REVIEW

Dietary Supplements and Risk of Cause-Specific Death, Cardiovascular Disease, and Cancer: A Systematic Review and Meta-Analysis of Primary Prevention Trials[1–3]

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ABSTRACT

Our aim was to assess the efficacy of dietary supplements in the primary prevention of cause-specific death, cardiovascular disease (CVD), and cancer by using meta-analytical approaches. Electronic and hand searches were performed until August 2016. Inclusion criteria were as follows: *1*) minimum intervention period of 12 mo; *2*) primary prevention trials; *3*) mean age ≥18 y; *4*) interventions included vitamins, fatty acids, minerals, supplements containing combinations of vitamins and minerals, protein, fiber, prebiotics, and probiotics; and *5*) primary outcome of all-cause mortality and secondary outcomes of mortality or incidence from CVD or cancer. Pooled effects across studies were estimated by using random-effects meta-analysis. Overall, 49 trials (69 reports) including 287,304 participants met the inclusion criteria. Thirty-two trials were judged as low risk–, 15 trials as moderate risk–, and 2 trials as high risk–of-bias studies. Supplements containing vitamin E (RR: 0.88; 95% CI: 0.80, 0.96) significantly reduced cardiovascular mortality risk, whereas supplements with folic acid reduced the risk of CVD (RR: 0.81; 95% CI: 0.70, 0.94). Vitamins D, C, and K; selenium; zinc; magnesium; and eicosapentaenoic acid showed no significant risk reduction for any of the outcomes. On the contrary, vitamin A was linked to an increased cancer risk (RR: 1.16; 95% CI: 1.00, 1.35). Supplements with β-carotene showed no significant effect; however, in the subgroup with β-carotene given singly, an increased risk of all-cause mortality by 6% (RR: 1.06; 95% CI: 1.02, 1.10) was observed. Taken together, we found insufficient evidence to support the use of dietary supplements in the primary prevention of cause-specific death, incidence of CVD, and incidence of cancer. The application of some supplements generated small beneficial effects; however, the heterogeneous types and doses of supplements limit the generalizability to the overall population. *Adv Nutr* 2017;8:27–39.

Keywords: dietary supplements, meta-analysis, systematic review, mortality, cardiovascular disease, cancer

Introduction

Data derived from the NHANES show that 50% of Americans, and two-thirds of elderly individuals (≥71 y of age), use dietary supplements on a regular basis (1). Overall, multivitamin-mineral (MVM)[8] supplements are the most popular, whereas calcium is the most widely used mineral dietary supplement. In the United States, people spend nearly $39 billion/y on dietary supplements (2). Data from European countries suggest a north-south disparity, with the highest dietary supplement consumption in Denmark and the lowest in Greece (3). Supplement use is more prevalent among women, older adults, persons who are better educated, those who are physically active, and those with a lower BMI (4). The EPIC (European Prospective Investigation into Cancer and Nutrition)–Heidelberg study indicated that regular users of dietary supplements had a better overall dietary quality (increased intakes of dairy products, fish, fruit and vegetables, and wine and the lowest intake of total meat) (5).

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[3] A Supplemental Appendix, Supplemental Tables 1–10, and Supplemental Figures 1–15 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://advances.nutrition.org.

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[8] Abbreviations used: CVD, cardiovascular disease; MVM, multivitamin-mineral; RCT, randomized controlled trial.

Noncommunicable diseases, such as cardiovascular disease (CVD) and cancer, are the leading causes of death worldwide (6). The rationale for taking dietary supplements has been suggested by many in vitro and animal studies that showed protection against chronic, low-grade inflammation and oxidative stress, both of which are suggested to be involved in the onset and progression of CVD and cancer. In industrialized nations, dietary supplements are taken to improve overall health, whereas in developing countries, supplements are often taken due to nutrient deficiencies (e.g., iron, vitamin A, zinc, and iodine) (7).

With respect to the effects of dietary supplements on clinical outcomes, a large number of pairwise meta-analyses of randomized controlled trials (RCTs) were conducted during the past decades, with conflicting results. Bjelakovic et al. (8) concluded that antioxidant supplements do not exert any protective effect on the risk of chronic diseases. Instead, β-carotene, vitamin A, and vitamin E were associated with an increased risk of mortality (8), whereas only vitamin D seemed to be inversely related to a reduction in overall mortality, by 3% (9). The evidence for other dietary supplements in the role of prevention of chronic diseases is ambiguous as well (10–12). The US Preventive Services Task Force in 2013 stated that there is insufficient evidence to assess the balance of benefit and harms of MVM single and paired supplements for the prevention of CVD and cancer, with the exception of β-carotene and vitamin E, both of which are explicitly not recommended (13).

Despite the great interest in this topic, we could not find a meta-analysis that included all different types of supplements and covered several clinical outcomes. Therefore, the aim of the study was to summarize the available evidence on dietary supplements and all-cause mortality, cause-specific mortality, and incidence of CVD and cancer, as well as to assess the efficacy and safety of different dietary supplements in primary prevention trials.

Methods

The review protocol was published previously (14) and is registered in the PROSPERO International Prospective Register of Systematic Reviews (crd.york.ac.uk/prospero/index.asp; identifier: CRD42014014801).

Data sources and searches. A literature search was performed in the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, PubMed (from 1966), EMBASE (from 1980), clinicaltrials.gov (http://clinicaltrials.gov/), and the WHO International Clinical Trials Registry Platform to look for ongoing trials until August 2016. A highly sensitive RCT filter was used with the PubMed search, as stated in the Cochrane Handbook ("randomized controlled trial" OR "randomized" OR "clinical trials as topic" OR "placebo" OR "randomly" OR "trial") NOT ("animals") (15). The full database search strategy for PubMed is available in the **Supplemental Appendix**. Moreover, the reference lists from the retrieved articles, systematic reviews, and meta-analyses were checked to search for further relevant studies. There was no restriction on language or publication year.

Eligibility criteria. Studies were included if they met the following criteria: *1*) randomized controlled design (identical placebo or no intervention) or trials of one supplement compared with another; *2*) minimum intervention period of 12 mo; *3*) primary prevention trial (defined as trials with the first occurrence of a chronic disease as the primary outcome); *4*) mean age ≥18 y; *5*) an intervention that used dietary supplements defined according to the Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002. The following dietary supplements were included according to previous systematic reviews and meta-analyses on dietary supplements and chronic diseases (9, 12, 16): vitamins [β-carotene; vitamins A, E, C (ascorbic acid), and D (cholecalciferol, ergocalciferol)]; B vitamins (thiamin, riboflavin, niacin, pyridoxine, cobalamin, folic acid); supplements containing a combination of different vitamins; FAs (n–3 FAs [EPA, DHA, α-linolenic acid (18:3n−3)]; n–6 FAs [linoleic acid (18:2n−6)]; monounsaturated fat (olive oil); minerals (magnesium, calcium, selenium, potassium, iron, zinc, copper, iodine); multiminerals; supplements containing combinations of both vitamins and minerals; protein (amino acids); fiber (psyllium, inulin, cellulose); probiotics; prebiotics; and synbiotics; *6*) oral intake (modalities of supplement intake such as liquid, pill, capsule, tablet, drops, ampoule, powdered); and *7*) assessment of clinical outcomes ("primary": all-cause mortality; "secondary": cardiovascular mortality, cancer mortality, cardiovascular incidence, and cancer incidence).

Exclusion criteria. The exclusion criteria were as follows: *1*) studies with a dietary or drug co-intervention that was not applied in all intervention or placebo and control groups; *2*) studies with intravenous or parenteral administration of vitamins or minerals; *3*) pregnant or lactating women; *4*) mean age ≥70 y; *5*) >75% of sample size assigned to secondary prevention trials [defined as trials undertaken to prevent recurrences or exacerbations of a disease that has already been diagnosed, such as in cancer survivors; survivors of myocardial infarction, stable or unstable angina pectoris, acute coronary insufficiency, coronary artery disease (verified by coronary angiography), stroke, hemodialysis, or chronic kidney disease; and subjects with the following diseases: gastrointestinal, neurological, ocular, dermatologic, rheumatoid, endocrinologic]; and *6*) follow-up time not reported.

Data extraction. Two authors (LS, MSM) independently screened titles and abstracts of all of the retrieved bibliographic records. Full texts of all potentially eligible records passing the title and abstract screening level were retrieved and examined independently by 2 reviewers (for each database) with the above-mentioned eligibility and exclusion criteria (17, 18). Disagreements were resolved by consensus or adjudication of another reviewer (HB).

After determination of the study selection, the following eligibility criteria were extracted: first author's last name; publication year; country of origin; study design; study duration; follow-up; study population; number of arms; participants' sex and age; sample size; BMI; percentages of obese subjects, current smokers, or former smokers; dietary supplement dosage (milligram per day, microgram per day, or International Unit per day); mode of administration; drug treatment; indication; specification of the control group; number of events (all-cause mortality, cardiovascular mortality, cancer mortality, cardiovascular incidence, cancer incidence); withdrawals and dropouts; adverse events; and funding source or conflicts of interest (e.g., industry funding). These variables were extracted for all studies after which the extracted data were verified by a second reviewer to reduce reviewer errors and bias.

Risk of bias assessment. We assessed the risk of bias of the included studies by using the risk of bias tool of the Cochrane Collaboration for the following domains: random-sequence generation, allocation concealment, blinding (performance and detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and industry bias (19). Studies were classified as being overall at low risk of bias only if none of the domains established a high risk of bias and at a moderate overall risk of bias if they were at high risk for 1 domain only. In all other cases, studies were classified as being overall at high risk of bias.

Statistical analysis. We performed standard pairwise meta-analyses that synthesized the relative effects from all studies that compared the same pair of interventions. For each outcome measure of interest, a random-effects model was used to determine the pooled relative effects of the different interventions. All analyses were performed at the RR scale because HRs could not be obtained for all studies, but we accounted for the different follow-up

periods in a subgroup analysis. Statistical heterogeneity between trials was measured by using the method of moments estimate for τ^2 and considering a value for I^2 of >50% to represent substantial heterogeneity (20). Number of events and sample size were summed for multiarm trials, as recommended by the Cochrane Handbook (to avoid unit of analysis error) (15).

We considered the following 12 classes of supplements: calcium, selenium, zinc, vitamin D, β-carotene, vitamin A, vitamin C, vitamin E, folic acid, magnesium, EPA, and vitamin K. Initially, we had planned to also perform a network meta-analysis comparing simultaneously all different supplements and classes to infer on the relative effects between every pair of interventions (14). However, the identified studies did not allow for this type of analysis due to concerns about the plausibility of the synthesis assumption and the scarcity of the evidence (see Results for details). Therefore, we restricted our quantitative synthesis of the data to the use of standard meta-analysis.

We performed the following subgroup analyses: *1*) supplements given singly or combined with others, *2*) supplements provided at low or high doses, and *3*) shorter-term trials (<5 y duration) compared with longer-term trials (≥5 y duration). We also conducted 2 sensitivity analyses: *1*) including only trials being overall at low risk of bias and *2*) with the use of the fixed-effects model with Mantel-Haenszel weights. To assess the potential for small-study effects we used funnel plots and the Egger test when ≥10 studies were available (21, 22). All of the analyses were performed by using RevMan 5.0 (Nordic Cochrane Centre) (23) and Stata 13 (StataCorp) (24).

Quality of meta-evidence. To evaluate the meta-evidence for the association between dietary supplements and all-cause mortality (defined as the quality of evidence of meta-analyses: confidence in the estimate), we applied the NutriGrade scoring system (25) (maximum of 10 points), which comprises the following items for meta-analyses of RCTs: *1*) risk of bias, study quality, study limitations; *2*) precision; *3*) heterogeneity; *4*) directness; *5*) publication bias; *6*) funding bias; and *7*) study design. On the basis of this scoring system we recommend 4 categories to judge the meta-evidence—high, moderate, low, and very low—taking into account the following cutoffs: ≥8 points (high meta-evidence), 6–7.99 points (moderate meta-evidence), 4–5.99 points (low meta-evidence), and 0–3.99 points (very low meta-evidence).

Results

Characterization of studies

The detailed steps of the study selection process are given as a flowchart in **Figure 1**. Overall, 49 trials (69 reports) met the inclusion criteria and 47 of them were included [1 study did not report the required outcome data (26), and 1 study reported no control or placebo group (27)] in the quantitative analysis (28–94). Nineteen trials were conducted in North America, 14 trials in Europe, 9 trials in Asia, and 7 trials in Australia and New Zealand.

Overall, 36 two-arm and 12 multiarm studies were included, which evaluated 12 individual supplements (**Supplemental Tables 1–4**). Thirty-nine of 49 trials were placebo-controlled trials.

All of the studies included were RCTs with a duration ranging between 1 and 11.2 y [except for the post-trial follow-up of the ATBC (Alpha-Tocopherol, Beta-Carotene Cancer Prevention) study with a follow-up of 18 y], published between 1985 and 2015, and enrolling 287,304 participants. The mean age varied between 36.8 and 69.2 y, with an overall mean age of 58.9 y. The most frequently reported baseline characteristics were postmenopausal and smoking status (Supplemental Table 2). Our inclusion and exclusion criteria focused on a generally healthy population. Therefore, studies that enrolled patients with chronic hemodialysis or end-stage renal disease; ambulatory elderly women with vitamin D insufficiency; and patients with chronic renal failure, femoral neck fractures or kidney transplant were excluded, even if the corresponding investigations were considered by an earlier meta-analysis to be primary prevention trials (95).

Risk of bias

Thirty-two trials were judged to be low risk–, 15 trials to be moderate risk–, and 2 trials to be high risk–of-bias studies. With regard to the specific items of the risk of bias assessment tool by the Cochrane Collaboration, 76–94% of the included studies indicate a low risk of bias for random-sequence generation, allocation concealment, blinding, incomplete data outcome, and selective reporting. However, only 2 of 49 trials indicated a low risk of bias for industry bias (**Supplemental Table 5**).

Standard pairwise meta-analyses

Most of the studies used combinations of supplements and thus were classified in ≥2 classes; hence, different classes could not be compared directly and we only conducted direct meta-analyses comparing each class with the placebo and control. Direct summary effects for all comparisons between the different classes are given in **Tables 1–5**.

All-cause mortality. A trend for a higher risk of all-cause mortality could be shown for vitamin E (RR: 1.02; 95% CI: 0.99, 1.05; I^2 = 0%), whereas for selenium (RR: 0.93; 95% CI: 0.85, 1.01; I^2 = 0%) and vitamin D (RR: 0.91; 95% CI: 0.83, 1.01; I^2 = 0%) a trend for an inverse association was shown. No important effects were observed for calcium, zinc, β-carotene, vitamin C, folic acid, magnesium, or EPA (Table 1) (**Supplemental Figures 1–11**).

Cardiovascular mortality and incidence. The pooled effect of vitamin E (RR: 0.88; 95% CI: 0.80, 0.96; I^2 = 0%) compared with placebo or no intervention showed a significant risk reduction for cardiovascular mortality. Folic acid supplementation was inversely related to cardiovascular incidence (RR: 0.81; 95% CI: 0.70, 0.94; I^2 = 0%). No effects were observed for calcium, selenium, zinc, β-carotene, vitamin A, vitamin C, vitamin D, vitamin K, magnesium, or EPA (Tables 2 and 3).

Cancer mortality and incidence. Vitamin A was associated with a significant 16% increased risk of cancer incidence (RR: 1.16; 95% CI: 1.00, 1.35; I^2 = 0%). In contrast, calcium supplements were associated with a reduced risk of cancer (RR: 0.37; 95% CI: 0.22, 0.63; I^2 = 0%). No important effect on cancer mortality could be observed for selenium, zinc, vitamin D, β-carotene, vitamin C, folic acid, vitamin K, or EPA, respectively (Tables 4 and 5).

Assessment of synthesis assumption for network meta-analysis

The use of network meta-analysis methodology requires that the different available direct comparisons are, on average, similar in terms of study and participant characteristics that may act as effect modifiers (96). With the present data, we did not have enough information to appropriately

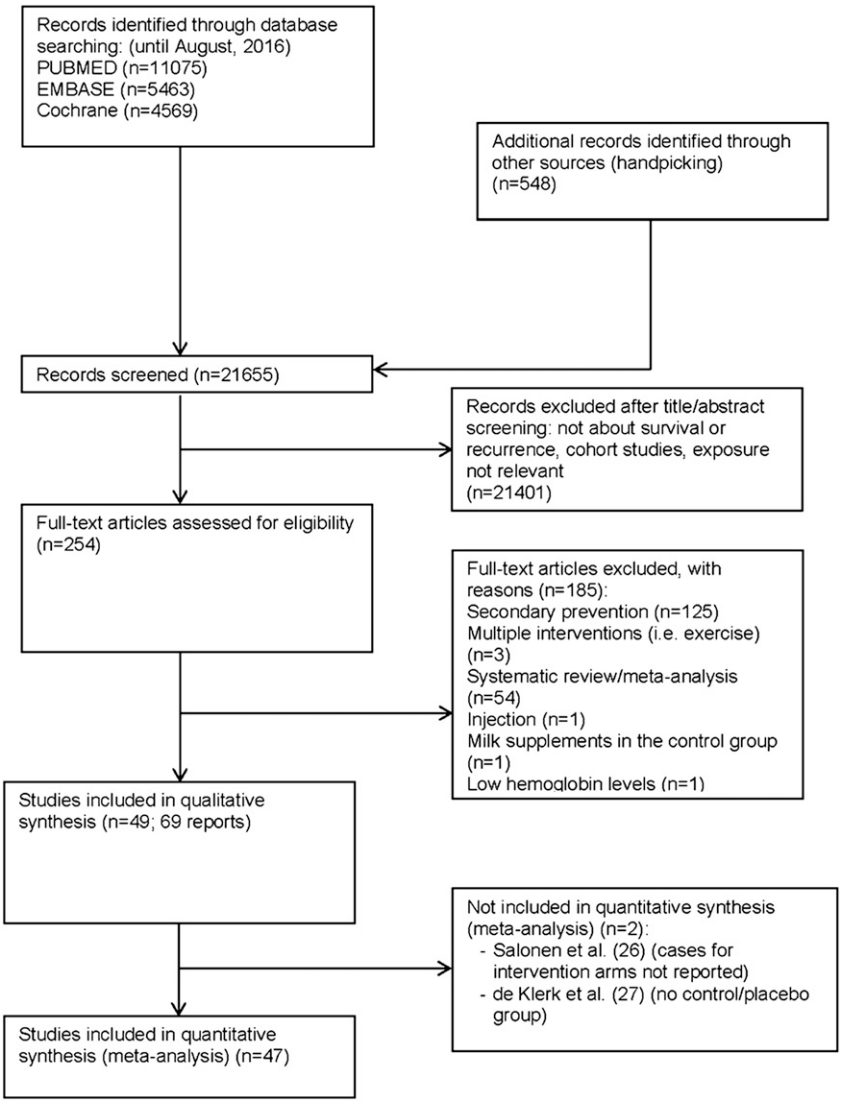

FIGURE 1 Flow diagram.

compare the distribution of such characteristics across comparisons and we could rely only on our clinical understanding. We believe that the different doses of the interventions administered are a potential threat for the plausibility of the synthesis assumption for a network meta-analysis. On the other hand, conducting the analysis in subgroups of low- and high-dose supplements would give very scarce networks that include only a subset of the 12 classes; hence, such a network meta-analyses would not have increased power compared with the direct evidence. For the aforementioned reasons, we decided to refrain from our initial plan and use only standard meta-analysis.

Subgroup analyses

Subgroup analyses showed that β-carotene given as a stand-alone supplement ($P = 0.003$) and at higher doses (≥30 mg/d) ($P = 0.003$) was significantly associated with all-cause mortality. Moreover, high-dose vitamin A (test for subgroup differences, $P = 0.03$) significantly increased the risk of all-cause mortality. Subgroup analyses suggest evidence that vitamin E supplementation (given singly and combined with other supplements) reduces the risk of cardiovascular mortality, whereas high-dose single applications of folic acid decrease cardiovascular risk. High-dose vitamin A supplementation was associated with an increased risk of cancer mortality. For cancer incidence, high doses of calcium given either as a single constituent or combined with other supplements showed inverse associations, whereas vitamins A and E (combined with other supplements) were associated with an increased risk of cancer. The third subgroup analysis, focusing on study length, was limited by the low number ($n = 9$) of longer-term (≥5 y) trials.

Sensitivity analyses

In trials with a low risk of bias, β-carotene and vitamin A were associated with an increased risk of all-cause mortality [RRs (95% CIs): 1.07 (1.04, 1.10) and 1.13 (1.04, 1.21); $I^2 = 0\%$ for both], and vitamin A also was associated with cancer mortality (RR: 1.25; 95% CI: 1.05, 1.48; $I^2 = 0\%$). Pooling

TABLE 1 Efficacy of dietary supplements and risk of all-cause mortality[1]

Factor (references)	Trials, *n*	RR	95% CI	I^2 (95% CI), %	Meta-evidence
Calcium (29, 33, 36, 39, 53, 57, 63, 72)	9	0.85	0.48, 1.53	0 (0, 65)	Moderate
Given singly	4	0.93	0.29, 2.96	0	
Combined with others	5	0.86	0.44, 1.69	0	
Low dose (<1200 mg/d)	7	0.86	0.33, 2.24	0	
High dose (≥1200 mg/d)	1	2.31	0.12, 42.7	NA	
Selenium[2] (31, 45, 54, 60, 86, 93)	5	0.93	0.85, 1.01	0 (0, 79)	Moderate
Given singly	3	0.94	0.85, 1.04	0	
Combined with others	3	0.92	0.81, 1.05	6	
Low dose (<120 μg/d)	3	0.81	0.63, 1.03	0	
High dose (≥120 μg /d)	2	0.94	0.86, 1.04	5	
Zinc[2] (combined with others and low dose, <50 mg/d) (30, 31, 45, 69)	4	0.92	0.82, 1.03	0 (0, 85)	Moderate
Vitamin D (28, 29, 38, 51, 53, 55, 57, 63, 68–70)	10	0.91	0.83, 1.01	0 (0, 62)	High
Given singly	2	0.34	0.04, 3.20	0	
Combined with others	8	0.92	0.83, 1.01	0	
Low dose (<500 IU/d)	4	0.92	0.83, 1.01	0	
High dose (≥500 IU/d)	6	0.75	0.39, 1.45	0	
β-Carotene[2] (30, 31, 43–45, 59, 80, 86, 91, 94)	10	1.02	0.96, 1.09	44 (0, 73)	Moderate
Given singly	5	1.06	1.02, 1.10	0	
Combined with others	6	1.01	0.92, 1.11	62	
Low dose (<30 mg/d)	6	0.99	0.90, 1.07	56	
High dose (≥30 mg/d)	4	1.10	1.03, 1.18	0	
Vitamin A (29–31, 43, 69, 89)	6	1.06	0.97, 1.16	14 (0, 78)	Moderate
Given singly	1	1.15	0.81, 1.65	NA	
Combined with others	4	1.04	0.91, 1.20	47	
Low dose (<25,000 IU/d)	4	0.95	0.84, 1.08	0	
High dose (≥25,000 IU/d)	2	1.12	1.04, 1.21	0	
Vitamin C[2] (29, 30, 45, 65, 69, 75, 86)	7	0.98	0.91, 1.05	0 (0, 71)	Moderate
Given singly	1	1.00	0.91, 1.11	NA	
Combined with others	6	0.98	0.91, 1.05	0	
Low dose (<500 mg/d)	5	0.93	0.83, 1.04	0	
High dose (≥500 mg/d)	2	1.01	0.93, 1.09	0	
Vitamin E[2] (29, 30, 40, 45, 48, 58, 60, 62, 64, 65, 69, 74, 75, 80, 86)	15	1.02	0.99, 1.05	0 (0, 54)	High
Given singly	9	1.02	0.99, 1.06	0	
Combined with others	9	0.99	0.32, 1.06	32	
Low dose (<400 IU/d)	7	0.98	0.89, 1.07	27	
High dose (≥400 IU/d)	8	1.01	0.95, 1.06	0	
Folic acid (31, 41, 47, 50)	4	0.96	0.75, 1.23	2 (0, 85)	Moderate
Given singly	2	1.00	0.60, 1.99	37	
Combined with others	2	0.25	0.03, 2.22	0	
Low dose (<5 mg/d)	2	1.49	0.38, 5.79	12	
High dose (≥5 mg/d)	2	0.91	0.59, 1.41	4	
Magnesium (combined with others and low dose, <500 mg/d) (31, 69)	2	0.97	0.10, 9.05	0 (NA)	Low
EPA (85)	1	1.08	0.91, 1.27	NA	Moderate

[1] NA, not applicable.
[2] Multiarm trials were combined.

vitamin E trials with low risk of bias resulted in a significant decrease in cardiovascular mortality (RR: 0.89; 95% CI: 0.81, 0.98; I^2 = 0%) but an increase in all-cause mortality (RR: 1.03; 95% CI: 1.00, 1.06; I^2 = 0%) (**Supplemental Tables 6–10**). We also conducted a sensitivity analysis for the primary outcome by using the fixed-effects model with Mantel-Haenzel weights. However, we observed no differences between these 2 models.

Small-study effects

Overall, only 4 meta-analyses included sufficient studies and allowed inspection of funnel plots. The funnel plots for the risk of all-cause mortality for vitamin D, β-carotene, and vitamin E indicate moderate to high symmetry, and for risk of cardiovascular mortality and vitamin E moderate asymmetry, suggesting that publication cannot be completely excluded as a factor that might influence some results on the present meta-analyses (**Supplemental Figures 12–15**). Egger's linear regression test showed no evidence for small-study effects for vitamin D (P = 0.68) or vitamin E for all-cause mortality (P = 0.50) or cardiovascular mortality (P = 0.90), but did show evidence for for β-carotene and the risk of all-cause mortality (P = 0.05).

NutriGrade

The NutriGrade meta-evidence score for all-cause mortality varied between 5.25 (low meta-evidence) for magnesium supplements and 8.5 (high meta-evidence) for vitamins D and E.

TABLE 2 Efficacy of dietary supplements and risk of cardiovascular mortality[1]

Factor (references)	Trials, *n*	RR	95% CI	I^2 (95% CI), %
Calcium (low dose, <1200 mg/d) (32, 72)	2	0.81	0.04, 15.9	47 (NA)
Given singly	1	3.48	0.18, 66.8	NA
Combined with others	1	0.17	0.01, 4.03	NA
Selenium[2] (54, 60, 86, 93)	3	0.89	0.74, 1.06	0 (0, 90)
Given singly	3	0.92	0.76, 1.13	0
Combined with others	1	0.82	0.64, 1.05	NA
Low dose (<120 μg/d)	1	0.75	0.32, 1.79	NA
High dose (≥120 μg/d)	2	0.90	0.75, 1.07	0
Zinc[2] (combined with others and low dose, <50 mg/d) (30)	1	0.83	0.65, 1.05	NA
Vitamin D (low dose, <500 IU/d) (32, 51, 68, 70)	3	0.91	0.76, 1.09	0 (0, 90)
Given singly	1	0.33	0.01, 7.96	NA
Combined with others	2	0.85	0.41, 1.76	9
β-Carotene[2] (30, 43, 44, 59, 80, 86, 89, 91)	8	1.01	0.92, 1.10	7 (0, 71)
Given singly	5	1.04	0.93, 1.16	0
Combined with others	4	0.95	0.84, 1.09	26
Low dose (<30 mg/d)	4	0.97	0.85, 1.10	29
High dose (≥30 mg/d)	4	1.06	0.93, 1.21	0 (0, 70)
Vitamin A (combined with others) (30, 43)	2	0.97	0.78, 1.21	58 (NA)
Low dose (<25,000 IU/d)	1	0.85	0.66, 1.09	NA
High dose (≥25,000 IU/d)	1	1.07	0.92, 1.24	NA
Vitamin C[2] (30, 65, 75, 86)	4	0.96	0.82, 1.13	0 (0, 85)
Given singly	1	1.06	0.83, 1.35	NA
Combined with others	4	0.94	0.80, 1.12	0
Low dose (<500 mg/d)	2	0.87	0.68, 1.12	0
High dose (≥500 mg/d)	2	1.03	0.84, 1.26	0
Vitamin E[2] (30, 48, 58, 60, 64, 65, 74, 75, 80, 86)	10	0.88	0.80, 0.96	0 (0, 62)
Given singly	7	0.88	0.79, 0.98	0
Combined with others	6	0.89	0.80, 1.00	0
Low dose (<400 IU/d)	4	0.87	0.76, 0.99	0
High dose (≥400 IU/d)	6	0.88	0.77, 1.01	8
Folic acid (given singly and high dose, ≥5 mg/d) (50)	1	1.00	0.66, 1.53	NA
Vitamin K (32)	1	0.34	0.01, 8.16	NA
EPA (85)	1	0.93	0.56, 1.55	NA

[1] NA, not applicable.
[2] Multiarm trials were combined.

Discussion

The findings of this large systematic review and meta-analysis of 49 primary prevention trials including 287,304 individuals do not support the intake of dietary supplements for the primary prevention of chronic diseases. However, supplementation of vitamin E may reduce the risk of cardiovascular mortality. Moreover, pooling results from folic acid trials indicates a potential decreased risk of CVD, whereas calcium supplements may reduce the risk of cancer. In line with previous meta-analyses, β-carotene (given singly and in high doses) and vitamin A were associated with an increased risk of all-cause mortality and cancer mortality.

Although RCTs are considered the gold standard for determining the clinical efficacy of a given intervention, there are unique limitations inherent to nutrient supplementation trials. For example, there can never be a nutrient-free state in study volunteers; thus, the placebo group in micronutrient supplementation trials does not represent a true placebo or nonexposed group. Consequently, treatment exposures are blunted between the groups, potentially contributing to a null effect (97). Another limitation is the inclusion of specific populations (e.g., smokers, postmenopausal women), which limits the generalizability to the overall population. A further limitation is the variation in the dietary supplements used by the reviewed studies, in terms of constituents (given singly or combined with other supplements) and dosages (low or high doses). Nevertheless, RCTs are considered the gold standard for determining the clinical efficacy of dietary supplements. Compared with observational studies, RCTs have a lower risk of confounding, and may provide causality. Moreover, we were not able to conduct a network meta-analysis to compare simultaneously all of the different supplements, as we had planned in the protocol of this study, due to the scarcity of the evidence and the clinical heterogeneity across the direct comparisons. However, we are willing to update this review and conduct a comprehensive network meta-analysis in the future if we identify a large number of homogenous trials. This will potentially allow us to also infer on the effect of individual supplements by using methodology for complex interventions (98).

Our meta-analysis showed a 12% reduction in cardiovascular mortality with vitamin E supplementation compared with placebo and control in primary prevention trials. Subgroup analyses showed significant effects for low-dose, given

TABLE 3 Efficacy of dietary supplements and risk of cardiovascular disease[1]

Factor (references)	Trials, *n*	RR	95% CI	I^2 (95% CI), %
Calcium[2] (32–34, 36, 39, 57, 72, 73)	8	0.94	0.51, 1.75	0 (0, 71)
Given singly	6	0.80	0.36, 1.75	0
Combined with others	3	0.97	0.45, 2.11	0
Low dose (<1200 mg/d)	7	1.22	0.53, 2.79	0
High dose (≥1200 mg/d)	1	0.68	0.27, 1.72	NA
Selenium[2] (31, 45, 54, 60, 90)	4	1.01	0.94, 1.07	0 (0, 85)
Given singly	2	1.03	0.95, 1.11	0
Combined with others	3	0.99	0.91, 1.06	0
Low dose (<120 μg/d)	2	0.97	0.77, 1.23	0
High dose (≥20 μg/d)	2	1.01	0.94, 1.08	0
Zinc[2] (combined with others and low dose, <50 mg/d) (31, 34, 45)	3	0.98	0.78, 1.23	0 (0, 90)
Vitamin D (32, 34, 51, 52, 55, 57, 68, 70)	7	1.01	0.95, 1.07	0 (0, 71)
Given singly	2	0.26	0.03, 2.31	0
Combined with others (low dose, <500 IU/d)	5	1.01	0.95, 1.07	0
High dose (≥500 IU/d)	2	0.87	0.33, 2.28	0
β-Carotene[2] (31, 44, 45, 59, 80)	5	0.98	0.92, 1.05	0 (0, 79)
Given singly	3	0.99	0.93, 1.07	0
Combined with others	3	0.96	0.87, 1.07	0
Low dose (<30 mg/d)	4	0.97	0.91, 1.04	0
High dose (≥30 mg/d)	2	1.14	0.87, 1.48	0
Vitamin A (low dose, <25,000 IU/d) (31)	1	0.32	0.01, 7.66	NA
Vitamin C[2] (45, 75)	2	0.98	0.87, 1.09	0 (NA)
Given singly	1	0.98	0.84, 1.14	NA
Combined with others	2	0.98	0.86, 1.11	0
Low dose (<500 mg/d)	1	0.98	0.77, 1.24	0
High dose (≥500 mg/d)	1	0.98	0.86, 1.11	0
Vitamin E[2] (45, 48, 58, 60, 64, 74, 75, 78, 80)	9	0.96	0.91, 1.02	21 (0, 62)
Given singly	8	0.97	0.90, 1.04	32
Combined with others	4	0.98	0.92, 1.04	0
Low dose (<400 IU/d)	4	0.99	0.87, 1.11	28
High dose (≥400 IU/d)	5	0.95	0.88, 1.03	29
Folic acid (given singly and high dose, ≥5 mg/d) (31, 47, 50)	3	0.81	0.70, 0.94	0 (0, 90)
Combined with others (<5 mg/d)	1	0.32	0.01, 7.66	NA
Vitamin K (low dose) (32, 34)	2	2.04	0.59, 7.03	0 (NA)
Given singly	1	3.05	0.13, 73.4	NA
Combined with others	1	1.90	0.50, 7.27	NA
Magnesium (combined with others and low dose, <500 mg/d) (31, 34)	2	1.08	0.33, 3.57	0 (NA)
EPA (85)	1	0.89	0.78, 1.02	NA

[1] NA, not applicable.
[2] Multiarm trials were combined.

singly, and low risk of bias vitamin E trials. Previous meta-analyses of RCTs reported conflicting results with regard to vitamin E supplementation. Myung et al. (95) pooled primary and secondary prevention trials and observed no significant effect of vitamin E supplementation for major cardiovascular events and cardiovascular death, whereas a 33% reduced risk of myocardial infarction could be observed. In line with these observations, a more recent meta-analysis confirmed the protective role of vitamin E in the prevention of myocardial infarction (99). Meta-analyses of cohort studies reported consistent inverse associations of vitamin E supplements on the risk of CVD (100). Although it seems that vitamin E has some beneficial effects on cardiovascular outcomes, a meta-analysis of clinical trials reported a significant increased risk of total mortality, including mainly secondary prevention trials for high-dose vitamin E (≥400 IU/d) (101). These results are limited by small sample sizes, secondary prevention trial designs, and low risk differences. Our observed null effects for vitamin E and the risk of cancer were confirmed by previous meta-analyses (102). The US Preventive Services Task Force in 2013 recommended against the use of vitamin E for the prevention of CVD and cancer (13).

In addition to the cardiovascular-protective effects of vitamin E, pooling of selenium trials indicated a trend for an inverse association for all-cause mortality. The interpretation of these results is limited by inconsistency among subgroup analyses and the low number of studies. A meta-analysis of observational studies reported a 15% reduction in coronary heart disease by comparing the highest with the lowest selenium concentration category, underlining the importance of selenium intake (103). Similar to our results, a meta-analysis of RCTs (but combining primary and secondary prevention trials) indicated a significant decrease in mortality, which was not confirmed in the low risk of bias analysis (16). In addition, previous meta-analyses indicated that selenium supplementation was associated with reduced cancer incidence in men but not in women (102).

Previous meta-analyses showed that vitamin B supplements (one-carbon metabolites) lowered the risk of stroke,

TABLE 4 Efficacy of dietary supplements and risk of cancer mortality[1]

Factor (references)	Trials, *n*	RR	95% CI	I^2 (95% CI), %
Calcium (low dose, <1200 mg/d) (69)	1	2.88	0.12, 67.3	NA
Selenium[2] (54, 60, 86, 93)	3	0.86	0.53, 1.40	77 (25, 93)
Given singly	3	0.87	0.52, 1.46	78
Combined with others	1	0.93	0.73, 1.20	NA
Low dose (<120 μg/d)	1	1.36	0.73, 2.54	NA
High dose (≥120 μg/d)	2	0.73	0.39, 1.36	85
Zinc[2] (combined with others and low dose, <50 mg/d) (30, 69)	2	0.92	0.75, 1.12	0 (NA)
Vitamin D (low dose, <500 IU/d) (51, 55, 69, 70)	3	0.90	0.78, 1.04	0 (0, 90)
Given singly	1	0.34	0.01, 8.31	NA
Combined with others	2	0.90	0.78, 1.04	0
β-Carotene (30, 43, 44, 59, 86, 89, 91)	7	1.03	0.89, 1.19	43 (0, 76)
Given singly	4	1.00	0.89, 1.13	0
Combined with others	3	1.09	0.81, 1.47	73
Low dose (<30 mg/d)	3	0.98	0.84, 1.14	29
High dose (≥30 mg/d)	3	1.12	0.91, 1.38	21
Vitamin A (combined with others) (30, 43, 69)	3	1.08	0.82, 1.43	62 (0, 89)
Low dose (<25,000 IU/d)	2	0.92	0.74, 1.13	0
High dose (≥25,000 IU/d)	1	1.24	1.05, 1.47	NA
Vitamin C (given singly) (30, 69, 86)	3	0.99	0.81, 1.21	0 (0, 90)
Low dose (<500 mg/d)	2	0.96	0.78, 1.18	0
High dose (≥500 mg/d)	1	1.36	0.73, 2.54	NA
Vitamin E[2] (30, 58, 60, 69, 78, 86)	6	1.00	0.87, 1.14	20 (0, 64)
Given singly	3	1.00	0.79, 1.28	45
Combined with others	4	0.93	0.79, 1.08	0
Low dose (<400 IU/d)	4	0.93	0.76, 1.14	0
High dose (≥400 IU/d)	1	1.01	0.81, 1.26	NA
Magnesium (69)	1	2.88	0.12, 67.3	NA

[1] NA, not applicable.
[2] Multiarm trials were combined.

but not CVD, myocardial infarction, coronary heart disease, cardiovascular death, or all-cause mortality (10). It was shown that folic acid supplementation had no significant effect on cardiovascular events, overall cancer, or mortality in high-risk patients (104). Compared with previous meta-analyses, we found new evidence for a beneficial effect of folic acid in the primary prevention of CVD. Supplementation with folic resulted in a 19% decrease in CVD risk compared with a placebo or control group. Our observations are largely based on a recently published Chinese multicenter trial in 20,702 hypertensive adults, which showed a 19% decreased risk of CVD (50). In addition, observational studies in the past have observed a link between low folate intake and risk of CVD (105, 106).

The effect of vitamin D supplementation yielded inconsistent results in the present meta-analysis. Nevertheless, we observed a trend for an inverse association for all-cause mortality. Although some meta-analyses reported a slight reduction in overall mortality (3–8%) by vitamin D supplementation (9, 107), there is no convincing evidence that vitamin D supplements can reduce mortality among men and women. The interpretation of these meta-analyses is limited by combining primary and secondary prevention trials, the lack of dose-response relations, and the older ages of participants.

Although of limited power, calcium supplementation was associated with a decreased risk of cancer incidence compared with control groups in the present meta-analysis. Nevertheless, these results should be interpreted with caution, because only a very low number of cancer cases were included in the meta-analysis (30 cancer cases in the intervention groups compared with 23 in the control groups). A meta-analysis of prospective observational studies showed that calcium supplements and nondairy products fortified with calcium significantly reduced the risk of colorectal cancer by 8% (108). In contrast, a meta-analysis of cohort studies showed that a 400-g/d increase in dietary calcium was positively associated with prostate cancer (109).

With regard to the harmful effects of dietary supplements, similar to our subgroup results Bjelakovic et al. (16) reported a 6% increase in the risk of mortality after β-carotene supplementation. Compared with low-dose β-carotene and vitamin A, only high-dose β-carotene and high-dose vitamin A were associated with all-cause mortality. Previous studies showed that β-carotene supplementation was associated with an increase in the incidence of cancer among smokers and with a trend toward increased cancer mortality (102). The ATBC and CARET (Carotene and Retinol Efficacy Trial) studies indicated that β-carotene significantly increases the risk of lung cancer, by accelerating the progression in smokers and asbestos-exposed workers (80). The biological mechanism by which β-carotene increases mortality remains unclear, which limits the evidence for a causal relation.

Because amounts of micronutrients included in most commercial MVM supplements are close to 100% of the RDA, dietary supplements contribute substantially to total nutrient intakes and their contribution to total daily nutrient

TABLE 5 Efficacy of dietary supplements and risk of cancer[1]

Factor (references)	Trials, *n*	RR	95% CI	I^2 (95% CI), %
Calcium (36, 57)	2	0.37	0.22, 0.63	0 (NA)
Given singly	2	0.41	0.22, 0.76	0
Combined with others	1	0.33	0.17, 0.66	NA
Low dose (<1200 mg/d)	1	0.13	0.01, 2.53	NA
High dose (≥1200 mg/d)	1	0.38	0.22, 0.66	NA
Selenium[2] (45, 54, 60, 87, 93)	4	0.85	0.68, 1.07	80 (47, 92)
Given singly	3	0.78	0.52, 1.18	85
Combined with others	2	0.99	0.87, 1.12	54
Low dose (<120 μg/d)	2	0.83	0.58, 1.19	27
High dose (≥120 μg/d)	2	0.84	0.53, 1.33	91
Zinc[2] (combined with others and low dose, <50 mg/d) (45, 66)	2	0.91	0.77, 1.07	0 (NA)
Vitamin D (51, 55, 57, 67, 82, 84)	6	0.81	0.41, 1.62	58 (0, 83)
Given singly	4	1.42	0.46, 4.32	0
Combined with others	2	0.60	0.21, 1.74	90
Low dose (<500 IU/d)	4	0.98	0.92, 1.05	0
High dose (≥500 IU/d)	2	0.92	0.08, 10.1	78
β-Carotene[2] (43–45, 59, 80)	5	1.02	0.96, 1.08	46 (0, 80)
Given singly	3	1.01	0.96, 1.07	16
Combined with others	3	1.03	0.92, 1.16	60
Low dose (<30 mg/d)	3	0.99	0.93, 1.07	51
High dose (≥30 mg/d)	2	1.09	0.96, 1.23	30
Vitamin A (combined with others) (43, 66)	2	1.16	1.00, 1.35	0 (NA)
Low dose (<25,000 IU/d)	1	1.33	0.30, 5.91	NA
High dose (≥25,000 IU/d)	1	1.16	1.00, 1.35	NA
Vitamin C[2] (45, 65, 75)	3	0.99	0.91, 1.06	0 (0, 90)
Given singly	1	1.00	0.91, 1.10	NA
Combined with others	3	0.99	0.91, 1.07	0
Low dose (<500 mg/d)	2	0.90	0.77, 1.06	0
High dose (≥500 mg/d)	1	1.01	0.93, 1.10	NA
Vitamin E[2] (48, 58, 60, 65, 74, 75, 80)	7	1.02	0.99, 1.06	0 (0, 71)
Given singly	6	1.01	0.98, 1.05	0
Combined with others	4	1.03	0.99, 1.08	0
Low dose (<400 IU/d)	2	1.01	0.95, 1.07	0
High dose (≥400 IU/d)	5	1.03	0.98, 1.07	0
Folic acid (given singly and high dose, ≥5 mg/d) (47)	1	1.04	0.53, 2.06	NA
Vitamin K (32)	1	3.05	0.13, 73.4	NA
EPA (85)	1	1.11	0.93, 1.33	NA

[1] NA, not applicable.
[2] Multiarm trials were combined.

supply should be considered. With this in mind, it might be safer to take a single daily MVM supplement instead of taking excessive amounts of single minerals or antioxidants. In fact, there is evidence that high-dose vitamin A, β-carotene, and vitamin E supplements may be harmful (101).

The development and progression of chronic diseases occur over decades; thus, the timing and duration of the nutrient interventions with respect to chronic disease etiology are difficult to determine. The included trials ranged from 1 to 11 y in duration (plus the longest post-trial follow-up of 18 y). We included only primary prevention trials; nevertheless, the influence of concomitant therapies or medication may not be negligible. Because the mean age of participants was 59 y, we should take into account that hypertension and prediabetes are important risk factors for CVD. Only a few studies reported information on drug intake.

Strengths. The strengths of the present meta-analysis include the a priori published systematic review protocol, the comprehensive literature search, the large number of included trials and supplements, the evaluation of several clinical endpoints, and the different types of analyses.

Limitations. Limitations of the present meta-analysis include the inability to evaluate the effects of supplements for populations who have deficiencies of vitamins and minerals at baseline and the limited number of participants in studies of supplements such as magnesium and vitamin K for all outcomes and of calcium and the risk of CVD and cancer. Moreover, only a few trials reported information on specific cancer types; therefore, we did not perform a meta-analysis. Although we were not able to conduct a network meta-analysis, as planned in the study protocol, we are willing to perform a network meta-analysis in the future if we identify a higher number of homogenous trials.

Conclusions. In conclusion, we found insufficient evidence to support the use of dietary supplements in the primary prevention of cause-specific death, incidence of CVD, and incidence of cancer. The application of some supplements

generated small beneficial effects; however, the heterogeneous types and doses of supplements limit the generalizability to the overall population. Future studies are needed to confirm the effects detected for vitamin E, folic acid, and calcium in the present meta-analysis.

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