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ORIGINAL ARTICLE

Association of Multivitamin and Mineral Supplementation and Risk of Cardiovascular Disease

A Systematic Review and Meta-Analysis

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BACKGROUND: Multiple studies have attempted to identify the association between multivitamin/mineral (MVM) supplementation and cardiovascular disease (CVD) outcomes, but the benefits remain controversial. We performed a systematic review and meta-analysis of the associations between MVM supplementation and various CVD outcomes, including coronary heart disease (CHD) and stroke.

METHODS AND RESULTS: We conducted a comprehensive search of Medline, Embase, and the Cochrane Library for studies published between January 1970 and August 2016. We included clinical trials and prospective cohort studies in the general population evaluating associations between MVM supplementation and CVD outcomes. Data extraction and quality assessment were independently conducted by 2 authors, and a third author resolved discrepancies. Eighteen studies with 2 019 862 participants and 18 363 326 person-years of follow-up were included in the analysis. Five studies specified the dose/type of MVM supplement and the rest did not. Overall, there was no association between MVM supplementation and CVD mortality (relative risk [RR], 1.00; 95% confidence interval [CI], 0.97–1.04), CHD mortality (RR, 1.02; 95% CI, 0.92–1.13), stroke mortality (RR, 0.95; 95% CI, 0.82–1.09), or stroke incidence (RR, 0.98; 95% CI, 0.91–1.05). There was no association between MVM supplements and CVD or CHD mortality in prespecified subgroups categorized by mean follow-up period, mean age, period of MVM use, sex, type of population, exclusion of patients with history of CHD, and adjustment for diet, adjustment for smoking, adjustment for physical activity, and study site. In contrast, MVM use did seem to be associated with a lower risk of CHD incidence (RR, 0.88; 95% CI, 0.79–0.97). However, this association did not remain significant in the pooled subgroup analysis of randomized controlled trials (RR, 0.97; 95% CI, 0.80–1.19).

CONCLUSIONS: Our meta-analysis of clinical trials and prospective cohort studies demonstrates that MVM supplementation does not improve cardiovascular outcomes in the general population.

Key Words: cardiovascular diseases ■ coronary disease ■ incidence ■ myocardial infarction ■ mortality ■ stroke

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WHAT IS KNOWN

- The prevalence of multivitamin/mineral supplement use is high in the United States and other developed countries.
- Most studies have demonstrated a net neutral effect of multivitamin/mineral supplements in cardiovascular health, but several studies have suggested possible benefit in certain cardiovascular outcomes.

WHAT THE STUDY ADDS

- In this systematic meta-analysis of 18 prospective cohort studies and randomized controlled trials, there was no benefit of multivitamin/mineral supplements on cardiovascular disease prevention in the general population.
- Our study supports present guidelines that recommend against the routine use of multivitamin/mineral supplements to promote cardiovascular health.

The use of multivitamin/mineral (MVM) dietary supplements is widespread in the United States and other developed countries.[1,2] This is because of the popular belief that MVM supplements may help maintain and promote health by preventing various diseases, including cardiovascular disease (CVD).[3] Numerous large-scale population-based studies and randomized controlled trials (RCTs) have been conducted to identify the potential benefit of MVM supplementation in the general population, but the results have been equivocal.[4–8] Several population studies have suggested that MVM use may be beneficial for certain cardiovascular outcomes, but most other studies showed no significant cardiovascular benefit.[7,9]

Based on the weak and controversial benefit of MVM supplements, the US Preventive Services Task Force and the National Institutes of Health recommend against the routine use of MVM supplements for the purpose of chronic disease prevention, including CVD.[10,11] However, the prevalence of MVM supplementation in the general population remains high; for example, the National Health and Nutrition Examination Survey 2011 to 2012 data showed ≈30% of the population in the United States as using MVM supplements.[1,12,13] According to projections from 1 financial report, the global nutritional supplement industry is expected to reach $278 billion USD by 2024.[14]

There have been multiple efforts to perform a systematic review and meta-analysis of the association between MVM supplementation and CVD outcomes. Most reviews and meta-analyses have focused on RCTs and investigated the association between various dietary supplements and chronic disease outcomes, including cancer.[15,16] Those studies have found insufficient evidence to support the routine use of MVM supplements, but specific CVD outcomes, such as incidence of coronary heart disease (CHD) or stroke mortality, were not assessed.[15,16] In this article, we hypothesized that there is a null association between MVM supplement use and multiple cardiovascular outcomes. We aimed to perform a comprehensive systematic review and meta-analysis by pooling the evidence from prospective cohort studies and clinical trials on the association of MVM supplement use and specific CVD outcomes.

METHODS

Data Sources and Searches

The data, analytic methods, and study materials will be available on request for purposes of reproducing the results or replicating the procedure. We performed a systematic search of Medline, Embase, and the Cochrane Central Register of Controlled Trials database without language restrictions between January 1970 and August 2016. Additional relevant studies were retrieved by bibliography review of selected articles and manual search. Details of search terms and strategy are provided in Appendix I in the Data Supplement. This study only used data available in published studies and was exempt from approval by the University of Alabama at Birmingham Institutional Review Board.

Eligibility Criteria

Studies satisfying the following eligibility criteria were selected for final review: (1) RCTs and prospective cohort studies investigating MVM supplementation. Other observational studies, such as case series or case-control studies were excluded; (2) studies involving ambulatory adults in the community without a disabling condition. Studies only targeting a population with specific conditions, such as prior myocardial infarction or certain vitamin deficiencies, were excluded; (3) studies reporting the adjusted relative risk (RR) of cardiovascular outcomes, including cardiovascular mortality, CHD mortality, stroke mortality, incidence of CHD, and incidence of stroke; and (4) studies meeting the predefined high-quality assessment criteria.

Data Extraction and Quality Assessment

Two investigators (J. Choi and S.Y. Kwon) independently performed eligible study selection and data extraction. Any disagreements were resolved through discussion with a third investigator (J. Kim). Data of interest extracted from the selected papers included study name (first author and year of publication), design, site, characteristics, population, outcome, definition of MVM, frequency and duration of MVM supplementation, exposure and follow-up assessment method, RR with 95% confidence interval (CI), and adjustment for known cardiovascular risk factors.

We evaluated the methodological quality of the included RCTs as good, fair, or poor based on the US Preventive Services Task Force quality assessment criteria.[16,17] The quality of prospective cohort studies was evaluated by the prespecified assessment tool described by Proper et al.[18] This tool was

validated to evaluate the methodological quality of prospective cohort studies.[18–21] Appendix II in the Data Supplement presents further details of the assessment criteria. A study was considered high quality if the score based on the validity/precision criteria was ≥7 of 9.[18] We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Meta-Analysis of Observational Studies in Epidemiology guidelines for the meta-analysis of observational studies.

Definition of MVM Use and Cardiovascular Outcome

The types and doses of MVM in each study are summarized in Table 1. The definition of MVM varied among included studies. In this analysis, we followed the National Institutes of Health definition, which defined MVM as dietary supplements comprising >3 vitamin and mineral ingredients.[10] Supplements containing herbs, hormones, or drugs were excluded from the analysis. We included studies that assessed MVM supplement use by a questionnaire or in a follow-up office visit. If multiple cardiovascular outcomes were reported based on the intensity of MVM use (frequency, duration, or number of pills), the result with more intense usage was used for the meta-analysis. Multiple cardiovascular outcomes were assessed in our meta-analysis. CVD mortality included CHD mortality and stroke mortality. Incident CHD events were defined as cardiac revascularization and fatal and nonfatal myocardial infarction. Incident stroke included fatal and nonfatal stroke, including ischemic and hemorrhagic stroke.

Data Synthesis and Statistical Analysis

The analyses of RCT studies were conducted according to the intention-to-treat principle. Cohort studies were typically analyzed using Cox proportional hazards regression, and we used the hazard ratio and 95% CI from the analytic model adjusted for most covariates in each cohort. We pooled RRs and hazard ratios of each cardiovascular outcome for MVM users compared with nonusers (we refer to RRs and hazard ratios generically as RRs in this article). Analyses were conducted under the assumption of a common effect across subgroups within each study, whereas the true effect could vary across studies. For studies that only reported the RRs in subgroups (men and women in the study by Watkins et al,[5] Park et al,[30] and Iso et al[25]), we first computed a weighted RR and SE for each study using a fixed effects model using the inverse-variance approach. Then, we calculated summary RRs across studies using DerSimonian and Laird random effects models based on log-transformed RRs (metan command in Stata).[35]

We used univariable meta-regression with restricted maximum likelihood estimates of between study variance (metareg command in Stata) to evaluate whether results were different by MVM use (≤5 and >5 years), follow-up period (≤10 and >10 years), sex (men and women), mean age (≤60 and >60 years), population characteristics (healthcare professional and nonhealthcare professional), adjustment for vegetable and fruit intake, adjustment for smoking, adjustment for physical activity, study design (RCTs and prospective cohort studies), and study site (United States and others).[36]

Influence analysis was performed to examine the influence of individual studies on the pooled meta-analysis outcome. Each study was sequentially excluded from the analysis, and a sensitivity plot was created.[37] Heterogeneity was quantified with the Higgins I^2 statistic, which describes the proportion of total variation in pooled estimates because of heterogeneity.[38] Begg funnel plot and Egger test were used to evaluate the potential bias of publication.[39,40] A P value <0.05 was used as the threshold for statistical significance. All statistical analyses were conducted using Stata statistical software package, version 12.0 (2011; StataCorp, College Station, TX).

RESULTS

Study Selection

A flowchart of the study selection for meta-analysis is presented in Figure 1. Initial literature search retrieved a total of 3249 articles after removal of duplicated articles. An additional article was identified through manual search.[29] After title and abstract review, 25 studies remained for full-text manuscript review. Among these, 6 studies did not meet the inclusion criteria and were excluded.[23,30,41–44] One study met the inclusion criteria, but the population was duplicated in another study; therefore, the study with the longer follow-up data was selected for final analysis.[45] As a result, 18 studies were included in the final analysis.

Study Characteristics

Table 1 summarizes the main characteristics of the 18 studies included in the final analysis. A total of 2 019 862 participants were included with a range between 8678 and 1 063 023 participants per each study. The mean age of participants was 57.8 years. Eleven studies were from the United States, 4 were from Europe, and 3 were from Japan. The duration of follow-up varied from 5 to 19.1 years, with a mean follow-up period of 11.6 years. Multiple studies reported >1 cardiovascular outcome, including CVD mortality (10 studies), CHD mortality (7 studies), stroke mortality (4 studies), CHD incidence (8 studies), and stroke incidence (4 studies).

All included studies targeted the general population, and 4 studies investigated a healthcare professional population specifically. Ten studies excluded subjects with a history of CVD, whereas 8 studies did not. One study excluded subjects who had medical conditions with a predicted survival of <3 years.[6] Five studies reported the type and ingredients of the MVM, whereas the rest of studies did not specify them. All included RCTs tested a single-formulation MVM, whereas cohort studies tested a broader range of MVM supplements available in the market. Exposure in the cohort studies was assessed by a questionnaire or a follow-up office visit.

All of the included authors reported RRs adjusted for possible confounding factors, except Iso et al,[25] who reported RRs adjusted only for age and sex. Ten stud-

Table 1. Characteristics of Studies Included in the Meta-Analysis (n=18)

	Author	Year	Country	Study Design	Cohort	Study Population	Sample Size	Mean Age, y	Sex (Men), %	Follow-Up, y	MVM Type and Dose	Exposure and Follow-Up Assessment	Outcome	Adjusted Variables
1	Losonczy et al[22]	1996	United States	Prospective cohort study	EPESE	General population without history of CVD and cancer.	11 178	76.3	36	6	Type and dose of MVM unspecified.	Questionnaire, death certificate, and *ICD* codes	CHD mortality	Age, sex, race/ethnicity, education, alcohol use, smoking, aspirin use, CHD, stroke, diabetes mellitus, cancer, hypertension, and BMI.
2	Rimm et al[23]	1998	United States	Prospective cohort study	NHS	Female health professionals aged 30–55 y without history of CVD, cancer, hypercholesterolemia, and diabetes mellitus.	80 082	Unspecified	0	14	Type and dose of MVM unspecified.	Questionnaire	CHD incidence	Age, BMI, smoking, menopausal status, aspirin use, Vitamin E supplement, physical activity, hypertension, family history of early CHD, alcohol use, quintiles of fiber intake, and saturated, polysaturated, and trans fat intake.
3	Watkins et al[5]	2000	United States	Prospective cohort study	CPS-II	General population.	1 063 023	Unspecified	42	7	Type unspecified. Dose of MVM unspecified but has subgroups based on frequency of use.	Questionnaire	CHD mortality, stroke mortality	Age, race/ethnicity, marital status, BMI, smoking status, employment, exercise, education, aspirin use, diuretic use, diabetes mellitus, hypertension, heart disease, stroke, estrogen use (women only), and vegetable intake.
4	Hercberg et al[24]	2004	France	Randomized controlled trial	SU.VI.MAX study	Healthy adult volunteer.	13 017	48.2	38.6	7.5	Combination of 120 mg of ascorbic acid, 30 mg of vitamin E, 6 mg of β carotene, 100 μg of selenium, and 20 mg of zinc.	Questionnaire, blood sample, death certificate, and *ICD* codes	CHD incidence	Randomized based on age, sex, occupation, education level, family situation, smoking, and contraceptive use.
5	Iso et al[25]	2007	Japan	Prospective cohort study	JACC	General population.	105 629	Unspecified	42	12.7	Type and dose of MVM unspecified.	Questionnaire	CHD mortality, stroke mortality	Age, sex, and area of study.
6	Messerer et al[26]	2008	Sweden	Prospective cohort study	COSM	Male population without history of CVD and cancer.	38 994	59.1	100	7.7	Estimated means of MVM used in the study population were 60 mg vitamin C, 9 mg vitamin E, 1.2 mg thiamine, 1.4 mg riboflavin, 1.8 mg vitamin B_6, 3 mg vitamin B_{12}, and 400 mg folic acid.	Questionnaire and database from Swedish Death Registry	CVD mortality	Age, BMI, smoking, education, marital status, physical activity, self-perceived health and recommended food score, hypertension, hyperlipidemia, and diabetes mellitus.

(*Continued*)

Table 1. Continued

	Author	Year	Country	Study Design	Cohort	Study Population	Sample Size	Mean Age, y	Sex (Men), %	Follow-Up, y	MVM Type and Dose	Exposure and Follow-Up Assessment	Outcome	Adjusted Variables
7	Ishihara et al[27]	2008	Japan	Prospective cohort study	JPHC	General population without history of CVD and cancer.	40 803	50	50	11.5	Type and dose of MVM unspecified.	Questionnaire	CHD incidence	Age, sex, smoking, alcohol use, BMI, diabetes mellitus, education, hypertension, physical activity, dietary intake of fish, and fatty acids.
8	Neuhouser et al[6]	2009	United States	Prospective cohort study	WHI	Female population without medical conditions with a predicted survival of ≤3 y.	161 806	63.9	0	7.9	MVM defined as preparations with 20–30 vitamins and minerals and nutrient levels of ≤100%.	Office visit and annual questionnaire	CHD incidence, stroke incidence, CVD mortality	Age, menopausal status, race/ethnicity, BMI, education, hypertension, alcohol use, smoking, physical activity, use of vitamin C, vitamin E, calcium, and single supplement, diabetes mellitus, hyperlipidemia, family history of cancer, family history of MI, and fruit and vegetable intake.
9	Pocobelli et al[28]	2009	United States	Prospective cohort study	The Vitamins and Lifestyle Study	General population.	77 673	51.6	48	5	MVM defined as a mixture containing at least 10 vitamins and minerals. Dose of MVM unspecified but has subgroups based on frequency of use.	Questionnaire	CVD mortality	Age, sex, race/ethnicity, marital status, education, smoking, physical activity, estrogen therapy, estrogen plus progestin therapy, aspirin use, hyperlipidemia, and fruit and vegetable intake.
10	Rautiainen et al[9]	2010	Sweden	Prospective cohort study	SMC	General population without history of CVD and cancer.	31 671	60.2	0	10.2	MVM generally contains doses close to RDA of vitamin A (0.9 mg), vitamin C (60 mg), vitamin D (5 μg), vitamin E (9 mg), thiamine (1.2 mg), riboflavin (1.4 mg), vitamin B_6 (1.8 mg), vitamin B_{12} (3 μg), and folic acid (400 μg). The minerals usually included are iron (10 mg), zinc (12 mg), copper (2 mg), calcium (120 mg), magnesium (50 mg), chromium (50 lg), selenium (40 μg), and iodine (150 μg).	Questionnaire	CHD incidence, CHD mortality	Age, smoking, education, BMI, physical activity, alcohol use, family history of CHD, hypertension, hyperlipidemia, and fruit and vegetable intake.

(*Continued*)

Table 1. Continued

	Author	Year	Country	Study Design	Cohort	Study Population	Sample Size	Mean Age, y	Sex (Men), %	Follow-Up, y	MVM Type and Dose	Exposure and Follow-Up Assessment	Outcome	Adjusted Variables
11	Mursu et al[29]	2011	United States	Prospective cohort study	Iowa Women's Health	General population.	38 722	61.6	0	19	Type and dose of MVM unspecified.	Questionnaire	CVD mortality	Age, education, place of residence, diabetes mellitus, hypertension, BMI, hormone replacement therapy, physical activity, smoking, alcohol use, saturated fatty acids, and fruit and vegetable intake.
12	Park et al[30]	2011	United States	Prospective cohort study	Multiethnic Cohort Study	General population.	182 099	59.9	45.2	11	Type unspecified. Dose of MVM unspecified but has subgroups based on frequency of use.	Questionnaire	CVD mortality	Smoking, ethnicity, BMI, alcohol consumption, education, physical activity, single supplement use, fruit and vegetable intake, hormone replacement therapy, and menopausal status.
13	Sesso et al[7]	2012	United States	Randomized controlled trial	Physicians' Health Study II	Male physicians without history of cancer.	14 641	64.3	100	11.2	Centrum silver (Pfizer), 1 tablet daily.	Questionnaire	CHD incidence, stroke incidence, CHD mortality, stroke mortality, CVD mortality	Randomized based on age, BMI, smoking, alcohol consumption, hypertension, hyperlipidemia, diabetes mellitus, diet (fruit and vegetable intake, red meat, whole grains), exercise, and family history.
14	Li et al[31]	2012	Germany	Prospective cohort study	EPIC-Heidelberg	General population without history of CVD and cancer.	23 943	50.6	46.2	11	Type and dose of MVM unspecified.	Questionnaire	CVD mortality	Age, sex, education, physical activity, BMI, smoking, intake of meat/meat products, and baseline regular use of nonsteroidal anti-inflammatory drugs.
15	Rautiainen et al[4]	2015	United States	Prospective cohort study	Women's Health Study	Female health professionals without history of CVD and cancer.	37 193	53.8	0	16.2	Type and dose of MVM unspecified.	Questionnaire	CHD incidence, stroke incidence, CHD mortality, CVD mortality	Age, BMI, smoking, physical activity, hormone replacement therapy, postmenopausal status, diabetes mellitus, hypertension, hyperlipidemia, family history of CHD, alcohol use, and fruit and vegetable intake.

(*Continued*)

Table 1. Continued

	Author	Year	Country	Study Design	Cohort	Study Population	Sample Size	Mean Age, y	Sex (Men), %	Follow-Up, y	MVM Type and Dose	Exposure and Follow-Up Assessment	Outcome	Adjusted Variables
16	Bailey et al[32]	2015	United States	Prospective cohort study	NHANES III	General population without history of CVD and congestive heart failure.	8678	56.9	45.7	18.7	MVM defined as products containing ≥3 vitamins and at least 1 mineral. Dose unspecified.	Questionnaire	CVD mortality	Sex, race/ethnicity, education, alcohol use, smoking, physical activity, BMI, hyperlipidemia, diabetes mellitus, and aspirin use.
17	Dong et al[33]	2015	Japan	Prospective cohort study	Japan Collaborative Cohort Study	General population without history of CVD and cancer.	72 180	57.2	41.8	19.1	Type and dose of MVM unspecified.	Questionnaire	Stroke mortality	Age, study area, sex, BMI, education, hypertension, diabetes mellitus, family history of stroke, alcohol use, smoking, physical activity, use of vitamin C or vitamin E supplement, dietary intakes of fish, red meat, fruits and vegetables, and total energy.
18	Rautiainen et al[34]	2016	United States	Prospective cohort study	Physicians' Health Study I Cohort	Male physicians without history of CVD and cancer.	18 530	52.9	100	12.2	Type unspecified. Dose of MVM unspecified but has subgroups based on frequency of use.	Questionnaire	CHD incidence, CVD incidence, stroke incidence, CHD mortality, CVD mortality	Age, BMI, smoking, physical activity, alcohol use, family history of CHD, diabetes mellitus, hypertension, hyperlipidemia, and fruit and vegetable intake.

BMI indicates body mass index; CHD, coronary heart disease; COSM, Cohort of Swedish Men; CPS-II, Cancer Prevention Study II; CVD, cardiovascular disease; EPESE, Established Populations for Epidemiological Studies of the Elderly; EPIC, European Prospective Investigation into Cancer and Nutrition; *ICD, International Classification of Diseases*; JACC, Japan Collaborative Cohort; JPHC, Japan Public Health Center-based Prospective; MI, myocardial infarction; MVM, multivitamin and mineral supplement; NHANES, National Health and Nutrition Examination Survey; NHS, Nurses' Health Study; RCT, randomized controlled trial; RDA, recommended daily allowance; SMC, Swedish Mammography Cohort; SU.VI.MAX, Supplémentation en Vitamins et Minéraux Antioxydants; and WHI, Woman's Health Initiative.

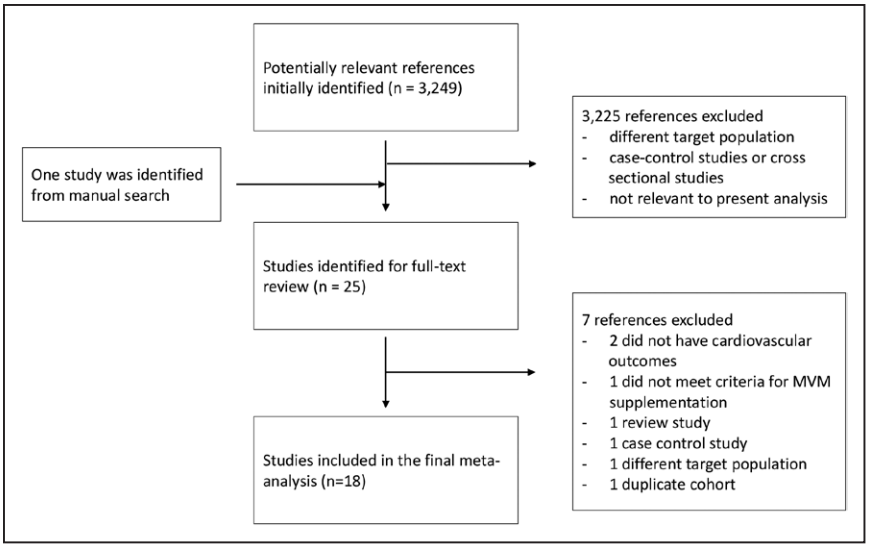

Figure 1. Flowchart of study selection.
MVM indicates multivitamin/mineral.

ies adjusted for self-reported vegetable and fruit intake as categorical variables. All included studies were high quality based on the predefined quality assessment criteria (Tables I and II in the Data Supplement).

Effect of MVM Supplementation on Risk of CVD, CHD, and Stroke Mortality

Figure 2 demonstrates the forest plot of RRs (95% CI) of the association between MVM supplementation and risk of CVD, CHD, and stroke mortality.

Ten studies reported CVD mortality as an outcome with a pooled sample of 616 970 participants. Meta-analysis of those studies revealed that MVM supplement use was not associated with the risk of CVD death (RR, 1.00; 95% CI, 0.97–1.04). There was no evidence of heterogeneity between studies (I^2=4.9%; Cochrane Q statistic, *P*=0.39) or publication bias (Begg test, *P*=0.28; Egger test, *P*=0.053; Figure IA in the Data Supplement).

Seven studies with a total of 1 281 865 participants examined the association between MVM use and CHD mortality. The use of MVM supplements was not associated with the risk of CHD mortality (RR, 1.02; 95% CI, 0.92–1.13). There was little evidence of heterogeneity across comparatives, (I^2=21.9%; Cochrane Q statistic, *P*=0.26), and no publication bias was found (Begg test, *P*=0.99; Egger test, *P*=0.52; Figure IB in the Data Supplement).

Four studies involving 1 255 473 participants investigated stroke mortality as an outcome. Across all the pooled studies, there was no evidence of an association between the use of MVM supplements and the risk of stroke mortality (RR, 0.95; 95% CI, 0.82–1.09). There was significant heterogeneity between comparatives (I^2=61.8%; Cochrane Q statistic, *P*=0.049) and no publication bias (Begg test, *P*=0.73; Egger test, *P*=0.75; Figure IC in the Data Supplement).

Effect of MVM Supplementation on Risk of CHD and Stroke Incidence

Eight cohort studies with 397 743 participants examined the association between MVM supplement use and the risk of incident CHD in the ambulatory population without a fatal underlying condition (Figure 2).

The pooled analysis demonstrated that subjects who use MVM supplements had a reduced risk of incident CHD (RR, 0.88; 95% CI, 0.79–0.97). There was evidence of significant heterogeneity between studies (I^2=55.8%; Cochrane Q statistic, *P*=0.027), but no publication bias was detected (Begg test, *P*=0.71; Egger test, *P*=0.33; Figure ID in the Data Supplement).

Meta-analysis of 4 studies comprising 236 059 participants reporting stroke events as an outcome showed that MVM supplementation was not related to stroke incidence (RR, 0.98; 95% CI, 0.91–1.05). There was no evidence of significant heterogeneity between studies (I^2=0.0%; Cochrane Q statistic, *P*=0.95), and no publication bias was observed (Begg test, *P*=0.73; Egger test, *P*=0.78; Figure IE in the Data Supplement).

Subgroup and Sensitivity Analyses

Table 2 demonstrates the results of subgroup and interaction analyses. Subgroup analyses were performed based on mean follow-up period (≤10 and >10 years), period of MVM use (≤5 and >5 years), mean age (≤60 and >60 years), sex, type of population, exclusion of individuals with history of CHD, adjustment for fruit and vegetable intake, adjustment for smoking, adjustment for physical activity, study design, and study site. Overall, there was no association between MVM supplementation and risk of CVD or CHD mortality in all subgroups. A significant interaction for CHD mortality was observed based on the adjustment for fruit and vegetable intake (interaction *P*=0.02) and adjustment

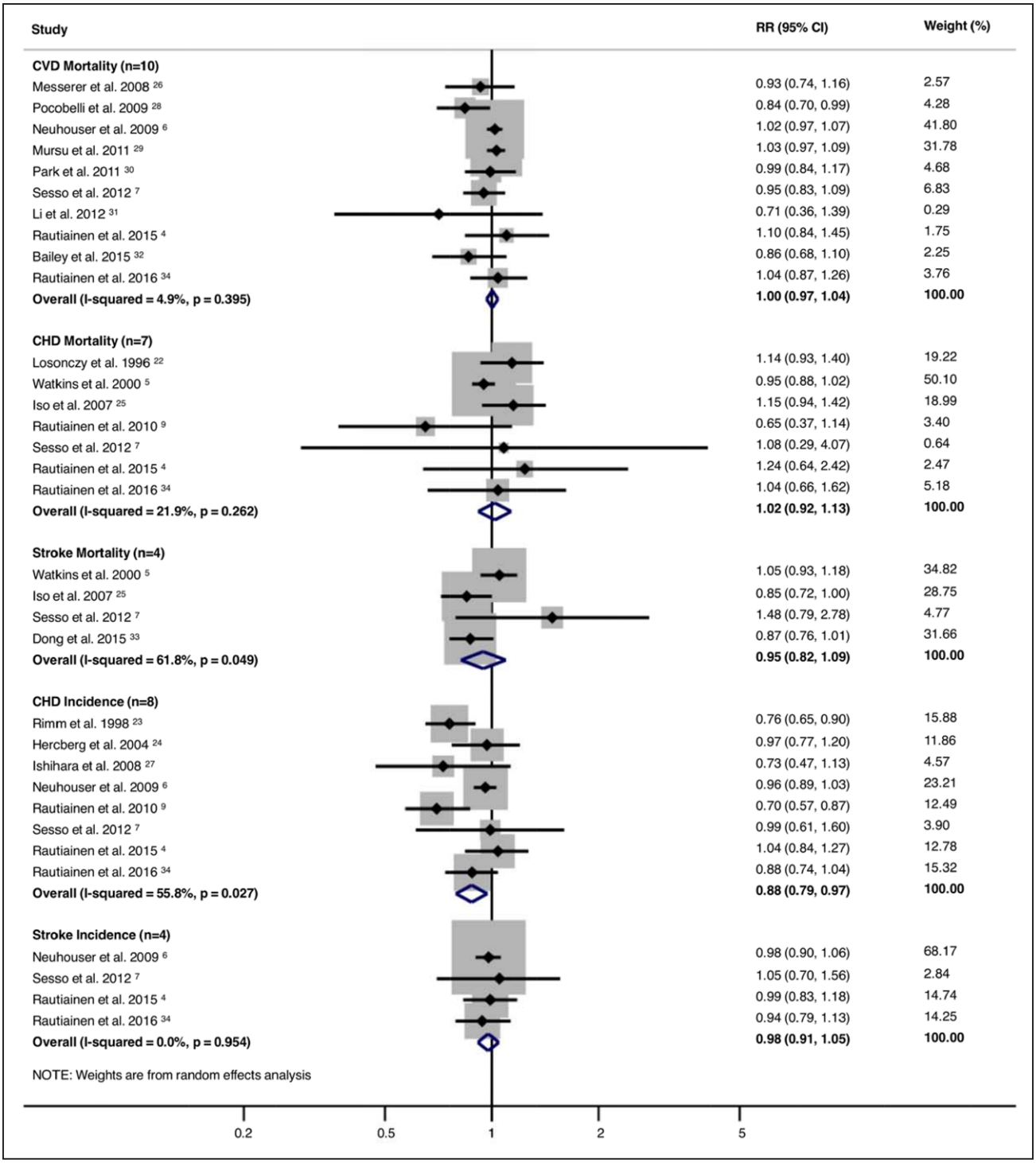

Figure 2. Association of multivitamin/mineral supplements and risk of cardiovascular disease (CVD) mortality, coronary heart disease (CHD) mortality, stroke mortality, CHD incidence, and stroke incidence.
Relative risks (RRs) of studies are denoted by gray squares. The lines of individual studies represent the 95% confidence intervals (CIs). The open diamond represents the 95% CI of pooled RRs. A random effects model was used for the meta-analysis.

for physical activity (interaction *P*=0.02), but no other interaction was observed.

The lower risk of CHD incidence with MVM supplementation was observed in studies that did not adjust for vegetable and fruit intake (RR, 0.77; 95% CI, 0.68–0.88). The association did not exist in studies that adjusted for diet (RR, 0.91; 95% CI, 0.82–1.01; interaction *P*=0.01). A subgroup analysis of studies conducted in countries other than the United States demonstrated an association between MVM supplement use and lower risk of CHD (RR, 0.74; 95% CI, 0.62–0.89). Studies conducted in the United States did not have this

Table 2. Subgroup and Interaction Analyses

Strata	No. of Studies	RR (95% CI)	I^2, %	Test for Interaction
CVD mortality				
Duration of MVM supplement use, y				
≤5	3[6,30,32]	1.01 (0.96–1.06)	0	0.66
>5	6[4,6,7,28,30,34]	1 (0.95–1.04)	0	
Sex				
Men	4[7,30,32,34]	0.97 (0.88–1.07)	0	0.34
Women	5[4,6,29,30,32]	1.02 (0.98–1.06)	0	
Type of population				
General population	7[6,26,28–32]	1.01 (0.97–1.04)	17.9	0.22
Healthcare professional population	3[4,7,34]	0.96 (0.90–1.03)	0	
Exclusion of individuals with history of CHD				
Studies excluded individuals with CHD	6[4,26,28,31,34]	0.95 (0.86–1.05)	11.2	0.34
Studies did not exclude individuals with CHD	5[6,7,28–30]	1.00 (0.97–1.03)	41.1	
Adjustment for diet				
Studies adjusted for vegetable and fruit diet	7[4,6,7,28–30,34]	1.00 (0.97–1.03)	23.3	0.17
Studies did not adjust for vegetable and fruit diet	3[26,31,32]	0.89 (0.75–1.04)	0	
Follow-up period, y				
≤10	3[6,26,28]	0.95 (0.83–1.08)	59.2	0.78
>10	7[4,7,29–32,34]	0.99 (0.95–1.04)	0.2	
Mean age, y				
≤60	7[4,26,28,30–32,34]	0.95 (0.87–1.03)	0	0.10
>60	3[6,7,29]	1.02 (0.98–1.06)	0	
Study site				
United States	8[4,6,7,28–30,32,34]	1.00 (0.97–1.03)	24.9	0.37
Others	2[26,31]	0.91 (0.73–1.12)	0	
CHD mortality				
Sex				
Men	3[5,7,25]	0.95 (0.86–1.04)	29.1	0.51
Women	3[5,9,25]	1.00 (0.89–1.12)	26.8	
Duration of MVM supplement use, y				
≤5	1[5]	0.99 (0.91–1.07)		0.45
>5	2[5,7]	0.95 (0.88–1.03)	0	
Exclusion of individuals with history of CHD				
Studies excluded individuals with CHD	3[5,9,22]	0.99 (0.94–1.04)	29	0.75
Studies did not exclude individuals with CHD	5[5,7,9,22,25]	0.97 (0.91–1.04)	49.7	0.75
Adjustment for diet				
Studies adjusted for vegetable and fruit diet	5[4,5,7,9,34]	0.95 (0.88–1.02)	0	0.02
Studies did not adjust for vegetable and fruit diet	2[22,25]	1.14 (0.99–1.32)	0	
Adjustment for smoking				
Studies adjusted for smoking	6[4,5,7,9,22,34]	0.97 (0.91–1.04)	5.4	0.12
Studies did not adjust for smoking	1[25]	1.15 (0.94–1.42)		
Adjustment for physical activity				
Studies adjusted for physical activity	5[4,5,7,9,34]	0.95 (0.88–1.02)	0	0.02
Studies did not adjust for physical activity	2[22,25]	1.14 (0.99–1.32)	0	
Follow-up period, y				
≤10	2[5,22]	0.97 (0.90–1.04)	46.7	0.65
>10	5[4,7,9,25,34]	1.01 (0.86–1.19)	41.5	
Mean age, y				
≤60	2[4,34]	1.10 (0.76–1.59)	0	0.89
>60	3[7,9,22]	1.07 (0.88–1.29)	40.9	
Study site				
United States	5[4,5,7,22,34]	0.97 (0.90–1.04)	36.9	0.31
Others	2[9,25]	1.08 (0.88–1.31)	43.6	
Stroke mortality				
Exclusion of individuals with history of CHD				
Studies excluded individuals with CHD	1[33]	0.87 (0.76–1.01)		0.17
Studies did not exclude individuals with CHD	3[5,7,25]	0.98 (0.90–1.08)	44.8	
Adjustment for diet				
Studies adjusted for vegetable and fruit diet	3[5,7,33]	0.99 (0.90–1.08)	44.0	0.11
Studies did not adjust for vegetable and fruit diet	1[25]	0.85 (0.72–1.00)		

(*Continued*)

Table 2. Continued

Strata	No. of Studies	RR (95% CI)	I^2, %	Test for Interaction
Adjustment for smoking				
Studies adjusted for smoking	3[5,7,33]	0.98 (0.91–1.07)	64.5	0.33
Studies did not adjust for smoking	1[25]	0.85 (0.72–1.00)		
Adjustment for physical activity				
Studies adjusted for physical activity	3[5,7,33]	0.98 (0.91–1.07)	64.5	0.33
Studies did not adjust for physical activity	1[25]	0.85 (0.72–1.00)		
CHD incidence				
Study design				
Randomized controlled trial	2[7,24]	0.97 (0.80–1.19)	0	0.49
Prospective cohort study	6[4,6,9,23,27,34]	0.90 (0.85–0.96)	67.5	
Period of MVM supplement use, y				
≤5	2[6,9]	0.95 (0.88–1.03)	0	0.73
>5	5[4,6,7,9,34]	0.88 (0.77–1.01)	50.6	
Type of population				
General population	4[6,9,24,27]	0.85 (0.68–1.07)	68.3	0.41
Healthcare professional population	4[4,7,23,34]	0.89 (0.79–1.01)	50.9	
Adjustment for diet				
Studies adjusted for vegetable and fruit diet	5[4,6,7,9,34]	0.91 (0.82–1.01)	56.5	0.01
Studies did not adjust for vegetable and fruit diet	3[23,24,27]	0.77 (0.68–0.88)	0	
Mean age, y				
≤60	5[4,23,24,27,34]	0.87 (0.79–0.96)	44.6	0.27
>60	2[6,9]	0.83 (0.61–1.13)	86.9	
Study site				
United States	5[4,6,7,23,34]	0.91 (0.83–1.00)	51	0.02
Others	3[9,24,27]	0.74 (0.62–0.89)	29.7	
Stroke incidence				
Exclusion of individuals with history of CHD				
Studies excluded individuals with CHD	2[4,34]	0.97 (0.85–1.09)	0	0.81
Studies did not exclude individuals with CHD	2[6,7]	0.98 (0.91–1.06)	0	

CHD indicates coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; MVM, multivitamin/mineral; and RR, relative risk.

association (RR, 0.91; 95% CI, 0.83–1.00; interaction P=0.02).

Influence analysis was performed by calculating pooled RRs after sequential removal of individual studies. Exclusion of any individual study did not significantly alter the pooled RR for any of the outcomes, as shown in Figure IIA through IIE in the Data Supplement.

DISCUSSION

Our meta-analysis of 18 studies involving 2 019 862 participants demonstrated no association between MVM supplementation and risk of CVD, CHD, or stroke mortality. MVM supplements were associated with a slightly lower risk of CHD incidence in the overall analysis, but no association was found with stroke incidence.

Studies have not demonstrated improved cardiovascular outcomes in the general population with a therapeutic supplementation of deficient vitamins, such as vitamin D.[46] Even sparser is the evidence of cardiovascular benefit in the general population without a confirmed vitamin deficiency, other than possible theoretical benefits suggested in in vitro studies.[47,48] Furthermore, several studies demonstrated that routine vitamin and mineral supplementation in certain populations, for instance in elderly patients, could lead to a worse outcome.[49–51] Our finding supports the hypothesis that the net effect of MVM supplementation in the general population for CVD prevention is neutral.

In our study, MVM supplement use was inversely related to the incidence of CHD when all studies were considered. However, this association was demonstrated only in cohort studies and not when subgroup analysis was performed on RCTs. There was significant heterogeneity among the cohort studies (I^2=67.5%) but no substantial heterogeneity among RCTs (I^2=0.0%). All included RCTs tested a uniform dose and ingredient of MVM, but most cohort studies did not specify the type and dose because use was assessed by self-report. Therefore, the marginal benefit of MVM use on CHD incidence seen in the overall outcome is likely because of the inherited limitations of prospective cohort studies, including residual confounding factors and inability to identify causation.

It is unclear why MVM supplement use was associated with lower risk of CHD incidence in studies done outside of the United States, whereas no benefit was found among studies performed in the United States. Nutritional studies have established that fruits and vegetables are a good source of many vitamins and are associated with a lower risk of stroke and CHD, with a strong dose-response relationship.[52,53] On the contrary, multivitamin supplements have not been shown to improve CVD outcomes, regardless of the baseline nutritional status.[54] A report from the Centers for Dis-

ease Control and Prevention revealed that 87% of the population in the United States do not meet the fruit and vegetable intake recommendations.[55] Multiple studies have shown that MVM supplement users also have higher intake of vitamins and minerals from their diet compared with nonusers.[56,57] It can be postulated that the marginal inverse association with CHD incidence seen in the studies done outside of the United States is because of the more unmeasured confounding variables in non-US studies and not because of regional benefits of MVM supplementation.

Our study has multiple strengths, including the large size of meta-analysis (>2 million participants included), with long-term follow-up (average 12 years), rigorous statistical methods examining for heterogeneity across studies, examination of associations of MVM for specific CVD outcomes, and examination of associations among many different subgroup populations. We undertook this analysis because, despite numerous studies strongly suggesting the neutral effect of MVM supplements on CVD prevention, the controversy did not end, and the scientific community continued to send a confusing signal to the public.[58] A fundamental benefit of meta-analysis is its ability to evaluate the body of evidence by combining the results from previously published studies. This helps to avoid making preemptive conclusions based on a few papers that may have type 1 error because of multiple testing and misguided result interpretation. Our findings will hopefully serve to dampen the widespread public enthusiasm for MVM use by conclusively showing null effects.

Nonetheless, there are potential limitations in this study. First, the MVM supplement formulation and dose were not uniform in the included studies. Only 5 studies specified the dose and type of MVM supplements. This lack of standardization reflects the real-world situation. The Food and Drug Administration does not review MVM supplements before they are marketed, and there is a wide variety of MVM supplements available in the market.[59] Two RCTs included in the analysis tested uniform MVM formulas, and the meta-analysis outcome of those studies matched the overall negative outcome. Second, most of the included studies assessed the use of MVM supplements by questionnaires and were unable to assess the frequency, dose, and compliance accurately. We attempted to perform a subgroup analysis of those who used MVM supplements more frequently but were unable to do so because of the lack of specific data. Third, prospective cohort studies were included in the main analysis, which are not free of potential confounding biases. However, most of the included studies adjusted for major cardiovascular risk factors, and our vigorous sensitivity analysis and subgroup analysis demonstrated a consistent neutral effect of MVM supplements on CVD outcomes. Moreover, inclusion of the RCTs did not alter the overall outcome.

In conclusion, our comprehensive meta-analysis demonstrates that MVM supplement use does not improve cardiovascular outcomes. Our study supports current professional guidelines that recommend against the routine use of MVM supplements for the purpose of CVD prevention in the general population.

ARTICLE INFORMATION

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Disclosures

None.

REFERENCES

1. Radimer K, Bindewald B, Hughes J, Ervin B, Swanson C, Picciano MF. Dietary supplement use by US adults: data from the National Health and Nutrition Examination Survey, 1999-2000. *Am J Epidemiol*. 2004;160:339–349. doi: 10.1093/aje/kwh207.
2. Gahche J, Bailey R, Burt V, Hughes J, Yetley E, Dwyer J, Picciano MF, McDowell M, Sempos C. Dietary supplement use among U.S. adults has increased since NHANES III (1988–1994). *NCHS Data Brief*. 2011;61:1–8.
3. Bailey RL, Gahche JJ, Miller PE, Thomas PR, Dwyer JT. Why US adults use dietary supplements. *JAMA Intern Med*. 2013;173:355–361. doi: 10.1001/jamainternmed.2013.2299.
4. Rautiainen S, Lee IM, Rist PM, Gaziano JM, Manson JE, Buring JE, Sesso HD. Multivitamin use and cardiovascular disease in a prospective study of women. *Am J Clin Nutr*. 2015;101:144–152. doi: 10.3945/ajcn.114.088310.
5. Watkins ML, Erickson JD, Thun MJ, Mulinare J, Heath CW Jr. Multivitamin use and mortality in a large prospective study. *Am J Epidemiol*. 2000;152:149–162.
6. Neuhouser ML, Wassertheil-Smoller S, Thomson C, Aragaki A, Anderson GL, Manson JE, Patterson RE, Rohan TE, van Horn L, Shikany JM, Thomas A, LaCroix A, Prentice RL. Multivitamin use and risk of cancer and cardiovascular disease in the Women's Health Initiative cohorts. *Arch Intern Med*. 2009;169:294–304. doi: 10.1001/archinternmed.2008.540.
7. Sesso HD, Christen WG, Bubes V, Smith JP, MacFadyen J, Schvartz M, Manson JE, Glynn RJ, Buring JE, Gaziano JM. Multivitamins in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. *JAMA*. 2012;308:1751–1760. doi: 10.1001/jama.2012.14805.
8. Hercberg S, Kesse-Guyot E, Druesne-Pecollo N, Touvier M, Favier A, Latino-Martel P, Briançon S, Galan P. Incidence of cancers, ischemic cardiovascular diseases and mortality during 5-year follow-up after stopping antioxidant vitamins and minerals supplements: a postintervention follow-up in the SU.VI.MAX Study. *Int J Cancer*. 2010;127:1875–1881. doi: 10.1002/ijc.25201.
9. Rautiainen S, Akesson A, Levitan EB, Morgenstern R, Mittleman MA, Wolk A. Multivitamin use and the risk of myocardial infarction: a population-

based cohort of Swedish women. *Am J Clin Nutr*. 2010;92:1251–1256. doi: 10.3945/ajcn.2010.29371.
10. NIH State-of-the-Science Panel. National Institutes of Health State-of-the-science conference statement: multivitamin/mineral supplements and chronic disease prevention. *Ann Intern Med*. 2006;145:364–371. doi: 10.7326/0003-4819-145-5-200609050-00136.
11. U.S. Preventive Services Task Force. Routine vitamin supplementation to prevent cancer and cardiovascular disease: recommendations and rationale. *Ann Intern Med*. 2003;139:51–55. doi: 10.7326/0003-4819-139-1-200307010-00013.
12. Bailey RL, Gahche JJ, Lentino CV, Dwyer JT, Engel JS, Thomas PR, Betz JM, Sempos CT, Picciano MF. Dietary supplement use in the United States, 2003-2006. *J Nutr*. 2011;141:261–266. doi: 10.3945/jn.110.133025.
13. Kantor ED, Rehm CD, Du M, White E, Giovannucci EL. Trends in dietary supplement use among US adults from 1999–2012. *JAMA*. 2016;316:1464–1474. doi: 10.1001/jama.2016.14403.
14. Grand View Research, Inc. Dietary Supplements Market Analysis By Ingredient (Botanicals, Vitamins, Minerals, Amino Acids, Enzymes), By Product (Tablets, Capsules, Powder, Liquids, Soft Gels, Gel Caps), By Application (Additional Supplement, Medicinal Supplement, Sports Nutrition), By End-Use (Infant, Children, Adults, Pregnant Women, Old-Aged) And Segment Forecasts To 2024. Report ID: 978-1-68038-919-7. https://www.grandviewresearch.com/industry-analysis/dietary-supplements-market. 2016. Accessed May 10, 2018.
15. Schwingshackl L, Boeing H, Stelmach-Mardas M, Gottschald M, Dietrich S, Hoffmann G, Chaimani A. Dietary supplements and risk of cause-specific death, cardiovascular disease, and cancer: a systematic review and meta-analysis of primary prevention trials. *Adv Nutr*. 2017;8:27–39. doi: 10.3945/an.116.013516.
16. Fortmann SP, Burda BU, Senger CA, Lin JS, Whitlock EP. Vitamin and mineral supplements in the primary prevention of cardiovascular disease and cancer: an updated systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2013;159:824–834. doi: 10.7326/0003-4819-159-12-201312170-00729.
17. US Preventive Services Task Force. *US Preventive Services Task Force Procedure Manual*. Rockville, MD: Agency for Healthcare Research and Quality; 2008.
18. Proper KI, Singh AS, van Mechelen W, Chinapaw MJ. Sedentary behaviors and health outcomes among adults: a systematic review of prospective studies. *Am J Prev Med*. 2011;40:174–182. doi: 10.1016/j.amepre.2010.10.015.
19. Hoogendoorn WE, van Poppel MN, Bongers PM, Koes BW, Bouter LM. Systematic review of psychosocial factors at work and private life as risk factors for back pain. *Spine (Phila Pa 1976)*. 2000;25:2114–2125.
20. Hayden JA, Côté P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med*. 2006;144:427–437.
21. Singh AS, Mulder C, Twisk JW, van Mechelen W, Chinapaw MJ. Tracking of childhood overweight into adulthood: a systematic review of the literature. *Obes Rev*. 2008;9:474–488. doi: 10.1111/j.1467-789X.2008.00475.x.
22. Losonczy KG, Harris TB, Havlik RJ. Vitamin E and vitamin C supplement use and risk of all-cause and coronary heart disease mortality in older persons: the established populations for epidemiologic studies of the elderly. *Am J Clin Nutr*. 1996;64:190–196. doi: 10.1093/ajcn/64.2.190.
23. Rimm EB, Willett WC, Hu FB, Sampson L, Colditz GA, Manson JE, Hennekens C, Stampfer MJ. Folate and vitamin B6 from diet and supplements in relation to risk of coronary heart disease among women. *JAMA*. 1998;279:359–364.
24. Hercberg S, Galan P, Preziosi P, Bertrais S, Mennen L, Malvy D, Roussel AM, Favier A, Briançon S. The SU.VI.MAX study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. *Arch Intern Med*. 2004;164:2335–2342. doi: 10.1001/archinte.164.21.2335.
25. Iso H, Kubota Y; Japan Collaborative Cohort Study for Evaluation of Cancer. Nutrition and disease in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). *Asian Pac J Cancer Prev*. 2007;8 suppl:35–80.
26. Messerer M, Håkansson N, Wolk A, Akesson A. Dietary supplement use and mortality in a cohort of Swedish men. *Br J Nutr*. 2008;99:626–631. doi: 10.1017/S0007114507812049.
27. Ishihara J, Iso H, Inoue M, Iwasaki M, Okada K, Kita Y, Kokubo Y, Okayama A, Tsugane S; JPHC Study Group. Intake of folate, vitamin B6 and vitamin B12 and the risk of CHD: the Japan Public Health Center-based prospective study cohort I. *J Am Coll Nutr*. 2008;27:127–136.
28. Pocobelli G, Peters U, Kristal AR, White E. Use of supplements of multivitamins, vitamin C, and vitamin E in relation to mortality. *Am J Epidemiol*. 2009;170:472–483. doi: 10.1093/aje/kwp167.
29. Mursu J, Robien K, Harnack LJ, Park K, Jacobs DR Jr. Dietary supplements and mortality rate in older women: the Iowa Women's Health Study. *Arch Intern Med*. 2011;171:1625–1633. doi: 10.1001/archinternmed.2011.445.
30. Park SY, Murphy SP, Wilkens LR, Henderson BE, Kolonel LN. Multivitamin use and the risk of mortality and cancer incidence: the multiethnic cohort study. *Am J Epidemiol*. 2011;173:906–914. doi: 10.1093/aje/kwq447.
31. Li K, Kaaks R, Linseisen J, Rohrmann S. Vitamin/mineral supplementation and cancer, cardiovascular, and all-cause mortality in a German prospective cohort (EPIC-Heidelberg). *Eur J Nutr*. 2012;51:407–413. doi: 10.1007/s00394-011-0224-1.
32. Bailey RL, Fakhouri TH, Park Y, Dwyer JT, Thomas PR, Gahche JJ, Miller PE, Dodd KW, Sempos CT, Murray DM. Multivitamin-mineral use is associated with reduced risk of cardiovascular disease mortality among women in the United States. *J Nutr*. 2015;145:572–578. doi: 10.3945/jn.114.204743.
33. Dong JY, Iso H, Kitamura A, Tamakoshi A; Japan Collaborative Cohort Study Group. Multivitamin use and risk of stroke mortality: the Japan collaborative cohort study. *Stroke*. 2015;46:1167–1172. doi: 10.1161/STROKEAHA.114.008270.
34. Rautiainen S, Rist PM, Glynn RJ, Buring JE, Gaziano JM, Sesso HD. Multivitamin use and the risk of cardiovascular disease in men. *J Nutr*. 2016;146:1235–1240. doi: 10.3945/jn.115.227884.
35. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177–188.
36. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? *Stat Med*. 2002;21:1559–1573. doi: 10.1002/sim.1187.
37. Viechtbauer W, Cheung MW. Outlier and influence diagnostics for meta-analysis. *Res Synth Methods*. 2010;1:112–125. doi: 10.1002/jrsm.11.
38. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539–1558. doi: 10.1002/sim.1186.
39. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50:1088–1101.
40. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629–634.
41. Angelo G, Drake VJ, Frei B. Efficacy of multivitamin/mineral supplementation to reduce chronic disease risk: a critical review of the evidence from observational studies and randomized controlled trials. *Crit Rev Food Sci Nutr*. 2015;55:1968–1991. doi: 10.1080/10408398.2014.912199.
42. Lamas GA, Boineau R, Goertz C, Mark DB, Rosenberg Y, Stylianou M, Rozema T, Nahin RL, Terry Chappell L, Lindblad L, Lewis EF, Drisko J, Lee KL. EDTA chelation therapy alone and in combination with oral high-dose multivitamins and minerals for coronary disease: the factorial group results of the Trial to Assess Chelation Therapy. *Am Heart J*. 2014;168:37–44.e5. doi: 10.1016/j.ahj.2014.02.012.
43. Wang C, Li Y, Zhu K, Dong YM, Sun CH. Effects of supplementation with multivitamin and mineral on blood pressure and C-reactive protein in obese Chinese women with increased cardiovascular disease risk. *Asia Pac J Clin Nutr*. 2009;18:121–130.
44. Holmquist C, Larsson S, Wolk A, de Faire U. Multivitamin supplements are inversely associated with risk of myocardial infarction in men and women–Stockholm Heart Epidemiology Program (SHEEP). *J Nutr*. 2003;133:2650–2654. doi: 10.1093/jn/133.8.2650.
45. Muntwyler J, Hennekens CH, Manson JE, Buring JE, Gaziano JM. Vitamin supplement use in a low-risk population of US male physicians and subsequent cardiovascular mortality. *Arch Intern Med*. 2002;162:1472–1476.
46. Scragg R, Stewart AW, Waayer D, Lawes CMM, Toop L, Sluyter J, Murphy J, Khaw KT, Camargo CA Jr. Effect of monthly high-dose vitamin D supplementation on cardiovascular disease in the vitamin D assessment study: a randomized clinical trial. *JAMA Cardiol*. 2017;2:608–616. doi: 10.1001/jamacardio.2017.0175.
47. McGreevy C, Williams D. New insights about vitamin D and cardiovascular disease: a narrative review. *Ann Intern Med*. 2011;155:820–826. doi: 10.7326/0003-4819-155-12-201112200-00004.
48. Esterbauer H, Gebicki J, Puhl H, Jürgens G. The role of lipid peroxidation and antioxidants in oxidative modification of LDL. *Free Radic Biol Med*. 1992;13:341–390.
49. Kern J, Kern S, Blennow K, Zetterberg H, Waern M, Guo X, Börjesson-Hanson A, Skoog I, Östling S. Calcium supplementation and risk of dementia in women with cerebrovascular disease. *Neurology*. 2016;87:1674–1680. doi: 10.1212/WNL.0000000000003111.
50. Anderson JJ, Kruszka B, Delaney JA, He K, Burke GL, Alonso A, Bild DE, Budoff M, Michos ED. Calcium intake from diet and supplements and the risk of coronary artery calcification and its progression among older adults: 10-year follow-up of the Multi-Ethnic Study of Atherosclerosis (MESA). *J Am Heart Assoc*. 2016;5:e003815. doi: 10.1161/JAHA.116.003815.

51. Cole BF, Baron JA, Sandler RS, Haile RW, Ahnen DJ, Bresalier RS, McKeown-Eyssen G, Summers RW, Rothstein RI, Burke CA, Snover DC, Church TR, Allen JI, Robertson DJ, Beck GJ, Bond JH, Byers T, Mandel JS, Mott LA, Pearson LH, Barry EL, Rees JR, Marcon N, Saibil F, Ueland PM, Greenberg ER; Polyp Prevention Study Group. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. *JAMA*. 2007;297:2351–2359. doi: 10.1001/jama.297.21.2351.
52. Dauchet L, Amouyel P, Dallongeville J. Fruit and vegetable consumption and risk of stroke: a meta-analysis of cohort studies. *Neurology*. 2005;65:1193–1197. doi: 10.1212/01.wnl.0000180600.09719.53.
53. He FJ, Nowson CA, MacGregor GA. Fruit and vegetable consumption and stroke: meta-analysis of cohort studies. *Lancet*. 2006;367:320–326. doi: 10.1016/S0140-6736(06)68069-0.
54. Rautiainen S, Gaziano JM, Christen WG, Bubes V, Kotler G, Glynn RJ, Manson JE, Buring JE, Sesso HD. Effect of baseline nutritional status on long-term multivitamin use and cardiovascular disease risk: a secondary analysis of the Physicians' Health Study II Randomized Clinical Trial. *JAMA Cardiol*. 2017;2:617–625. doi: 10.1001/jamacardio.2017.0176.
55. Moore LV, Thompson FE. Adults meeting fruit and vegetable intake recommendations - United States, 2013. *MMWR Morb Mortal Wkly Rep*. 2015;64:709–713.
56. Bailey RL, Fulgoni VL III, Keast DR, Dwyer JT. Dietary supplement use is associated with higher intakes of minerals from food sources. *Am J Clin Nutr*. 2011;94:1376–1381. doi: 10.3945/ajcn.111.020289.
57. Foote JA, Murphy SP, Wilkens LR, Hankin JH, Henderson BE, Kolonel LN. Factors associated with dietary supplement use among healthy adults of five ethnicities: the multiethnic cohort study. *Am J Epidemiol*. 2003;157:888–897.
58. Guallar E, Stranges S, Mulrow C, Appel LJ, Miller ER III. Enough is enough: stop wasting money on vitamin and mineral supplements. *Ann Intern Med*. 2013;159:850–851. doi:10.7326/0003-4819-159-12-201312170-00011.
59. Roseland JM, Holden JM, Andrews KW, Zhao C, Schweitzer A, Harnly J, Wolf WR, Perry CR, Dwyer JT, Picciano MF, Betz JM, Saldanha LG, Yetley EA, Fisher KD, Sharpless KE. Dietary supplement ingredient database (DSID): preliminary USDA studies on the composition of adult multivitamin/mineral supplements. *J Food Compost Anal*. 2008;21(suppl 1): S69–S77.

Association of Multivitamin and Mineral Supplementation and Risk of Cardiovascular Disease: A Systematic Review and Meta-Analysis

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SUPPLEMENTAL MATERIAL

Appendix 1: Search terms and strategy

Pubmed: ("multivitamin"[Title/Abstract] or "multivitamins"[Title/Abstract] or "vitamins"[Title/Abstract] or "multimineral"[Title/Abstract] or "dietary supplements"[Title/Abstract] or "dietary supplement"[Title/Abstract] or "mineral supplement"[Title/Abstract] or "mineral supplements"[Title/Abstract]) AND ("cardiovascular diseases"[MeSH Terms] OR "cerebrovascular disorders"[MeSH Terms] OR "coronary artery disease"[Title/Abstract] OR "coronary disease"[Title/Abstract] OR "myocardial ischemia"[Title/Abstract] OR "stroke"[Title/Abstract] OR "cerebrovascular accident"[Title/Abstract] OR "cerebrovascular disorders"[Title/Abstract] OR "cerebral infarction"[Title/Abstract] OR "cerebral hemorrhage"[Title/Abstract])

Embase: (Multivitamin or Multimineral) AND (Cardiovascular disease or Coronary artery disease or Myocardial ischemia or Stroke)

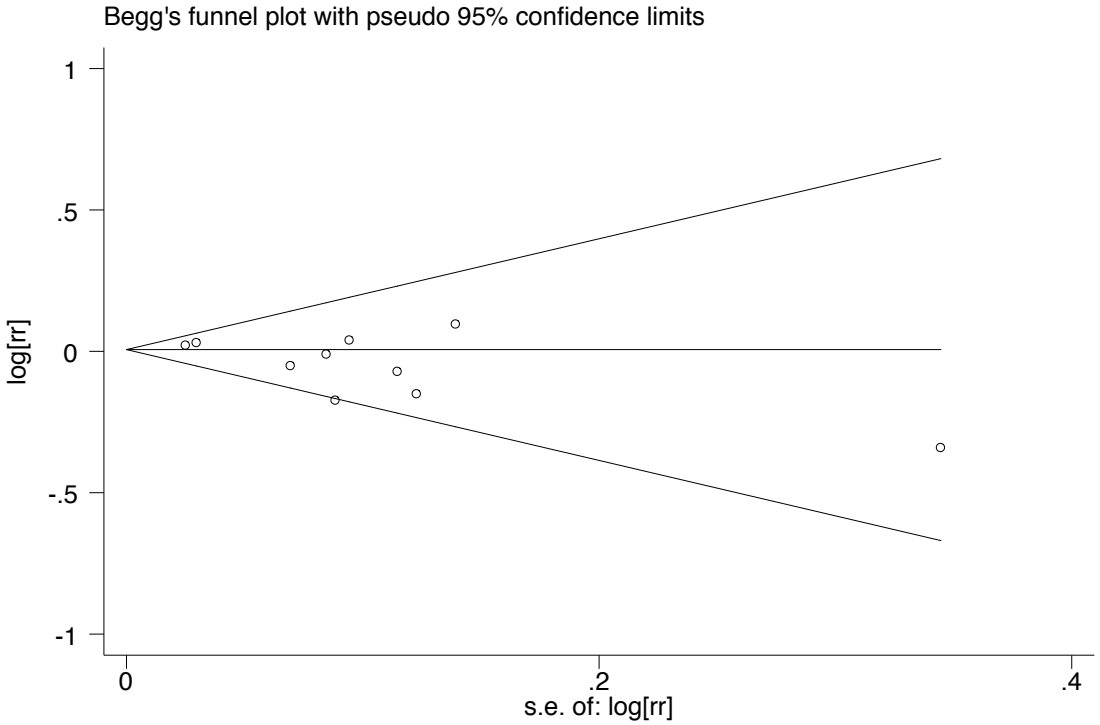
Cochrane library: (Multivitamin or Multimineral) AND Cardiovascular disease

Appendix 2: Quality assessment criteria for included studies

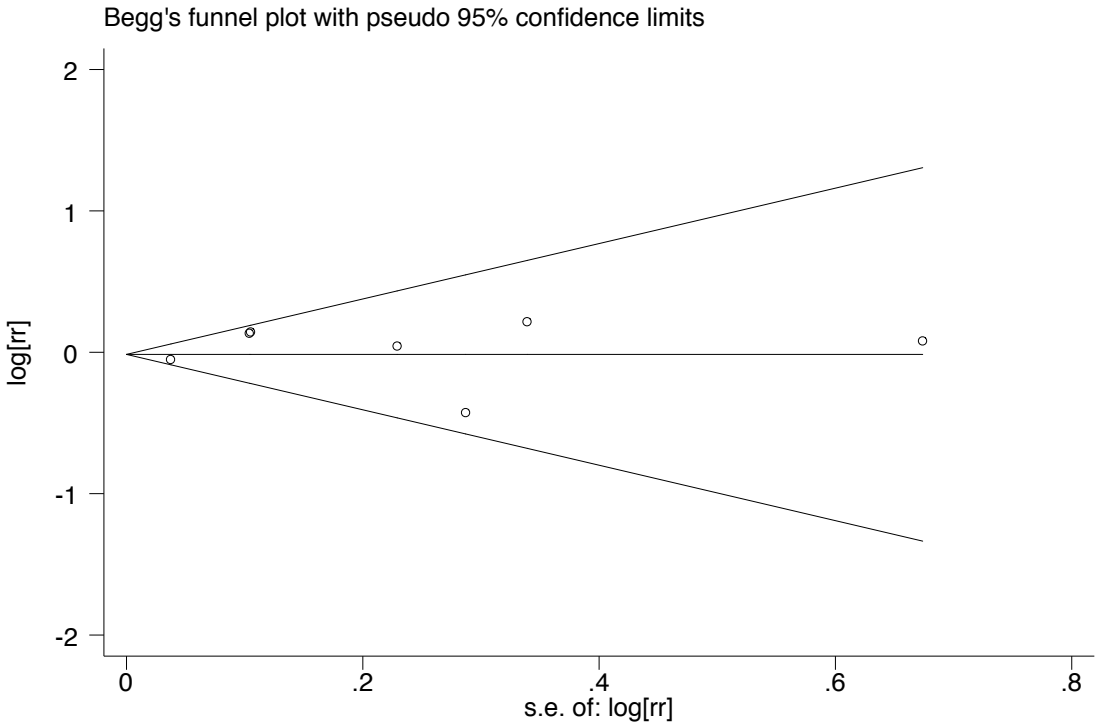
A quality assessment tool was used to evaluate the methodologic quality of each study. This tool consisted of 15 assessment items, 6 for informativeness assessment and 9 for validity/precision (V/P) assessment. Study population and participation, study attrition, data collection, and data analyses of each study were evaluated using this assessment criteria. Each item was valued as positive and given 1 point when there was proper information provided in

the study, negative and no point given when no adequate information was described, and unknown (?) when the description was unclear or insufficient.

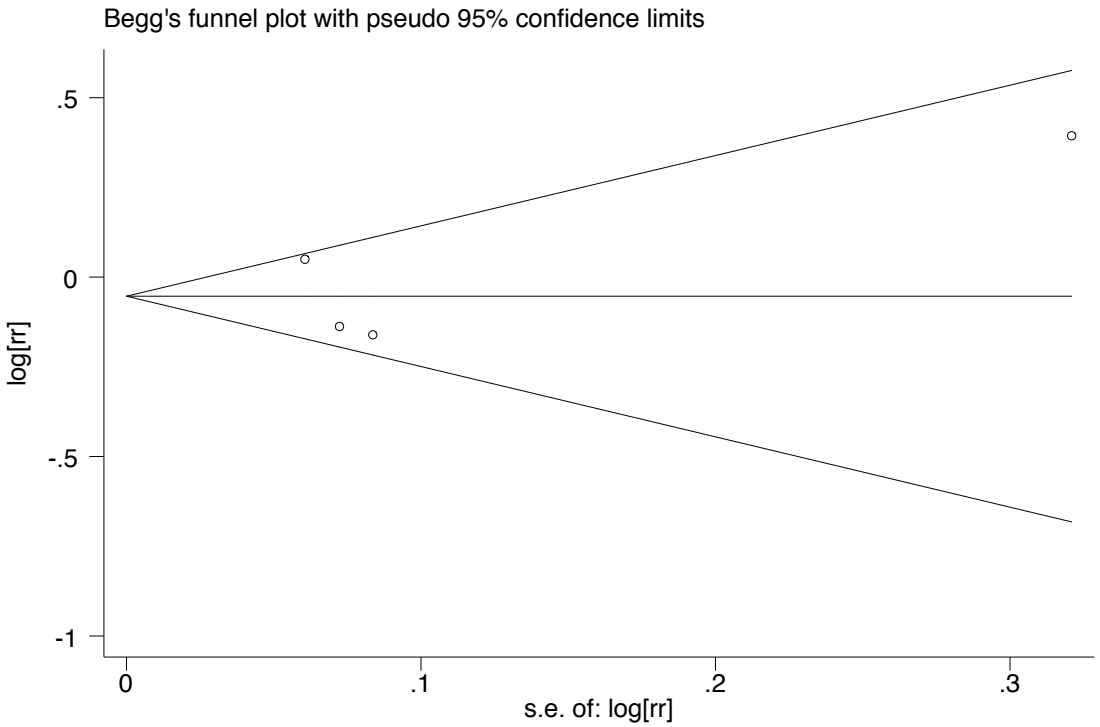
Appendix Figure 1A. Begg's funnel plot of studies reporting CVD mortality as the primary outcome.



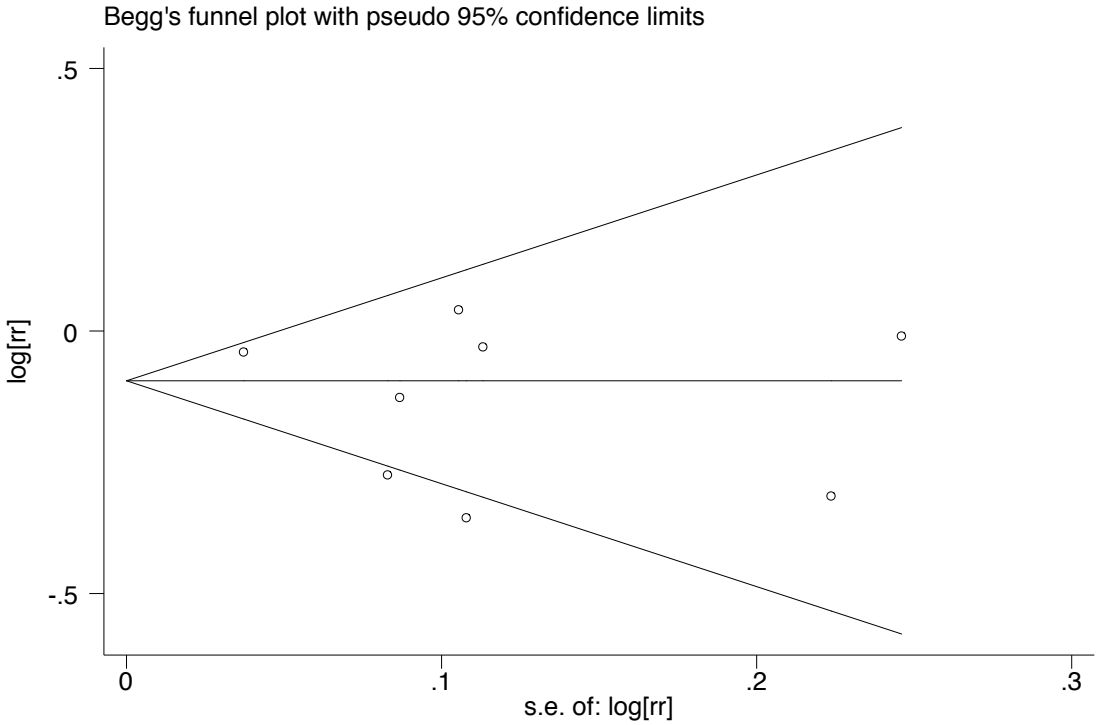
Appendix Figure 1B. Begg's funnel plot of studies reporting CHD mortality as the primary outcome.



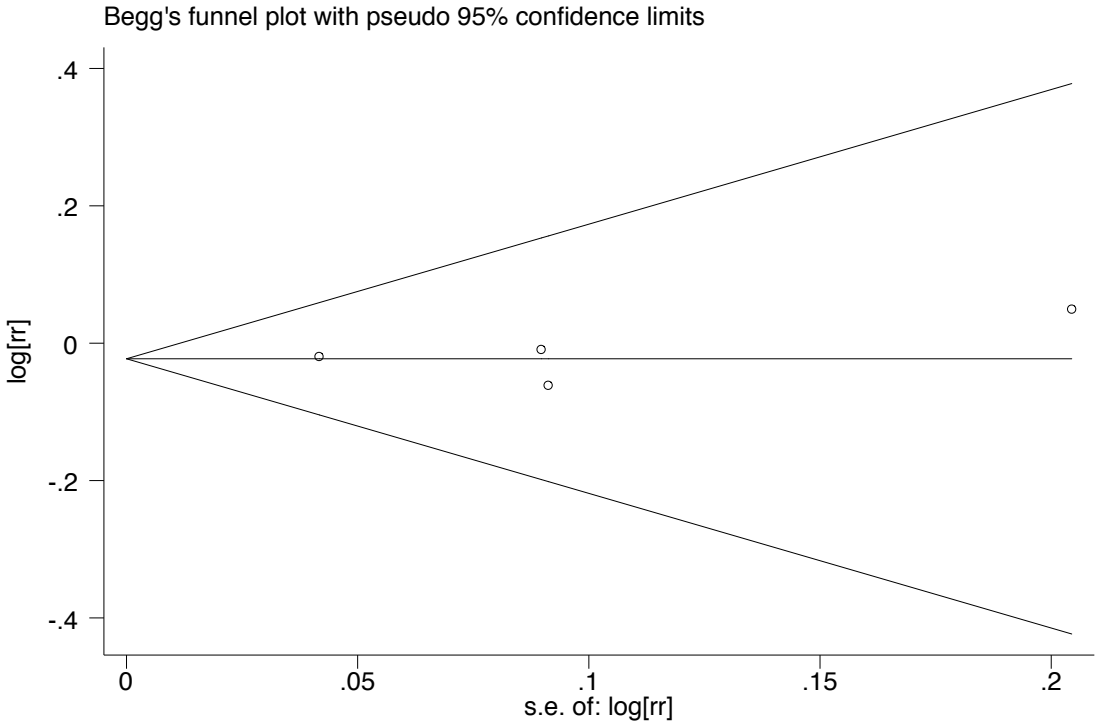
Appendix Figure 1C. Begg's funnel plot of studies reporting stroke mortality as the primary outcome.



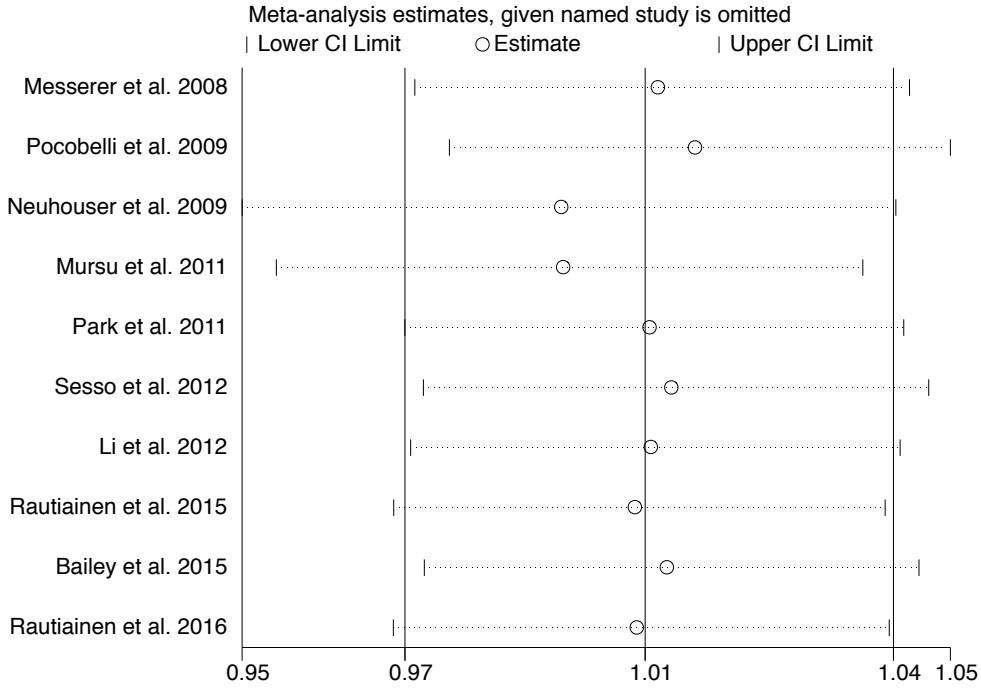
Appendix Figure 1D. Begg's funnel plot of studies reporting incidence of CHD as the primary outcome.



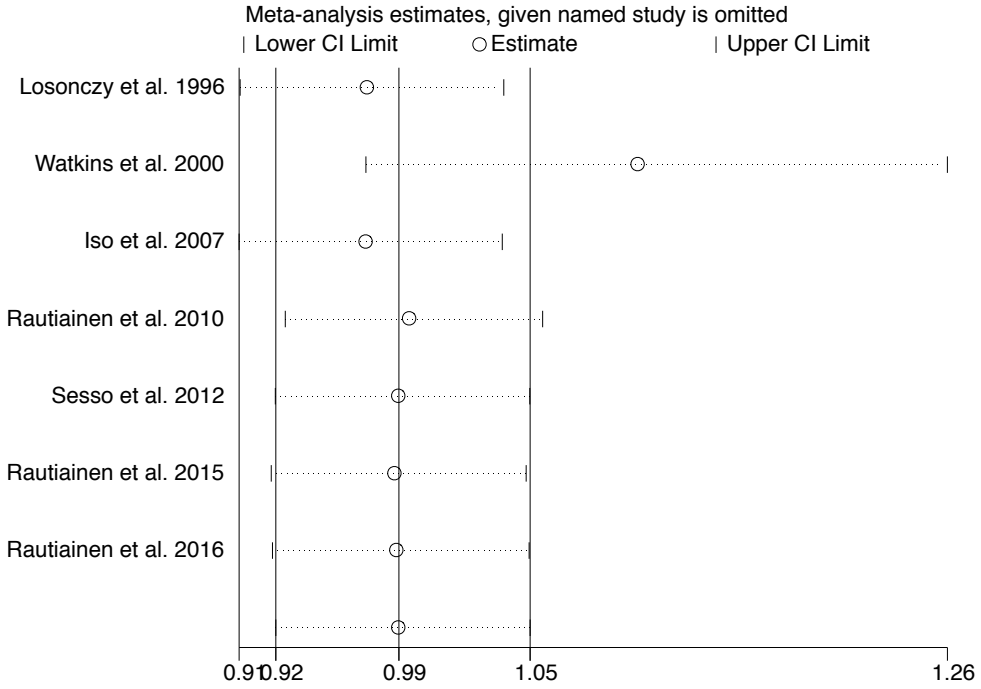
Appendix Figure 1E. Begg's funnel plot of studies reporting incidence of stroke as the primary outcome.



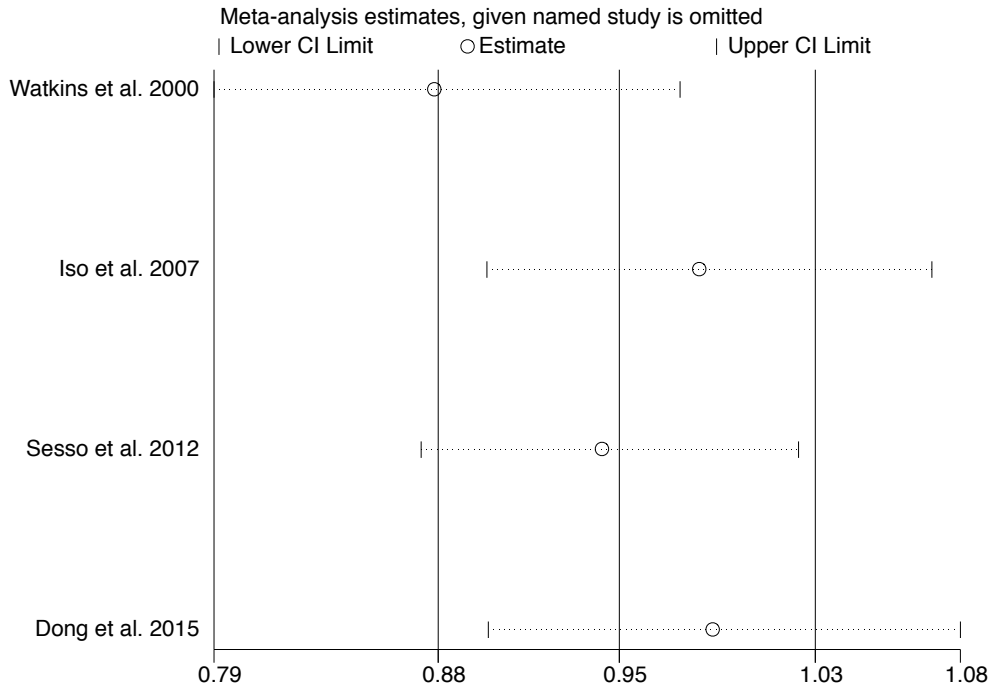
Appendix Figure 2A. Influence analysis of studies reporting CVD mortality as the primary outcome.



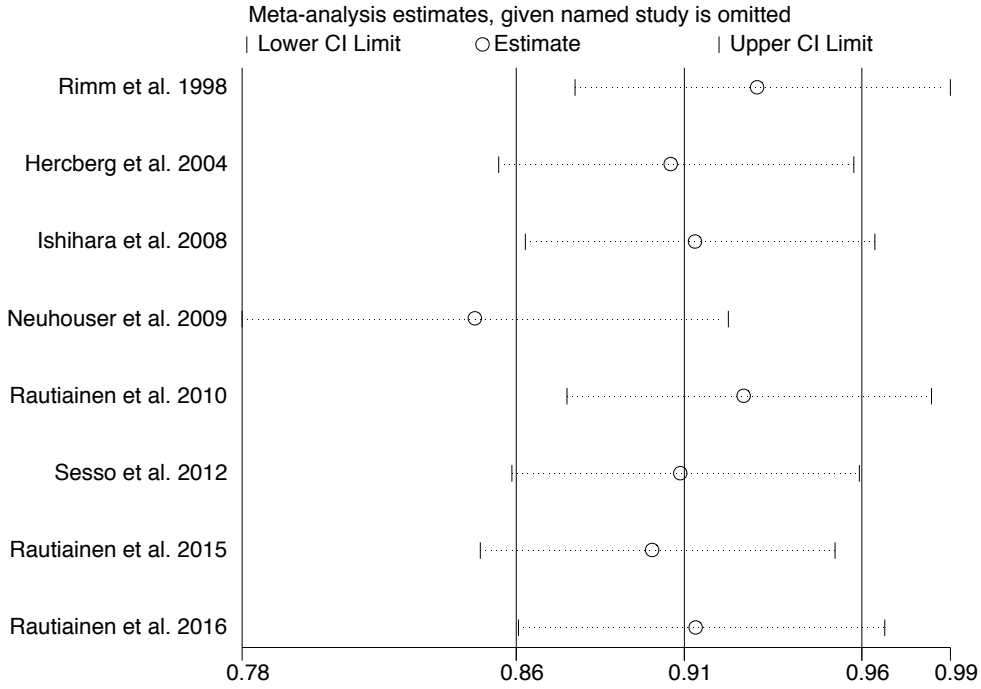
Appendix Figure 2B. Influence analysis of studies reporting CHD mortality as the primary outcome.



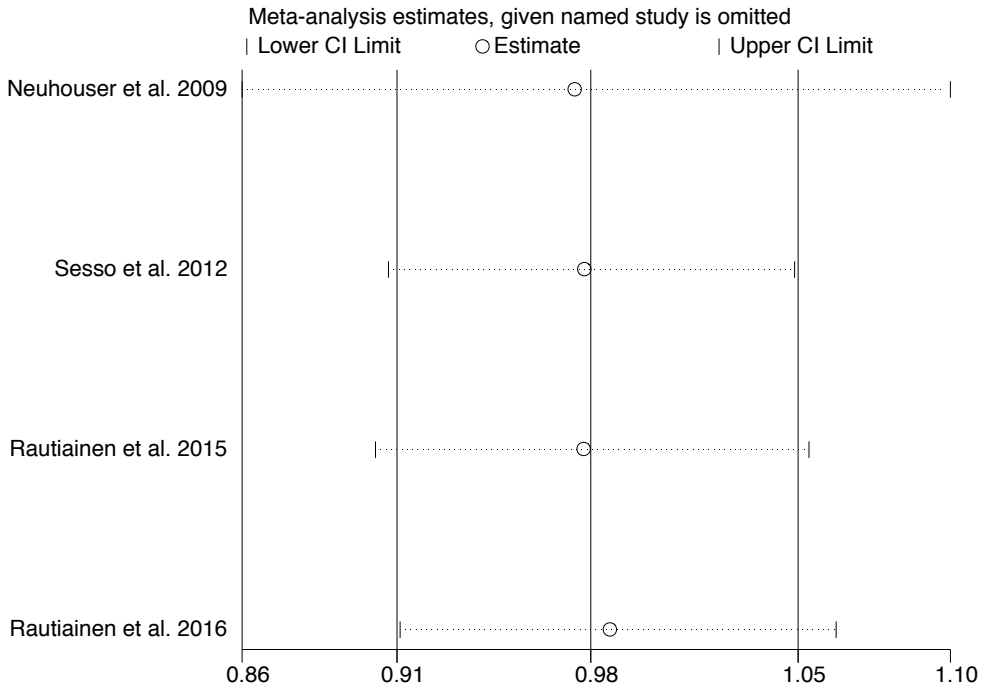
Appendix Figure 2C. Influence analysis of studies reporting stroke mortality as the primary outcome.



Appendix Figure 2D. Influence analysis of studies reporting incidence of CHD as the primary outcome.



Appendix Figure 2E. Influence analysis of studies reporting incidence of stroke as the primary outcome.



Appendix table 1. Criteria for Quality Assessment of Included Randomized Controlled Trials (n= 2)

Study name	Study design	Maximum follow-up, y	Supplement type	Treatment duration, y	Participants, n	Mean Age, y	Women, %	Outcome	Mortality	Harms
SU.VI.MAX [1]	RCT	13	3 vitamins, 2 minerals	7.5 (median)	13,017	49	59	CHD Incidence: No difference	No difference	No difference
PHS-II [2]	2x2x2x2 factorial RCT	11.2	13 vitamins, 17 minerals	11.2(median)	14,641	64	0	CHD incidence, CVD incidence, stroke incidence, CVD mortality: no difference	No difference	No difference

Study name	Study design	Study design	Participants randomly assigned, n	Summary of findings	consistency	Overall risk for bias	Major limitations	applicability	Overall study quality
SU.VI.MAX [1]	RCT	Efficacy	13,017	No benefit for CHD incidence	Consistent	Good	Only 3 vitamins included in the supplements	Moderate to high	Good
PHS-II [2]	Factorial RCT	Efficacy	14,641	No benefit for CVD incidence and mortality	Consistent	Good	Population was male physicians only	High	Good

Appendix table 2. Criteria for Quality Assessment of Included Prospective Cohort Studies (n= 16)

Study	Study population and participation						Study attrition	
	Adequate description of source population	Adequate description of sampling frame, recruitment methods, period of recruitment and place of recruitment (setting and geographic location)	Participation rate at baseline at least 80%, or if the nonresponse was not selective (show that baseline study sample does not significantly differ from population of eligible subjects)	Adequate description of baseline study sample (i.e., individuals entering the study) for key characteristics	Provision of the exact *n* at each follow-up measurement	Provision of exact information on follow-up duration	Response at short-term follow-up (up to 12 months) was at least 80% of the *n* at baseline and response at long-term follow-up was at least 70% of the *n* at baseline	Information on not selective nonresponse during follow-up measurements
Losonczy et al. [3]	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Rimm et al. [4]	Yes	Yes	yes	Yes	No	Yes	No	Yes
Watkins et al. [5]	Yes	Yes	yes	Yes	No	Yes	Not presented	Not presented
Iso et al. [6]	Yes	No	Not presented	Yes	No	No	Not presented	Not presented
Messerer et al. [7]	Yes	Yes	Yes	Yes	No	Yes	Yes	Not presented
Ishihara et al. [8]	Yes	Yes	Not presented	Yes	No	No	Not presented	Not presented
Neuhouser et al. [9]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pocobelli et al. [10]	Yes	Yes	Yes	Yes	No	Yes	No	Yes
Rautiainen et al. [11]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Mursu et al. [12]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Park et al. [13]	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Li et al. [14]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Rautiainen et al. [15]	Yes	yes	Yes	Yes	No	Yes	Yes	Yes
Bailey et al. [16]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Dong et al. [17]	Yes	Yes	Not presented	Yes	No	Yes	Not presented	Yes
Rautiainen et al. [18]	Yes	Yes	Yes	Yes	No	Yes	Yes	yes

Study	Data collection			Data analyses				Score
	Adequate description of measurement and definition of Multivitamin and mineral use	Multivitamin use was assessed at a time prior to the measurement of the health outcome	Adequate measurement of the health outcome: objective measurement of the health outcome done by trained personnel by means of standardized protocols of acceptable quality and not by self-report	The statistical model used was appropriate	The number of cases was at least 10 times the number of the independent variables	Presentation of point estimates and measures of variability (CI or SE)	No selective reporting of results (yes for no selective reporting, no for presence of selective reporting)	
Losonczy et al. [3]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	13
Rimm et al. [4]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	13
Watkins et al. [5]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	12
Iso et al. [6]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	13
Messerer et al. [7]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	13
Ishihara et al. [8]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Neuhouser et al. [9]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	15
Pocobelli et al. [10]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	13
Rautiainen et al. [11]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	14
Mursu et al. [12]	Yes	Yes	Yes	Yes	Yes	Yes	yes	14
Park et al. [13]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	13
Li et al. [14]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	14
Rautiainen et al. [15]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	14
Bailey et al. [16]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	14
Dong et al. [17]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	12
Rautiainen et al. [18]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	14

Appendix References

1. Hercberg S, Galan P, Preziosi P, Bertrais S, Mennen L, Malvy D, Roussel AM, Favier A, Briançon S. The SU.VI.MAX Study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. *Arch Intern Med*. 2004;164:2335-2342.
2. Sesso HD, Christen WG, Bubes V, Smith JP, MacFadyen J, Schvartz M, Manson JE, Glynn RJ, Buring JE, Gaziano JM. Multivitamins in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. *JAMA*. 2012;308:1751-1760.
3. Losonczy KG, Harris TB, Havlik RJ. Vitamin E and vitamin C supplement use and risk of all-cause and coronary heart disease mortality in older persons: the Established Populations for Epidemiologic Studies of the Elderly. *Am J Clin Nutr*. 1996;64:190-196.
4. Rimm EB, Willett WC, Hu FB, Sampson L, Colditz GA, Manson JE, Hennekens C, Stampfer MJ. Folate and vitamin B6 from diet and supplements in relation to risk of coronary heart disease among women. *JAMA*. 1998;279:359-364.
5. Watkins ML, Erickson JD, Thun MJ, Mulinare J, Heath CWJ. Multivitamin use and mortality in a large prospective study. *Am J Epidemiol*. 2000;152:149-162.
6. Iso H, Kubota Y, Japan CCSFEOC. Nutrition and disease in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). *Asian Pac J Cancer Prev*. 2007;8 Suppl:35-80.
7. Messerer M, Håkansson N, Wolk A, Akesson A. Dietary supplement use and mortality in a cohort of Swedish men. *Br J Nutr*. 2008;99:626-631.
8. Ishihara J, Iso H, Inoue M, Iwasaki M, Okada K, Kita Y, Kokubo Y, Okayama A, Tsugane S, JPHC SG. Intake of folate, vitamin B6 and vitamin B12 and the risk of CHD: the Japan Public Health Center-Based Prospective Study Cohort I. *J Am Coll Nutr*. 2008;27:127-136.

9. Neuhouser ML, Wassertheil-Smoller S, Thomson C, Aragaki A, Anderson GL, Manson JE, Patterson RE, Rohan TE, van Horn L, Shikany JM, Thomas A, LaCroix A, Prentice RL. Multivitamin use and risk of cancer and cardiovascular disease in the Women's Health Initiative cohorts. *Arch Intern Med*. 2009;169:294-304.

10. Pocobelli G, Peters U, Kristal AR, White E. Use of supplements of multivitamins, vitamin C, and vitamin E in relation to mortality. *Am J Epidemiol*. 2009;170:472-483.

11. Rautiainen S, Akesson A, Levitan EB, Morgenstern R, Mittleman MA, Wolk A. Multivitamin use and the risk of myocardial infarction: a population-based cohort of Swedish women. *Am J Clin Nutr*. 2010;92:1251-1256.

12. Mursu J, Robien K, Harnack LJ, Park K, Jacobs DR. Dietary supplements and mortality rate in older women: the Iowa Women's Health Study. *Arch Intern Med*. 2011;171:1625-1633.

13. Park SY, Murphy SP, Wilkens LR, Henderson BE, Kolonel LN. Multivitamin use and the risk of mortality and cancer incidence: the multiethnic cohort study. *Am J Epidemiol*. 2011;173:906-914.

14. Li K, Kaaks R, Linseisen J, Rohrmann S. Vitamin/mineral supplementation and cancer, cardiovascular, and all-cause mortality in a German prospective cohort (EPIC-Heidelberg). *Eur J Nutr*. 2012;51:407-413.

15. Rautiainen S, Lee IM, Rist PM, Gaziano JM, Manson JE, Buring JE, Sesso HD. Multivitamin use and cardiovascular disease in a prospective study of women. *Am J Clin Nutr*. 2015;101:144-152.

16. Bailey RL, Gahche JJ, Lentino CV, Dwyer JT, Engel JS, Thomas PR, Betz JM, Sempos CT, Picciano MF. Dietary supplement use in the United States, 2003-2006. *J Nutr*.

2011;141:261-266.

17. Dong JY, Iso H, Kitamura A, Tamakoshi A. Multivitamin use and risk of stroke mortality: the Japan collaborative cohort study. *Stroke*. 2015;46:1167-1172.

18. Rautiainen S, Rist PM, Glynn RJ, Buring JE, Gaziano JM, Sesso HD. Multivitamin Use and the Risk of Cardiovascular Disease in Men. *J Nutr*. 2016;146:1235-1240.