknowledge.com/	1945 to October 2005.	antioxidant* or vitamin* and supplement* not children	8884

FEEDBACK

Study employed inappropriate statistical analysis, 5 June 2008

Summary

Study employed inappropriate statistical analysis

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The review by Bjelakovic et al. (2008) has statistical inconsistencies, which bring its conclusions into doubt. Moreover, its statistical assumptions are biologically unsound. Furthermore, Bjelakovic et al. used non-blind selection of trials and post hoc selection of statistical tests.

1. The study selected the trials in a non-blind fashion, thereby introducing bias. Blinding is crucially important, as previous knowledge may cause reviewers to distort comparisons.[1] More importantly, the authors have not addressed this critical objection, despite it having been published as a specific and direct refutation of the earlier version of this review.[2] This study is thus a statement of the opinion of the authors and depends on their prior prejudice.

2. The results of this conflicting review should be considered a tentative modification of the prior probability of substantial positive effects (Bayes' theorem). Since the claimed effects are relatively small, and the N value is large, the importance of these effects may be considered minimal in the light of existing knowledge.

3. The presentation of results appears biased. For example, one of the main reported results claimed increased risk with beta-carotene if selenium was not included. We might ask what the results would be if selenium were included, or if vitamins C and E were excluded, and so on. The analyses in the last section (10.13-10.16) exclude selenium, but each of the antioxidants studied, that is vitamin A (which is not an antioxidant) and the other interventions, could have been excluded. However, results for the exclusion of selenium alone are reported. The authors' suggestion that this is not post hoc design because it is based on their previous review on antioxidants and gastrointestinal cancer, appears to be a circular argument. The current review contains 10 trials of antioxidant supplements in gastrointestinal cancers, and the studies in the two reviews overlap.

4. Did using only the first period from crossover trials introduce bias? To show that this is not the case the results from the full datasets could have been provided.

5. The review reported no effect on mortality, in the more appropriate random effects model. The fixed effects model is inappropriate in this heterogeneous group of studies involving multiple interventions. It is not acceptable that such heterogeneity is ignored.[3] Pooled studies must be compatible. The use of two such analytical approaches (tests) should be balanced by a decrease in the acceptable confidence level, which was not done.

6. The review does not state how many statistical tests on subgroups were actually performed, nor how many results were unreported. Failure to include a full description of the analyses invalidates all conclusions, as they could have arisen from repeated testing.

7. The analyses performed included multiple subgroups and comparisons, yet the authors report no specific calculation to support the validity of this procedure. Again, the potential for bias is substantial.

8. The reported statistics are inconsistent; for example, the abstract claims: low-bias risk trials on selenium found no significant effect on mortality (RR 0.91, 95% CI 0.76 to 1.09) but analysis 01.12 gives "0.90 [0.80, 1.01]" for low risk trials and exactly the same output results for high risk trials. Moreover, the combined result showed a significant benefit "0.90 [0.83, 0.98]".

9. It is invalid to assume that weighting studies based on the N value alone minimizes bias, especially if a small number of large studies receive a high weighting. Systematic bias from the methods employed occurs in experiments regardless of their scale. For example, on page 185, two studies, ATBC and CARET, involving smokers (and asbestos workers), were weighted 47.3% of the total. Overall, the presentation of statistical results in the review suggests a high degree of experimenter choice. The review does not provide sufficient detail of the actual and totality of tests performed to evaluate the results with true statistical meaning.

The conclusions cannot be considered as more than the prior prejudice of the authors. Cochrane should make clear the subjective nature of this review.

1 Higgins J.P.T. Green S. (2006) Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]. In: The Cochrane Library, Issue 4, John Wiley & Sons, Ltd.
2 S. Hickey H.J. Roberts and L.A. Noriega (2007) Poor methodology in meta-analysis of
vitamins, JOM, 22(1), 8-10.
3 Hemilä H. (2007) Antioxidant Supplements and Mortality. Vol. 298 No.

Reply

We have read the letter from Hickey et al with interest. Overall, we disagree that our statistical analyses are inappropriate. As described in our review, our analyses were planned in advance. We do not understand why our assumptions are 'biologically unsound'. We employ methodology of reviewing systematically all randomised trials we could identify. This is the soundest scientific method incorporating biological knowledge regarding interpretation of beneficial and harmful effects of interventions. We used the Cochrane well-established procedure for selecting trials for inclusion in our review and no one can accuse us of performing a biased selection of trials. The selection of statistical analyses was not post hoc, but ac-cording to our protocol and to the standard methodology within the Cochrane Hepato-Biliary Group.

We know that our conclusions have stirred a debate and have received several comments from people who disagree with our approach and suggest a number of different subgroup analyses, sensitivity analyses, and other post-hoc analyses to test the overall result. However, since systematic reviews with meta-analyses are observational, although based on data that were originally gathered in a prospective and controlled manner, we believe that it is crucial to maintain a rigorous approach. Therefore, we have not changed our analytical strategy, but will of course consider all relevant comments in future reviews. Below please also see our point-to-point reply to the comments.

1. The selection of trials was based on criteria specified in our protocol and described in the methods section of our review. None of the authors of the review have participated in clinical trials that were excluded or included in the present review. We were of course familiar with some of the literature at the protocol stage. There were no financial, academic, or personal interests on the side of the authors that may be construed as a conflict of interest. Furthermore, to the best of our knowledge there is no clear evidence demonstrating the negative effects of selecting trials in a non-blinded manner. This is what is usually conducted in Cochrane systematic reviews. And where are - by the way - the trials that we wrongly included and excluded?

When results like our present become published, many people may react based on different backgrounds. Hickey and co-authors accuse us for not having responded to a previous critical objection published by them in JOM, ie, Journal of Orthomolecular Medicine. First, we do not have access to this journal. Second, none of the authors have sent us their objections. Third, Hickey and co-authors should know that the usual academic procedure is to submit such objections to JAMA, which in 2007 published an abbreviated version of our review. Had they done so, we would of course have responded to any of their objections.

2. We have assessed the evidence regarding the primary and secondary preventive effects of antioxidant supplements with traditional meta-analytic methodology of randomised clinical trials. Randomised clinical trials - and especially those having low risk of bias - are to be found at the top of the evidence hierarchy. We did not employ Baysian meta-analyses. That Hickey and co-authors might have had prior probabilities being more positive towards antioxidant supplements than a neutral prior could be due to them placing too much confidence in results of observational studies and in basic research findings from in vivo and in vitro studies. The literature is loaded with examples where evidence from randomised trials does not concur with evidence from lower levels of the evidence hierarchy. That antioxidant supplements could be another of these examples does not come as a surprise to us.

3. Our 2004 Cochrane Hepato-Biliary Group systematic review on antioxidant supplements including 14 randomised trials, among which only 9 trials provided data on overall mortality, led us to observe an increased mortality in participants on antioxidant supplements. At that time we were informed in an Editorial accompanying our paper in The Lancet that this conclusion could be wrong due to the fact that we had only included the randomised trials that looked on antioxidant supplement prevention of gastrointestinal cancers. Our present Cochrane Hepato-Biliary Group systematic review on antioxidant supplements is a response to the request for a broader meta-analysis, including all randomised preventive trials on antioxidant supplements that report mortality. We do, therefore, agree with Hickey and co-authors that the results of our previous review influenced our present review, now including 67 randomised trials. It is also correct that our analyses excluding selenium trials can be seen as a post-hoc decision. However, it should be seen as a post-hoc decision following our findings in our 2004 Cochrane Hepato-Biliary Group systematic review on antioxidant supplements. It is not a post-hoc decision taken following the analyses of data in our present review. We think this distinction is of central importance to the inferences drawn from our analyses. So, when we write: "The sensitivity analysis removing selenium trials from our analysis to evaluate their influence on our conclusions was therefore not a post hoc decision", we should have added perhaps "taken after the analyses of trials in the present review". Of course, we let us informed of our previous results. Isn't this the whole meaning of doing research?

In retrospect, we are not so sure that we did a fair mix of antioxidants by including selenium. We feel that it is fair science to take this understanding into consideration, now that we have looked at a larger group of antioxidant trials. If we do not learn from previous mistakes, where would we end up?

Hickey and co-authors do not consider vitamin A as an antioxidant. We refer the reader to our discussion on that topic in our review.

Hickey and co-authors point to the fact that there is an overlap between our primary systematic review on antioxidant supplements for prevention of cancer and our present review on antioxidants on prevention of mortality. This overlap is not at all surprising or wrong. We would have been accused of slicing up the evidence if we had excluded previously reviewed trials that contained information on mortality in our present review.

4. Among the 67 included trials, only two trials (Gililan 1977; Prince 2003) are of cross-over design. We did not include data from the second period of cross-over trials to avoid mixing acute effects with more protracted effects (ie, carry over effects). This could have biased our analyses. The exclusion of the second phase from cross-over trials is an unlikely cause of bias. First, the vast majority of the cross-over trials were trials with relatively short duration and, therefore, not very likely to inform us on mortality data. Second, as antioxidants seem to increase mortality, the inclusion of the second phase of cross-over trials would have risked our results to become biased towards no difference (when in fact a difference exists in reality). Third, the approach we used on cross-over trials is the approach selected in the majority of Cochrane reviews including cross-over trials (Lathyris DN, Trikalinos TA, Ioannidis JP. Evidence from crossover trials: empirical evaluation and comparison against parallel arm trials. Int J Epidemiol. 2007;36(2):422-30).
5. The random-effects model analyses provided a more conservative estimate of the effects of antioxidants than the fixed-effect model analyses, based on the fact that the former analysis puts more weight on small trials (which are more often biased) compared to the latter analyses, which weight more the results from larger trials. Such larger trials are considered trustworthier both considering the risk for systematic error and risk for random error.

When we look at the analyses based on the 47 low-bias risk trials, we would like to draw attention to the fact that our random-effects model and our fixed-effect model analyses fully concur: RR 1.05, 95% CI 1.02 to 1.08, P = 0.003 in the random-effects model compared to RR 1.05, 95% CI 1.03 to 1.08, P = 0.00001 in the fixed-effect model. In these analyses, on which we place our largest confidence, we find no substantial heterogeneity (I^2 = 7.5%). So, we do not understand the accusation that we ignored heterogeneity and that we did not see increased mortality in the antioxidant supplemented group by using the random-effects model.

6. We did not exclude any analyses. We agree that we conducted a number of analyses and this may make it difficult to evaluate all of our findings. We also agree that meta-analyses as presently conducted both within and outside The Cochrane Collaboration run the risk of reaching statistically significant results due to repeated testing of accumulating data in cumulative meta-analyses (Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. J Clin Epidemiol 2008;61:64-75).

In response to this criticism, we would like to draw attention to the following. First, the P-values we observed were generally small and unlikely to be affected by, eg, Bonferroni correction. Second, we observed a detrimental effect of antioxidant supplements. It is more likely that there are unpublished trial results with detrimental data than unpublished trials with positive results. Therefore, significant negative findings in meta-analyses should be considered firmer evidence than if we were dealing with positive observations. This is due to the strong publication bias that appears to affect most areas of clinical research. We are in the process of analysing our data with trial sequential analyses.

7. We agree that subgroup analyses may open for biased results. The grouping of trials according to bias-risk was planned in our protocol. The subgroup analyses excluding trials with potential confounders were conducted to present as fair comparisons between antioxidant supplements and placebos as possible - running the risk of loosing the statistical power that meta-analysis introduces. From these analyses, we got the clear impression that these 'fairest' comparisons only substantiated the detrimental effect of antioxidant supplements observed in our primary analyses (relative risk of death due to antioxidant supplements after exclusion of all trials with potential confounding 1.16, 95% CI 1.09 to 1.23, P < 0.00001 without significant heterogeneity (I^2 = 0.0%)). This is equal to an increased mortality caused by antioxidant supplements of 16%.

8. Hickey and co-authors are correct. The intervention effects regarding selenium is wrongly quoted in the abstract: RR 0.91, 95% CI 0.76 to 1.09 should become RR 0.90, 95% CI 0.80 to 1.01, as we correctly report in the results section. We have now amended this mistake.

We do not advice to base conclusions that include high-bias risk trials. Such results are likely to be biased.

9. Contrary to what Hickey and co-authors seem to assume we have put much effort into weighting both systematic errors and random errors in our reviews. It is through putting focus on both types of errors that we obtain clinical research results that are internally valid and can be used for discussing external validity. Hickey and co-authors note that both the ATBC trial and the CARET trial carry a large weight. We notice that having these trials included does not cause substantial heterogeneity (I^2 = 7.5%), and both trials included almost 50 000 of the about 181 000 participants in the low-bias risk trials. So no wonder the two trials carry a large weight. In this post hoc decision-making process, should these two trials be excluded due to the smokers and asbestos workers participating in them or should they stay because they both fulfilled our a priory-defined inclusion criteria?

To elucidate the impact of the two trials on our findings, we excluded them from the analysis of the 47 low-bias risk trials. Comparing the intervention effect of antioxidant supplements in the remaining 45 randomised trials did not show any significant difference compared to the meta-analysis of the effect in the ATBC and CARET trials (test of interaction, z = -1.44, P = 0.15). When we excluded the CARET trial from the 19 trials without any potential confounders and compared the remaining 18 trials to the results of the CARET trial, we did not observe significant differences (test of interaction, z = -0.22, P = 0.83).

So, we do not think our analyses are biased by any prejudice, but as always regarding bias: others may be better to judge than oneself. In a similar vein, we would like to draw the readers' attention to the previous publications of Hickey and co-authors as well as the institutions they work. These pieces of information make us ask: 'What kind of bias may they have?'

Contributors

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Subjective, selective, and biased, 5 June 2008

Summary

Subjective, selective, and biased

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The review on antioxidant supplements and mortality by Bjelacovic et al (2008) essentially is a repeated publication of a review that has been highly criticized. The criticisms cover both the background biology and the statistical methods employed.

Main conclusions
The report's main conclusion, "we found no evidence to support antioxidant supplements for primary or secondary prevention", is not derived from the nature of the study, which was on mortality. The sole outcome measure in this review was all-cause mortality.

The report's secondary finding "vitamin A, beta-carotene, and vitamin E may increase mortality." is in the author's conclusions. This result was only produced by statistical manipulation when the effects of selenium were excluded, and the number of statistical tests was not reported.

The report's third finding, "future randomized trials could evaluate the potential effects of vitamin C and selenium for primary and secondary prevention", is inappropriate, given the nature of this study of mortality. The additional statement "such trials should be closely monitored for potential harmful effects" implies bias and a lack of appreciation that such factors are normally monitored in well-designed trials.

The report's final main finding, "antioxidant supplements need to be considered medicinal products and should undergo sufficient evaluation before marketing", is a political statement that is not justified by the scientific content of this review.

Statistical problems

1. The authors refer to the previous publication of their review but ignore the detailed scientific and methodological criticisms that it attracted.[1,2]

2. A meta-analysis of mortality should not be used as a vehicle to promote a controversial viewpoint on the role of nutrition in primary or secondary prevention of disease. Moreover, the authors of such studies should be required to answer the existing major criticisms in their work before producing a repeated publication.

The study pooled study data from both the sick and the healthy and included several other interventions that increased the variability in the data. This increased variability could hide positive effects. The sick had a variety of conditions each of which needed to be considered separately in the design. Pooling these groups is not biologically valid because of the different sources of variation in the data. Pooling sick and healthy groups confuses nutrition and pharmacology.

3. Studies with no deaths were excluded, 405 studies showed no deaths compared with the 67 included studies, and relative statistics were reported. Any inference about the role of supplements in causing such deaths is unwarranted; there may have been deaths that had no relation to supplement use. There was no valid calculation to demonstrate that gross bias did not result. In the classic book "How to Lie with Statistics", Darrel Huff used relative measure to show how statistics can mislead.[3]

4. The report of the "sensitivity analysis" involving 14 studies with no deaths to show that excluding such studies had no effect was flawed. The studies were not listed. Similarly, the reports of the analysis with one death were insufficiently well described for the reader to evaluate their meaning.

5. "Participants lost to follow-up were considered survivors." There is no justification for this assumption, no estimate of the proportions in each of the groups for each statistical test employed, and no calculation of its impact on the results.

6. The selection of trials defined as "high bias" or "low bias", with inadequate criteria, gives differing results. Since the selection process was not blind, these results are unreliable, since a greater bias than that controlled could arise from the subjective selection.

7. Two large trials with positive results (GISSI and NIT1) were allocated to the high-risk group, the reasons are not clear and may be inappropriate.

Pharmacology and nutrition

1. The use of placebo controls in study selection is inappropriate and poor science, as placebo effects would not cause or prevent death, which is a definitive and objective outcome.[4]

2. Vitamin A is not a dietary antioxidant. The author's suggestion that vitamin A has antioxidant activity is spurious, as numerous dietary substances have some redox activity.

3. Dietary antioxidants have complex redox mechanisms and it is oversimplistic to assume that consumption of a particular dose or molecular form of an "antioxidant" will produce a physiological antioxidant effect.[5]

4. The antioxidant supplements studied were a small subset of available dietary supplements Several redox active substances, such as rutin, coenzyme Q10, and iron, used in the included studies were not addressed in the analysis.

5. The doses of Vitamin C studied were too small and too infrequent to be effective.[6] Taken alone, this point invalidates the vitamin C element of the study. Claims for the effects of vitamin C relate to doses 10-100 times larger than those in the Bjelakovic paper.

6. The paper fails to distinguish between different forms of selenium, such as sodium selenite or methylselenocysteine, which have different pharmacological and redox effects. Without a description of the different forms, the results are unclear and confusing.

7. The term "vitamin E", as used in the paper, is vague. Vitamin E is a generic term for members of two families of molecules, the tocopherols and the tocotrienols. In addition, several other lipid-soluble antioxidants show vitamin E activity. The tocopherols consist of a set of four molecules, alpha-, beta-, delta-, and gamma-tocopherols, and the tocotrienols are similarly grouped. These molecules are subdivided further, in terms of molecular configuration. Taking alpha-tocopherol as an example, the naturally occurring RRR-alpha-tocopherol is usually called d-alpha-tocopherol. Synthetic "dl-alpha-tocopherol" consists of roughly equal amounts of the eight possible stereoisomers (RRR, RRS, RSR, RSS, SSS, SSR, SRS and SRR) and may contain several additional unnatural molecules. Basic pharmacology indicates that each of these molecules has specific effects in the body and thus the indiscriminate results for "vitamin E" are misleading.
8. The authors' suggestion that the effect of antioxidants is one of the most adequately researched areas indicates a lack of knowledge of fundamental questions in redox biology and medicine.
9. Trials that included children and pregnant women were excluded from the study "since they may be in need of certain antioxidant supplements". This introduces bias against antioxidants.
10. The authors claim that unpublished studies of antioxidants are more likely to be negative than positive. They provide no direct or specific evidence to support this claim. The equally valid counter argument is that some commercial sources of funding would prefer not to publish trials favouring antioxidants to profitable drugs.

Conclusions
As Sir Bradford Hill pointed out in his landmark "rules" paper,7 epidemiology should rigorously conform to the constraints of basic science and physiology. This study by Bjelakovic is a particularly confused application of statistical methods, as it involves a varied intake of antioxidant supplements, other nutrients, and drugs, in heterogeneous populations of both sick and healthy people. With such diversity, the meaning of results is unclear and the study's conclusions have little validity.

The authors may wish to return to their analysis to provide sufficient information for an objective assessment of their results to be made. Without such a re-analysis, this review may be considered biased.

1 Hickey S. Roberts H.J. Noriega L.A. (2007) Poor methodology in meta-analysis of vitamins, JOM, 22(1), 8-10.
2 Albanes D. (2007) Antioxidant Supplements and Mortality. JAMA, 298(4), 402-403.
3 Huff D. (1993) How to Lie With Statistics, W. W. Norton & Company.
4 Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. Cochrane Database of Systematic Reviews 2003, Issue 1. Art. No.: CD003974.
5 Block G. Jensen C.D. Morrow J.D. Holland N. Norkusc E.P. Milneb G.L. Hudesa M.
Dalvia T.B. Crawford P.B. Fung E.B. Schumacherd L. Harmatz P. (2008) The effect of vitamins C and E on biomarkers of oxidative stress depends on baseline level, Free Radical Biology and Medicine, doi:10.1016/j.freeradbiomed.2008.04.005.
6 S. Hickey H.J. Roberts and R.F. Cathcart (2005) Dynamic flow, JOM, 20(4), 237-244.
7 Hill A.B. (1965) The environment and disease: Association or causation? Proc Roy Soc Med, 58, 295-300.

Reply

As stated in our review, an abbreviated version of the review was published in JAMA (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(8):842-857). We have previously answered to all critical comments raised to that paper (Gluud LL, Bjelakovic G, Nikolova D, Simonetti RG, Gluud C. Antioxidant supplements and mortality-Reply. JAMA. 2007;298(4):402-403).
On 'Main conclusions'

We have responded to major parts of these allegations in the letter by Hickey et al above, and we refer readers to those responses.

We are well aware of the correct way to monitor trials dealing with potential harmful interventions. The fact is, however, that the vast majority of trials are insufficiently monitored. For example, only 27% of the clinical trials (470) used a data monitoring committee and only 7% (116) reported some form of interim analysis out of 1772 randomised trials published in eight major journals during 2000 to 2005 (Tharmanathan P, Calvert M, Hampton J, Freemantle N. The use of interim data and Data Monitoring Committee recommendations in randomized controlled trial reports: frequency, implications and potential sources of bias. BMC Med Res Methodol. 2008;8:12).

We agree with Schuitemaker and co-authors that our request for more proper regulatory overview is urgently needed concerning antioxidant supplements, and that our statement may be seen as a political statement. We expressed this with the hope that some politicians and regulatory authorities will act as brave individuals and not servants of the industry.
On 'Statistical problems'
1. We have responded to the criticism raised in JAMA (Gluud LL, Bjelakovic G, Nikolova D, Simonetti RG, Gluud C. Antioxidant supplements and mortality-Reply. JAMA. 2007;298(4):402-403). This is the normal and usual academic procedure. Schuitemaker and co-authors accuse us for not having responded to a previous critical objection published by them in JOM, ie, Journal of Orthomolecular Medicine. First, we do not have access to this journal. Second, none of the authors have sent us their objections. Third, Schuitemaker and co-authors should know that the usual academic procedure is to submit such objections to JAMA, which in 2007 published an abbreviated version of our review. Had they done so, we would, of course, have responded to any of their objections.

2. We produced the abbreviated version of our review for the JAMA and the long version for The Cochrane Library more or less in parallel. The short version is about 15 printed pages long, and had a much shorter review process. The long version is about 200 printed pages long and had a much longer and elaborate review process. That Cochrane Reviews are published both as electronic versions in The Cochrane Library with sister publications in paper journals are an often encountered procedure.

It was part of our protocol that we would include both healthy participants and patients without active diseases. The effect of antioxidants did not differ significantly between the two subgroups.

As every trial is accounted for and displayed we do not understand the accusation that we are hiding positive effects.

3. We have dealt with this issue extensively in our review. Trials without deaths were excluded. First, they provide very little information. Second, most of these trials were not 'preventive trials', but rather explanatory trials assessing the impact of antioxidant supplements on potential surrogate outcome measures. Third, we assessed the influence of trials with zero events in the treatment or control group by re-calculating the random-effects meta-analyses with 0.5, 0.05, and 0.005 continuity corrections. Fourth, we also performed additional meta-analyses including one large hypothetical trial with one event in the treatment and control group and a sample size corresponding to the total number of participants in the 405 zero events trials. All these analyses confirmed the results of our primary analyses.
4. We have dealt with this issue extensively in our review as well as above. We refer the reader to these for further explanation. We do not know what Schuitemaker and co-authors refer to when they speak of "sensitivity analysis involving 14 studies".

5. Schuitemaker and co-authors point to the fact that we considered any drop-outs as survivors. First, all low-bias risk trials had adequate reporting of follow-up. The details are reported in Table of included trials. Here, Schuitemaker and co-authors can see trial for trial how well follow-up was reported. All low-bias risk trials had adequate reporting of follow-up. Second, the trials having losses to follow up usually had few losses. Third, the outcome in question was all-cause mortality, an outcome that could usually be determined in the countries in which the trials were performed. Fourth, we had chosen the option to consider drop-outs as survivors at the protocol stage - which is among the options one may choose according to 16.1.2 of the Cochrane Collaboration Handbook (Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.5 [updated May 2005]. In: The Cochrane Library, Issue 3, 2005. Chichester, UK: John Wiley & Sons, Ltd.). Considering that antioxidant supplements seem to increase mortality, we think we might have biased our analyses for the benefit of antioxidant supplements.

We will acknowledge that missing data may bias meta-analyses and when updating this review we shall examine this aspect in greater detail.

6. We think Schuitemaker and co-authors erred on these points and recommend them to read the Cochrane Collaboration Handbook (Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.5 [updated May 2005]. In: The Cochrane Library, Issue 3, 2005. Chichester, UK: John Wiley & Sons, Ltd.).
7. Again we think Schuitemaker and co-authors erred on these points and recommend them to read our criteria for including a trial among the low-bias risk trials as well as the Table describing the included studies. Here, we describe that GISSI was not placebo controlled (ie, there was no intervention in the control group). Therefore, this trial was considered having a high risk of bias. In the Table describing the included studies we also describe that NIT1 had inadequate follow-up as losses to follow-up were not reported. Therefore, this trial was considered a high risk of bias trial.

On 'Pharmacology and nutrition'
1. We think Schuitemaker and co-authors erred on these points and re-commend that they re-read Hróbjartsson and Gøtzsche's article on placebo. Placebo is not given to cause or prevent death. Placebo is given to blind participants, investigators, and assessors to avoid reporting bias, collateral intervention bias, and outcome assessment bias.

2. Schuitemaker and co-authors do not consider vitamin A as an antioxidant. We refer the reader to our discussion on that topic in our review.

3. We agree with Schuitemaker and co-authors that the antioxidant field has been influenced by a measure of naivety. We think their criticism should go to the investigators and companies behind the conducted trials - we are only reviewing and meta-analysing the evidence that we are able to find.

4. We agree. We only looked at a handful of antioxidant supplements. We still think that we assessed some of the more commonly used antioxidants, which can be witnessed by the large number of randomised trials that we identified. Meta-analyses cannot cover all interventions. We strongly support further systematic reviews of other antioxidant supplements.
5. But claims are not valid proof.
6. We may agree. But again, we followed our protocol to look at selenium irrespective of form.
7. We may agree. But again, we followed our protocol to look at 'vitamin E' irrespective of form.
8. We may obtain consensus when we explain that what we meant was that this area was one of the best researched areas when we take into account the very large number of low-bias risk trials with large participant groups. Hereby both systematic error and random error are contained, and internal validity maximised. Where else does one find 47 trials offering such high internal validity?
9. Not at all. We are not dealing with children, pregnant women, or patients with active disease because some of these groups may be in need of one or more antioxidant supplements.
10. The problem with publication bias has been known for more than 50 years. This bias usually affects trials with neutral and harmful findings (Dickersin K, Rennie D. Registering clinical trials. JAMA. 2003;290(4):516-23). Now Schuitemaker and co-authors suggest that the pharmaceutical industry has withheld positive studies showing benefits of antioxidant supplements. We do not think this is very likely. First, the industry supporting the included trials had produced a median of 6 publications per trial (range 1 to 44 publications per trial). This is an extraordinary marketing achievement, considering that randomised trials are usually only published twice (Gluud C, Nikolova D. Likely country of origin in publications on randomised controlled trials and controlled clinical trials during the last 60 years. Trials. 2007;8:7). Second, the same industry has been sued and ordered to pay very large fines due to cartel price fixing (and it has been able to pay) (Connor JM. Global Price Fixing. Second Ed., Springer-Verlag, Berlin Heidelberg, 2007). Witnessing the exorbitant large fines, we are quite confident that this industry has not had a net loss on these products. But we must admit, we do not know.

On 'Conclusions'
The recommendations that Sir Bradford Hill outlined in 1965 - before the introduction of systematic reviews - did not say that basic science and physiology should trump systematic reviews of low-bias risk trials. Although basic science and physiology should be studied intensely, it may never make us ignore empirical research results.

As stated above, we intend to analyse our data from different aspects in future updates to try to accommodate the concerns that have been raised.

Contributors

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Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases, 14 September 2008

Summary

Feedback by Enrico Magosso*, Kah Hay Yuen*, Yogheswaran Gopalan* *School of Pharmaceutical Sciences Universiti Sains Malaysia, 11800 Penang Malaysia
correspondence to: magosso.fd08@student.usm.my
It is indeed impressive the authors have put together this review involving over 230,000 patients in 67 trials. The antioxidants considered in the trials were vitamin A, vitamin E (mostly as alpha-tocopherol), beta-carotene, vitamin C and selenium, used either alone or in combination.

However, this range of antioxidants has to be considered as extremely limited compared to those found in nature and other natural compounds with antioxidant properties are increasingly being described. For example vitamin E is the generic name given to a family of 8 homologue compounds comprising alpha, beta-, gamma- and delta-tocopherols as well as alpha-, beta-, gamma- and delta-tocotrienols. These homologues have been shown to exert individual functions (Brigelius-Flohè and Traber, 1999; McIntyre et al., 2000; Schaffer et al., 2004). Tocopherols and tocotrienols share similar structural features of the chromanol ring or 'head' and are similarly named as alpha-, beta-, gamma- and delta- depending on the number and position of the methyl groups attached to the 'head'. The main chemical difference between tocopherols and tocotrienols lies in the phytyl chain or 'tail', saturated in the former and unsaturated in the latter. Natural alpha-tocopherol occurs only as d- (or RRR-) isomer, while synthetic alpha-tocopherol (that is derived from petroleum) is the d,l-racemic mixture. Tocotrienols are of natural origin and are exclusively d-isomers. The majority of investigations have used the form of vitamin E that is alpha-tocopherol (mostly of synthetic origin) to the extent that alpha-tocopherol and vitamin E became synonymous.
Sen and co-authors have highlighted the tangible differences, in efficacy as well as in toxicity, between tocopherols and tocotrienols. The following passage is taken from Sen et al. (2006): 'An expanding body of evidence support that members of the vitamin E family are functionally unique. In recognition of this fact, title claims in manuscripts should be limited to the specific form of vitamin E studied. For example, evidence for toxicity of a specific form of tocopherol in excess may not be used to conclude that high-dosage "vitamin E" supplementation may increase all-cause mortality. Such conclusion incorrectly implies that tocotrienols are toxic as well under conditions where tocotrienols were not even considered.'
Similar arguments apply to beta-carotene, which is a single homologue of a range of about 600 carotenoids found in nature, 50 of which exert the role of vitamin A precursors and occurring as cis/trans racemic mixture at a variable ratio (Schieber and Carle, 2005; Krinsky and Johnson, 2005). Lyn (2000) in his review suggested 'the efficient uptake of synthetic all-trans beta-carotene [?] appears to make the synthetic form more desirable for effective absorption. But the tendency of synthetic beta-carotene to alter normal serum trans/cis ratios in favor of the trans-isomer may not be a beneficial effect' and that 'the consequences of using all-trans synthetic beta-carotenes are at this point unknown'. It has been suggested the negative outcome in clinical trials involving beta-carotene might be ascribed to the use of the purified, synthetic form (Ben-Amotz and Levy, 1996; Lyn, 2000).
In the review entitled 'The use of antioxidant therapies during chemotherapy', Drisko and co-authors (2003) highlighted the importance of natural mixed carotenoids, suggesting that 'the use of synthetic beta-carotene as a single agent rather than natural mixed carotenoids may actually promote cancer formation'.

In all but a handful of studies considered in this review synthetic alpha-tocopherol and synthetic beta-carotene were used.

In addition to many examples in which different isomers of the same compound present different level of activity and toxicity, the FDA does not register new pharmaceuticals without chiral definition (FDA, 1992; FDA, 1995; FDA 1997).

We believe certain aspects of the review should consider the following to reflect objectively several facts:
1) The origin of the antioxidants, either synthetic or natural, was not mentioned with regard to the included studies. Thus assuming that there are not biological differences between the two sources.
2) Tocotrienols were not present in any of the preparations administered in the studies considered, but the authors did not differentiate them from the generic name of vitamin E or alpha-tocopherol and thus shared the same detrimental effect on survival rate.
3) Since the authors' conclusion as currently stated all but prohibit further antioxidant trials it will be helpful to perform a subgroup analysis by natural or synthetic origin of the antioxidants administered and the range of antioxidants to which the conclusion is applicable needs to be stated.

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Submitter has modified conflict of interest statement:
EM, KHY, YG research on tocotrienols has been funded by Malaysian Palm Oil Board and supported by pharmaceutical industry.

Reply

Magosso, Yuen, and Gopalan wrote:
It is indeed impressive the authors have put together this review involving over 230,000 patients in 67 trials. The antioxidants considered in the trials were vitamin A, vitamin E (mostly as alpha-tocopherol), beta-carotene, vitamin C and selenium, used either alone or in combination.

- ***We thank Magosso, Yuen, and Gopalan for these most positive comments.***

Magosso, Yuen, and Gopalan wrote:
However, this range of antioxidants has to be considered as extremely limited compared to those found in nature and other natural compounds with antioxidant properties are increasingly being described. For example vitamin E is the generic name given to a family of 8 homologue compounds comprising alpha, beta-, gamma- and delta-tocopherols as well as alpha-, beta-, gamma- and delta-tocotrienols. These homologues have been shown to exert individual functions (Brigelius-Flohè and Traber, 1999; McIntyre et al., 2000; Schaffer et al., 2004). Tocopherols and tocotrienols share similar structural features of the chromanol ring or 'head' and are similarly named as alpha-, beta-, gamma- and delta- depending on the number and position of the methyl groups attached to the 'head'. The main chemical difference between tocopherols and tocotrienols lies in the phytyl chain or 'tail', saturated in the former and unsaturated in the latter. Natural alpha-tocopherol occurs only as d- (or RRR-) isomer, while synthetic alpha-tocopherol (that is derived from petroleum) is the d,l-racemic mixture. Tocotrienols are of natural origin and are exclusively d-isomers. The majority of investigations have used the form of vitamin E that is alpha-tocopherol (mostly of synthetic origin) to the extent that alpha-tocopherol and vitamin E became synonymous. Sen and co-authors have highlighted the tangible differences, in efficacy as well as in toxicity, between tocopherols and

tocotrienols. The following passage is taken from Sen et al. (2006): 'An expanding body of evidence support that members of the vitamin E family are functionally unique. In recognition of this fact, title claims in manuscripts should be limited to the specific form of vitamin E studied. For example, evidence for toxicity of a specific form of tocopherol in excess may not be used to conclude that high-dosage "vitamin E" supplementation may increase all-cause mortality. Such conclusion incorrectly implies that tocotrienols are toxic as well under conditions where tocotrienols were not even considered.'

- We are aware of the facts mention above. However, we could not include trials with tocotrienols, gama tocopherol, or any other form of vitamin E because such randomised trials have not been published. The majority of the trials conducted tested alpha-tocopherol. We will in future updates try to highlight this issue.

Magosso, Yuen, and Gopalan wrote:

Similar arguments apply to beta-carotene, which is a single homologue of a range of about 600 carotenoids found in nature, 50 of which exert the role of vitamin A precursors and occurring as cis/trans racemic mixture at a variable ratio (Schieber and Carle, 2005; Krinsky and Johnson, 2005). Lyn (2000) in his review suggested 'the efficient uptake of synthetic all-trans beta-carotene [?] appears to make the synthetic form more desirable for effective absorption. But the tendency of synthetic beta-carotene to alter normal serum trans/cis ratios in favor of the trans-isomer may not be a beneficial effect' and that 'the consequences of using all-trans synthetic beta-carotenes are at this point unknown'. It has been suggested the negative outcome in clinical trials involving beta-carotene might be ascribed to the use of the purified, synthetic form (Ben-Amotz and Levy, 1996; Lyn, 2000).

In the review entitled 'The use of antioxidant therapies during chemotherapy', Drisko and co-authors (2003) highlighted the importance of natural mixed carotenoids, suggesting that 'the use of synthetic beta-carotene as a single agent rather than natural mixed carotenoids may actually promote cancer formation'.

- The answer is as above. We included trials with beta-carotene that we were able to identify. We will in future updates try to highlight the raised issues.

Magosso, Yuen, and Gopalan wrote:

In all but a handful of studies considered in this review synthetic alpha-tocopherol and synthetic beta-carotene were used.

- We included the trials that we were able to identify according to our protocol. Further trials and systematic reviews have to access whether there are certain benefits or harms connected to 'synthetic' as well as 'natural' vitamins.

Magosso, Yuen, and Gopalan wrote:

In addition to many examples in which different isomers of the same compound present different level of activity and toxicity, the FDA does not register new pharmaceuticals without chiral definition (FDA, 1992; FDA, 1995; FDA 1997).

- It would be much better for the FDA and other regulatory agencies to require that dietary supplements sold to the public claiming health benefits are subjected to adequate assessment of benefits and harms before market release, similar to any other drug.

Magosso, Yuen, and Gopalan wrote:

We believe certain aspects of the review should consider the following to reflect objectively several facts:

1) The origin of the antioxidants, either synthetic or natural, was not mentioned with regard to the included studies. Thus assuming that there are not biological differences between the two sources.

- We mentioned the form of antioxidant used in the table 'Characteristics of included studies'. The origin of the antioxidants was mentioned in the majority of the trials, but in some of them not.

Magosso, Yuen, and Gopalan wrote:

2) Tocotrienols were not present in any of the preparations administered in the studies considered, but the authors did not differentiate them from the generic name of vitamin E or alpha-tocopherol and thus shared the same detrimental effect on survival rate.

- We were not able to identify such trials. In case that at any future review updates, we identify randomised trials with tocotrienols, we will include them in our meta-analyses. As already stated, we will address this issue in further updates.

Magosso, Yuen, and Gopalan wrote:

3) Since the authors' conclusion as currently stated all but prohibit further antioxidant trials it will be helpful to perform a subgroup analysis by natural or synthetic origin of the antioxidants administered and the range of antioxidants to which the conclusion is applicable needs to be stated.

- If we identify enough number of trials with natural antioxidant supplements, we can perform subgroup analyses. However, we are of the opinion that we have fulfilled the main Cochrane criterion to look at the totality of evidence for the effects of a specific intervention. If you are aware of any randomised trials with 'natural' antioxidant supplements that is not included in our analyses, we will appreciate to receive this information from you.

A large population based randomised clinical trial (Physician Health Study II[1]) has recently been completed. Its authors concluded that neither vitamin E nor vitamin C supplementation reduced the risk of major cardiovascular events. A second trial (SELECT[2]) stopped supplementation after the Data and Safety Monitoring Committee reviewed the available data and found that selenium and vitamin E supplements failed to prevent prostate cancer. Participants taking vitamin E had a small increase in prostate cancer, while participants taking only selenium were more likely to develop diabetes. These results strongly support the findings of our review.

1. Sesso HD, Buring JE, Christen WG, Kurth T, Belanger C, MacFadyen J, Bubes V, Manson JE, Glynn RJ, Gaziano JM. Vitamins E and C in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. JAMA 2008;300:2123-33.
2. http://www.crab.org/select/ (Assessed 19 November 2008).

Contributors

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WHAT'S NEW

Last assessed as up-to-date: 19 February 2008.

11 November 2008	Feedback has been incorporated	Replies to the comments by E Magosso, K.H. Yuen, and Y Gopalan.

HISTORY

Protocol first published: Issue 2, 2003

Review first published: Issue 2, 2008

12 August 2008	Feedback has been incorporated	Replies to two multi-author comments.
17 April 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

GB had full access to all data in the review and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: GB, DN, LLG, RGS, CG.

Acquisition of data: GB, DN, CG.

Analysis and interpretation of data: GB, DN, LLG, RGS, CG.

Drafting of the manuscript: GB, DN, LLG, RGS, CG.

Critical revision of the manuscript for important intellectual content: GB, DN, LLG, RGS, CG.

Statistical analysis: GB, LLG, RGS, CG.

Obtained funding: CG.

Administrative, technical, or material support: DN, CG.

Study supervision: GB, CG.

DECLARATIONS OF INTEREST

None known. The funding sources had no role in the conduct of the study, collection of data, management, analysis, interpretation of the data, or preparation of the manuscript.

SOURCES OF SUPPORT

Internal sources

- The Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Denmark.

External sources

- Knowledge and Research Centre for Alternative Medicine (ViFAB), Denmark.

NOTES

The protocol for this review was published with a title 'Antioxidats for preventing gastrointestinal cancers'. The contents of this review have already been published in JAMA (Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. JAMA 2007;297(8):842-857) with corrections appearing in JAMA 2008 (Data Errors in: Mortality in randomized trials of antioxidant supplements for primary and secondary prevention: systematic review and meta-analysis. JAMA 2008;299(7):765-766). The present version of the review incorporates all these corrections. Furthermore, we have realised that we included a quasi-randomised study in our JAMA version. This study has been excluded of our present Cochrane review. This has not materially changed the results.

In Issue 1 2009, we made the following change for the AMDS trial (AMDS 1996Low). Being mislead by the wording of the text in one of its publications, we had registered it as a beta-carotene trial. Our revision of the published literature on this trial confirmed that it was a vitamin A trial. Now this is corrected throughout the text. This correction led to minor changes in the values in the analyses, but did not lead to any significant change of results nor conclusions.

INDEX TERMS

Medical Subject Headings (MeSH)

*Health Status; *Mortality; Antioxidants [*administration & dosage; adverse effects]; Ascorbic Acid [administration & dosage; adverse effects]; beta Carotene [administration & dosage; adverse effects]; Primary Prevention [*methods]; Randomized Controlled Trials as Topic; Selenium [administration & dosage; adverse effects]; Vitamin A [administration & dosage; adverse effects]; Vitamin E [administration & dosage; adverse effects]

MeSH check words

Humans