

# Multivitamin-multimineral supplementation and mortality: a meta-analysis of randomized controlled trials<sup>1–3</sup>

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## ABSTRACT

**Background:** Multivitamins are the most commonly used supplement in the developed world. Recent epidemiologic findings suggest that multivitamin use increases the risk of mortality.

**Objective:** We aimed to determine whether multivitamin-multimineral treatment, used for primary or secondary prevention, increases the risk of mortality in independently living adults.

**Design:** We performed a meta-analysis of randomized controlled trials. Multiple electronic databases were systematically searched from March to October 2012. Randomized controlled primary or secondary prevention trials were considered for inclusion. Eligible trials investigated daily multivitamin-multimineral supplementation for  $\geq 1$  y. Cohorts described as institutionalized or as having terminal illness (tertiary prevention) were excluded. The number of deaths and the sample size of each study arm were extracted independently by 2 researchers. Twenty-one articles were included in the analysis, which generated a total pooled sample of 91,074 people and 8794 deaths. These trials were pooled in a meta-analysis, and the outcomes were expressed as RRs and 95% CIs.

**Results:** The average age of the pooled sample was 62 y, and the average duration of supplementation was 43 mo. Across all studies, no effect of multivitamin-multimineral treatment on all-cause mortality (RR: 0.98; 95% CI: 0.94, 1.02) was observed. There was a trend for a reduced risk of all-cause mortality across primary prevention trials (RR: 0.94; 95% CI: 0.89, 1.00). Multivitamin-multimineral treatment had no effect on mortality due to vascular causes (RR: 1.01; 95% CI: 0.93, 1.09) or cancer (RR: 0.96; 95% CI: 0.88, 1.04). No statistical evidence of heterogeneity or publication bias was observed.

**Conclusion:** Multivitamin-multimineral treatment has no effect on mortality risk. *Am J Clin Nutr* 2013;97:437–44.

## INTRODUCTION

Multivitamins represent the most commonly used vitamin supplement in the United States and other developed nations (1, 2). Over the past decade, multivitamin use has increased (3), particularly among older individuals (4), who consume such supplements for the purpose of health maintenance (5). Despite what appears to be an increasing trend in multivitamin use, controversy surrounds their safety (6).

The Iowa Women's Health Study recently reported that multivitamin use was associated with an increased risk of mortality in elderly women (7). However, this study used an observational design, and the results were potentially biased by factors including indication (6) and the tendency for supplement use to be higher in

those with a history of disease (8). Other large observation epidemiology studies have similarly provided little consensus about the safety of multivitamin use (9, 10). More conclusive evidence regarding the risk of mortality associated with multivitamin use can be obtained through randomized controlled trials (RCTs)<sup>4</sup>. A recently updated Cochrane review examined the association between vitamin supplementation and all-cause mortality (11, 12). However, this review focused solely on antioxidant vitamins as opposed to multivitamins.

Because of the wide prevalence of multivitamin use and the consideration that these supplements are more likely to be used over longer time periods (13), there is a need to establish the safety and efficacy of multivitamins as opposed to treatment with specific vitamins. The current review aimed to systematically examine the literature and to quantify the effects of chronic multivitamin-multimineral (MVMM) supplementation on mortality through a meta-analysis of RCTs. The association of MVMM treatment with all-cause mortality was examined, as was mortality from vascular disease or cancer, through a total of 3 questions. Both primary and secondary prevention trials were examined.

## SUBJECTS AND METHODS

### Data sources and searches

We searched Medline (PubMed; <http://www.ncbi.nlm.nih.gov/pubmed>), The Cochrane Database of Systematic Reviews (<http://www.thecochranelibrary.com>), Cochrane Central Register of Controlled Trials (<http://www.thecochranelibrary.com>), Cumulative Index to Nursing and Allied Health Literature Plus (<http://www.ebscohost.com/academic/cinahl-plus-with-full-text/>), and the Database of Abstracts of Reviews of Effects ([http://onlinelibrary.wiley.com/o/cochrane/cochrane\\_cldare\\_articles\\_fs.html](http://onlinelibrary.wiley.com/o/cochrane/cochrane_cldare_articles_fs.html)) from March to October 2012. Searching was performed by using the following

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<sup>4</sup> Abbreviations used: CVD, cardiovascular disease; MVMM, multivitamin-multimineral; RCT, randomized controlled trial.

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string of search terms with truncations: vitamin\* or mineral\* or multivitamin\* or antioxidant\* or anti-oxidant\* or micronutrient\*. When possible, search results were automatically filtered by using the following limits: clinical trials or meta-analysis, human studies, and all adult samples. The search was not limited to any specific years of publication. Scopus (<http://www.scopus.com/home.url>) was used to search the references of all studies included in the review.

### Study selection

Randomized and controlled primary or secondary prevention trials were considered appropriate for review. To limit heterogeneity between the included trials, the following inclusion criteria were enforced: the trial must have been randomized and controlled, the participants must have been supplemented with a daily MVMM formulation in at least one study arm, the MVMM must have been taken orally and administered as a monotherapy within the treatment arm, the supplementation must have taken place for  $\geq 1$  y, and the cohort must not have been institutionalized or have had a terminal illness (tertiary prevention). Furthermore, each trial must have reported on the number of deaths in both the control and MVMM groups, or these data must have been made available on request. As recommended (14, 15), studies without deaths were excluded from the analyses (*see* Supplemental Table 1 under “Supplemental data” in the online issue).

To be eligible for inclusion, trials must have supplemented participants with a daily MVMM. Our definition of an MVMM was kept consistent with that of previous work (8, 16–18), whereby an MVMM was defined as a supplement containing  $\geq 3$  micronutrients, except when supplements contained  $\geq 3$  B vitamins only. This criterion reflects the considerations that B vitamins exert similar biological actions (16, 17) and that combinations of B vitamins are often marketed as B complex supplements as opposed to an MVMM. Trials that administered an MVMM with omega-3 (n-3) fatty acids or pharmaceutical medications were excluded. An MVMM containing small quantities of herbs and flavonoids was included in a review given that these compounds are commonly added to MVMM supplements in small dosages. To reduce heterogeneity between interventions, vitamin-enriched foods were excluded.

### Data extraction and quality assessment

The primary outcome was the effects of MVMM treatment on all-cause mortality. In addition, we examined the association between MVMM treatment and the risk of mortality due to vascular causes and cancer, respectively. These analyses were chosen given that cardiovascular disease (CVD) and cancer are 2 of the most prominent causes of death in the developed world (19). Moreover, many trials have been conducted to examine the effects of vitamin treatment on the progression of CVD and cancer (12).

In accordance with Cochrane guidelines (15, 20), each trial was objectively accessed across the following criteria: allocation sequence generation, allocation concealment, blinding, complete outcome data reporting, selective outcome reporting, and other apparent biases. Studies with a high or unclear risk of bias on any of these criteria were classified as having a high risk of bias, given that they might exaggerate the intervention effects (21).

Two researchers (Tia Di Biase and Joanne Goodall, Swinburne University, Hawthorn, Australia) independently completed database searching and assessed the suitability of each trial for inclusion. These researchers were blind to the study aim of assessing mortality, which limited bias. Discrepancies were resolved in consultation with the principal study investigators (MPP and HM), who also rechecked each relevant study against the inclusion criteria before independently assessing each trial’s risk of bias and completing data extraction. Discrepancies resulting from this process were resolved according to mutual consensus.

For the purpose of the meta-analysis, we extracted the number of deaths and sample size separately for both the control and MVMM groups. Again, to limit bias, this process was completed once each study had been assessed against the inclusion criteria and after risk of bias assessments were performed. When a trial satisfied all inclusion criteria, but did not report mortality data, the corresponding author of the study was e-mailed and asked for the number of deaths and sample size in each group. Study authors were similarly contacted when the number of deaths or sample size was inadequately reported in the article (*see* Supplemental Table 1 under “Supplemental data” in the online issue). If the requested information was not supplied, the study was excluded from review. When a study had more than one MVMM group, the number of deaths and sample size were summed across the appropriate arms and entered into statistical software as one group (15).

### Data synthesis and analysis

The extracted mortality data were pooled in a meta-analysis with the use of Comprehensive Meta-Analysis (version 2; Biostat Englewood). The following quantitative analyses were decided on a priori: the effect of MVMM supplementation on all-cause mortality, mortality of vascular origin (including stroke and cerebrovascular disease), and mortality due to cancer. With respect to all-cause mortality, subanalyses were performed to examine the association between MVMM treatment and mortality across 1) trials with and without a high risk of bias, 2) primary and secondary prevention trials separately, and 3) trials conducted in high- and low-income countries separately [countries were grouped according to the World Bank Rankings (22)]—a total of 8 possibilities. These subanalyses were not performed for cause-specific mortality, given that the number of trials assessing cause-specific mortality was expected to be limited.

The results were reported as RRs and 95% CIs. Intention-to-treat analyses were implemented with the MVMM and placebo arm sample sizes reflecting the number of participants randomly assigned. Consistent with similar research in this area (12), a continuity correction of  $k = 0.5$ /opposite arm sample size was applied to trials in which no events were reported in one arm (14, 15). For each analysis, heterogeneity between studies was examined by using the Cochrane  $Q$  statistic and Higgins  $I^2$  statistic (23). A fixed-effects model was used when there was no evidence of statistical heterogeneity, and a random-effects model was reported in the presence of statistical heterogeneity [when  $P < 0.10$  for the Cochrane  $Q$  statistic (24)]. For the overall analysis, fixed-effects meta-regression was used to investigate whether event rates (log RRs, 95% CIs) were associated with predefined covariates, including the duration of supplementation, the mean age of the sample, the percentage of withdrawals, and the number of constituents in the

MVMM arm. Meta-regression was performed only for the overall all-cause mortality analysis, because the usefulness of this measure is limited when the number of included trials is small (25). The presence of bias was investigated by using Begg's adjusted rank correlations (26) and Egger's regression tests (27).

**RESULTS**

**Qualitative summary**

A total of 21,390 articles were screened across all databases (Figure 1). There were 655 potentially relevant studies, of which 21 satisfied the inclusion criteria and were included in the review. The total pooled sample was 91,074 people with 8794 deaths.

The characteristics of included studies are shown in Table 1. The average age of the pooled sample was 62 y, and the mean duration of follow-up was 43 mo. The pooled sample was roughly sex-balanced, with males accounting for ~54% of the total sample. Although it was not necessary for inclusion, all included studies were described as placebo-controlled and double-blind. Four studies (28–31) were identified as having either an unclear or high risk of bias across one or more of the bias-risk criteria (see Supplemental Figure 1 under “Supplemental data” in the online issue). All but 5 studies were conducted in Europe or North America (high-income countries), with 3 studies conducted in China (upper-middle-income country) (28, 31, 32) and 1 each in Gambia (low-income country) (33) and Venezuela (upper-middle-income country) (34). All except 9 trials (28, 30, 31, 33–38) reported exclusion criteria related to current or past dietary supplement use. Across trials, supplements contained an average of 14 different constituents (see Supplemental Table 2 under “Supplemental data” in the online issue).

Thirteen studies involved primary prevention, 4 involved secondary prevention of CVD (36–39), 3 involved secondary prevention of cancer (32, 34, 40), and 1 involved secondary prevention of ocular disease (41). Although predominantly a pri-

mary prevention study, the Physicians' Health Study 2 (42) included some people with a history of cancer at baseline. Because mortality data was obtained for these participants separately, the appropriate data from this study was included in both our sub-analyses of primary prevention and secondary prevention of cancer.

**The effects of multivitamins on all-cause mortality**

Across all pooled studies (Figure 2), no significant effect of MVMM supplementation on all-cause mortality was observed (RR: 0.98; 95% CI: 0.94, 1.02). There was little evidence of heterogeneity between studies when the Higgins  $I^2$  (15.72%) and the Cochrane  $Q$  ( $P = 0.25$ ) statistics were used. There was also no evidence of bias among studies (Begg:  $P = 0.74$ ; Egger:  $P = 0.36$ ). Removal of the 4 studies with a high risk of bias (28–31) did not significantly alter either the risk estimate (RR: 0.99; 95% CI: 0.95, 1.04) or the heterogeneity statistics ( $I^2$ : 16.97%;  $P = 0.26$ ). Again, there was no evidence of publication bias (Begg:  $P = 0.84$ ; Egger:  $P = 0.83$ ). In a meta-regression, the log of the risk estimate was not associated with the duration of treatment (logRR: 0.05; 95% CI: -0.06, 0.17), the number of constituents in the MVMM (logRR: 0.02; 95% CI: -0.05, 0.08), the mean age of each cohort (logRR: -0.23; 95% CI: -0.86, 0.41), or the number of dropouts in each trial (logRR: -0.18; 95% CI: -0.38, 0.02).

Across the 13 primary prevention trials (28–31, 33, 35, 41–47), a trend for MVMM supplementation to reduce the risk of all-cause mortality was found (RR: 0.94; 95% CI: 0.89, 1.00;  $n = 60,967$ ). There was little evidence of heterogeneity ( $I^2$ : 7.62%; Cochrane  $Q$  statistic:  $P = 0.37$ ) or publication bias (Begg:  $P = 0.50$ ; Egger:  $P = 0.16$ ).

When the 4 studies that assessed secondary prevention of CVD (36–39) were pooled, no significant effect of MVMM supplementation on all-cause mortality was found (RR: 1.04; 95% CI: 0.98, 1.11;  $n = 22,778$ ). No evidence of heterogeneity ( $I^2$ : 0.00%; Cochrane  $Q$  statistic:  $P = 0.87$ ) or bias (Begg:  $P = 0.73$ ; Egger:  $P = 0.70$ ) was found. Across the 4 studies that assessed the secondary prevention of cancer (32, 34, 40, 42), no significant effect of MVMM supplementation on all-cause mortality was found (RR: 0.94; 95% CI: 0.84, 1.05;  $n = 7032$ ), again with no evidence of heterogeneity ( $I^2$ : 0.00%; Cochrane  $Q$  statistic:  $P = 0.65$ ) or bias (Begg:  $P = 1.00$ ; Egger:  $P = 0.71$ ).

Across the 16 trials conducted in high-income countries, no significant effect of MVMM supplementation on all-cause mortality was found (RR: 0.99; 95% CI: 0.95, 1.04;  $n = 53,913$ ). There was little evidence of heterogeneity ( $I^2$ : 22.17%; Cochrane  $Q$  statistic:  $P = 0.20$ ) or bias (Begg:  $P = 0.56$ ; Egger:  $P = 0.35$ ). We could not examine the association between supplementation and mortality in low-income countries given that only one trial (33) fell into this category.

**The effects of multivitamins on mortality due to cancer, tumors, and malignancy**

Nine studies reported on MVMM supplementation and death due to cancer (28, 32, 35, 36, 39, 42, 45, 47, 48), with a pooled sample of 69,600 and 2620 deaths. Across studies (Figure 3), no effect of multivitamin supplementation on mortality due to cancer was found (RR: 0.96; 95% CI: 0.88, 1.04). Neither heterogeneity ( $I^2$ : 0.00%; Cochrane  $Q$  statistic:  $P = 0.71$ ) nor publication bias (Begg:  $P = 0.75$ ; Egger:  $P = 0.73$ ) was detected.

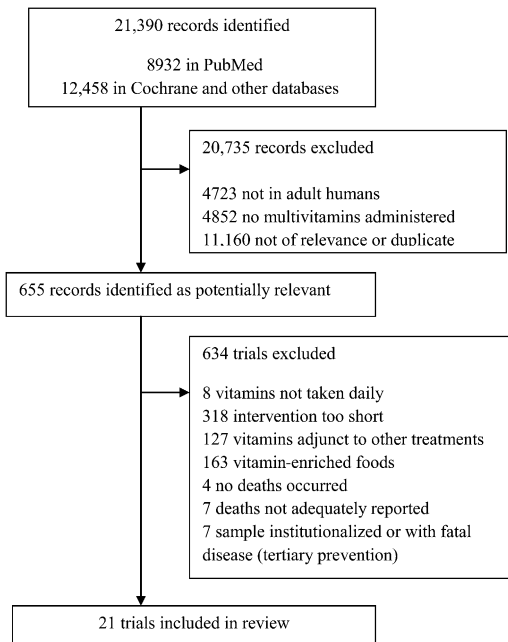


FIGURE 1. Flowchart for the systematic review.

**TABLE 1**  
Characteristics of the included trials<sup>1</sup>

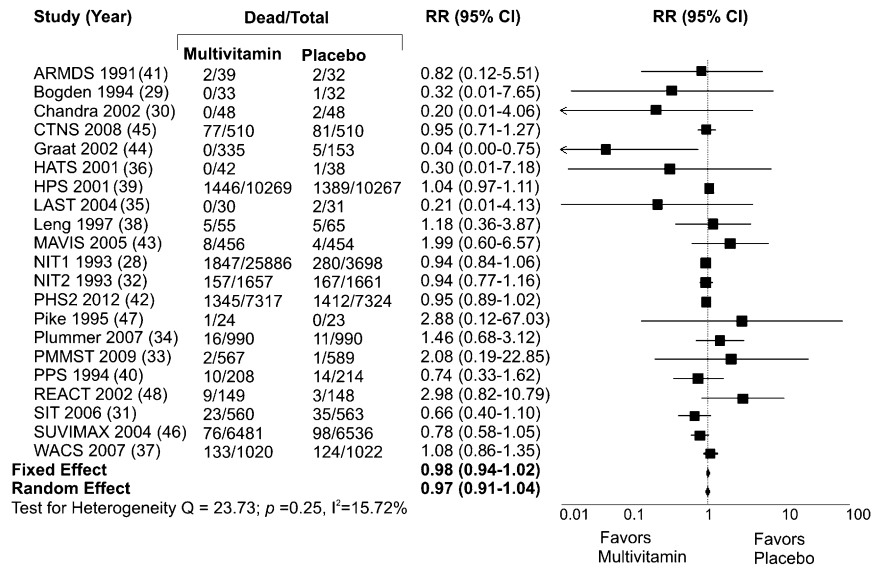
Study name, year, reference	Design	Duration, y	No. of subjects <sup>2</sup>	Prevention type	Geographic location	Participants	Age <sup>3</sup> , y	Male, %	ITT	Dropout rate, %	Bias risk
ARMDS, 1996 (41)	PC, DB, PG	1.5	71	Primary	US	ARMDS, without other ocular disease	72	93	No	17	Low
Bogden, 1994 (29) <sup>4</sup>	PC, DB, PG	1	65	Primary	US	Healthy independently living	59–85	29	No	14	High
Chandra, 1992 (30)	PC, DB, PG	1	96	Primary	Canada	Healthy independently living	66–86	43	Yes	10	High
CTNS, 2008 (45)	PC, DB, PG	1.3	1020	Primary	Italy	No or early cataract, otherwise healthy	55–75	55	Yes	15	Low
Graat, 2002 (44)	PC, DB, FAC	1.3	488	Primary	Netherlands	Healthy independently living	73	50	Yes	16	Low
HATS, 2001 (36)	PC, DB, PG	3	80	Secondary	Canada and US	CHD, low HDL, and normal LDL cholesterol	53	87	Yes	9	Low
HPS, 2002 (39)	PC, DB, FAC	5	20,536	Secondary	UK	High risk of death due to CHD over 5 y, no other prominent medical problems	40–80	75	Yes	NS	Low
LAST, 2004 (35)	PC, DB, PG	1	61	Primary	US	ARMDS, otherwise healthy	75	97	No	16	Low
Leng, 1997 (38)	PC, DB, PC	2	120	Secondary	UK	Intermittent claudication and ankle-brachial pressure index <1	66	68	Yes	38	Low
MAVIS, 2005 (43)	PC, DB, PG	1	910	Primary	UK	Recruited irrespective of chronic disease	72	53	Yes	13	Low
NIT1, 1993(28)	PC, DB FAC	5	29,584	Primary	China	Without debilitating disease and esophageal/stomach cancer	40–69	45	Yes	NS	High
NIT2, 1993 (32)	PC, DB, PG	6	3318	Secondary	China	Esophageal dysplasia, otherwise healthy	40–69	44	Yes	1	Low
PHS2, 2012 (42)	PC, DB, FAC	11.2	14,641	Primary/secondary	US	Male physicians, some with baseline CVD or cancer	64	100	Yes	NS	Low
Pike, 1995 (47)	PC, DB, PG	1	47	Primary	US	Healthy independently living	61–79	28	Yes	26	Low
Plummer, 2007 (34)	PC, DB, PG	3	1980	Secondary	Venezuela	High risk of gastric cancer, otherwise healthy	35–69	48	Yes	32	Low
PMMST, 2009 (33) <sup>4</sup>	PC, DB, PG	1	1156	Primary	Gambia	Women not pregnant, breastfeeding, or anemic	17–45	0	Yes	51	Low
PPS, 1994 (40) <sup>4</sup>	PC, DB, FAC	3.1	422	Secondary	US	Adenoma without additional polyps, otherwise healthy	61	78	No	14	Low
REACT, 2002 (48)	PC, DB, PG	2.8	297	Secondary	US and UK	Minimal cataract, without diabetes or severe renal failure	66	41	Yes	43	Low
SIT, 2006 (31)	PC, DB, FAC	7.3	1123	Primary	China	Without life-threatening illness	35–64	52	Yes	13	High
SUVIMAX, 2004 (46)	PC DB, PG	7.5	13,017	Primary	France	Lack of disease likely to threaten 5-y survival	35–60	39	Yes	13	Low
WACS, 2007 (37)	PC, DB, FAC	9.4	2042	Secondary	US	CVD or ≥3 CVD risk factors	61	0	No	19	Low

<sup>1</sup> ARMDS, age-related macular degeneration; ARMDS, Age-Related Macular Degeneration Study; CHD, coronary heart disease; CTNS, Clinical Trial of Nutritional Supplements and Age-Related Cataract; CVD, cardiovascular disease; DB, double-blind; FAC, factorial design; HATS, HDL-Atherosclerosis Treatment Study; HPS, Heart Protection Study; ITT, intention to treat; LAST, Lutein Antioxidant Supplementation Trial; MAVIS, Mineral And Vitamin Intervention Study; NIT, Nutrition Intervention Trials in Linxian, China; NS, not specified; PC, placebo-controlled; PG, parallel groups; PHS2, Physicians' Health Study 2; PMMST, Periconceptional Micronutrient Supplementation Trial; PPS, Polyp Prevention Study; REACT, Roche European American Cataract Trial; SIT, Shandong Intervention Trial; SUVIMAX, SUpplementation en Vitamines et Minéraux Anti-oxydants; WACS, Women's Antioxidant Cardiovascular Study.

<sup>2</sup> For multivitamin and placebo groups only.

<sup>3</sup> Mean age of sample reported when the range was not specified.

<sup>4</sup> Includes data obtained from the study author on request.



**FIGURE 2.** Meta-analysis of multivitamin-multimineral supplementation on all-cause mortality ( $n = 76,433$ ). “Favors Multivitamin” indicates that multivitamin reduces mortality risk. ARMDS, Age-Related Macular Degeneration Study; CTNS, Clinical Trial of Nutritional Supplements and Age-Related Cataract; HATS, HDL-Atherosclerosis Treatment Study; HPS, Heart Protection Study; LAST, Lutein Antioxidant Supplementation Trial; MAVIS, Mineral And Vitamin Intervention Study; NIT, Nutrition Intervention Trials in Linxian, China; PHS2, Physicians Health Study 2; PMMST, Periconceptual Multimicronutrient Supplementation Trial; PPS, Polyp Prevention Study; REACT, Roche European American Cataract Trial; SIT, Shandong Intervention Trial; SUVIMAX, Supplémentation en Vitamines et Minéraux Anti-oxydants; WACS, Women’s Antioxydant Cardiovascular Study.

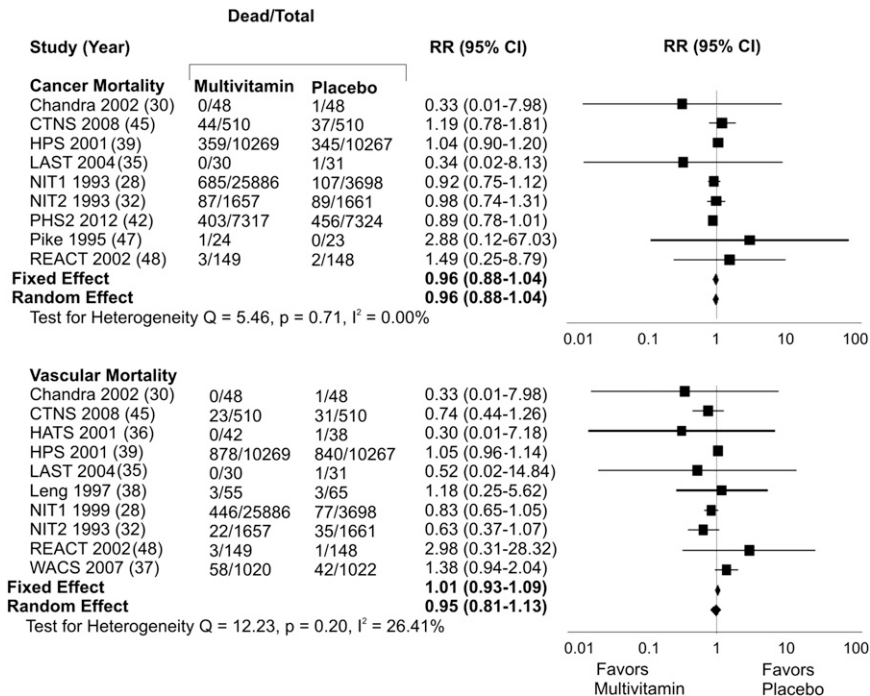
**The effects of multivitamins on vascular mortality**

Ten studies (28, 30, 32, 35–39, 45, 48) reported on the effects of MVMM supplementation and mortality of vascular causes. The total pooled sample was 57,154 with 2465 reported deaths. Across studies (Figure 3), no effect of MVMM supplementation on vascular mortality was found (RR: 1.01; 95% CI: 0.93–1.09). There was little evidence of heterogeneity between studies ( $I^2$ :

26.41%; Cochrane  $Q$  statistic:  $P = 0.20$ ) and no publication bias was detected (Begg  $P = 1.00$ , Egger  $P = 0.36$ ).

**Post hoc analysis**

A post hoc analysis was conducted to determine whether there was a differential effect of MVMM supplements containing only



**FIGURE 3.** Meta-analyses of multivitamin-multimineral supplementation on cancer- ( $n = 54,959$ ) and vascular-related ( $n = 57,154$ ) mortality. “Favors Multivitamin” indicates that multivitamin reduces mortality risk. CTNS, Clinical Trial of Nutritional Supplements and Age-Related Cataract; HATS, HDL-Atherosclerosis Treatment Study; HPS, Heart Protection Study; LAST, Lutein Antioxidant Supplementation Trial; NIT, Nutrition Intervention Trials in Linxian, China; PHS, Physicians Health Study; REACT, Roche European American Cataract Trial; WACS, Women’s Antioxydant Cardiovascular Study.

antioxidants and supplements containing antioxidants combined with a wider range of ingredients on all-cause mortality (*see* Supplemental Table 2 under “Supplemental data” in the online issue). No influence of either class of supplements on all-cause mortality was observed (*see* Supplemental Results under “Supplemental data” in the online issue).

## DISCUSSION

Due to the increasing popularity of MVMM use (3), it is important to ascertain any potential harms or benefits associated with chronic intake. Findings from this systematic review and meta-analysis of 21 RCTs, comprising >91,000 individuals, indicated no influence of MVMM supplementation on all-cause mortality. This risk estimate was not influenced by trial bias. Subanalyses revealed a nonsignificant trend for MVMM treatment to reduce the risk of all-cause mortality when used for primary prevention. MVMM supplementation had no effect on the risk of mortality from vascular causes or cancer.

Highly publicized reports from several recent epidemiologic studies (7, 49) have led to considerable concern regarding potential harm associated with MVMM use. The current findings suggest that this level of alarm may be unwarranted. The Iowa Women’s Health Study (7) reported an increased risk of mortality, over a period of ~19 y, for several individual vitamins and minerals. A smaller risk was reported for multivitamins. Other epidemiologic studies provided no clarification on this issue. The Multiethnic Cohort Study (9) indicated no relation between multivitamin use and total mortality in residents of 2 US states, whereas the larger, US-wide Cancer Prevention Study II (10) identified an increased mortality risk in male smokers only. Multiplicity can be an issue in epidemiologic trials and lead to erroneous conclusions (50). Trials that have examined the mortality risk of multiple vitamins, across multiple participant groups (7, 10), may have a greater potential of false-positive findings. Observational studies provide only a limited inference of causality but tend to have the advantage of longer duration. The current review included trials of up to 11 y in length, and meta-regression suggested that risk estimates were not influenced by the duration of multivitamin treatment. Because the average follow-up period was ~3.6 y, longer-duration RCTs may be required to fully assess the long-term safety and efficacy of multivitamin intake.

A previous systematic review and meta-analysis of RCTs (12, 51) indicated that  $\beta$ -carotene, vitamin A, and vitamin E, individually or combined with other antioxidant supplements, significantly increased the risk of all-cause mortality. These results are contrary to those of the current study, which focused on multivitamin supplementation. It is likely that the risks associated with vitamin use are associated with both the dosage and frequency of use. There are some concerns that high-dose vitamin E supplements may be harmful (52), and excessive intake of vitamin A can produce adverse side effects (53). Concentrations of vitamins A and E were substantially higher and were administered at potentially excessive levels in some of the trials examined by this previous review (12, 51, 54, 55), which were not included in the current investigation. Therefore, taking a single daily multivitamin may be safer than taking excessive amounts of single vitamins or antioxidants. In the community, MVMM use is more prevalent than use of individual high-dose

supplements (2). Subsequently, our findings may have greater applicability to the general population as compared with previous meta-analyses (51, 52), which have included high-dose individual vitamins or those isolated from formulations.

MVMM use is particularly popular in developed countries (8), where nutritional deficiency is less prevalent than in developing countries (56), which means that individuals are more likely to meet their daily vitamin requirements from dietary sources. This is an important issue because the safety of MVMM use may be influenced by the level of nutrient intake from dietary sources and concomitant supplement use (57). As most commercially available MVMMs approximate the recommended daily value, excessive nutrient intake may be more likely in those who use multiple dietary supplements than in those who take a daily MVMM (8). Reducing the likelihood of polysupplementation, most studies we reviewed either excluded participants who were regular vitamin users at the time of enrollment or requested that participants discontinue relevant supplementation for the trial duration. Therefore, the safety of MVMMs identified in this review may be less applicable to those who supplement with a multivitamin in addition to individual vitamins.

Although the current meta-analysis suggests that MVMM can be used safely, the available evidence does not suggest that MVMMs protect against all-cause mortality, mortality due to vascular disease, or mortality due to cancer. Although a trend was found for MVMM supplementation to reduce the risk of all-cause mortality when used for primary prevention, this result did not reach statistical significance. These findings correspond to a past systematic review of RCTs, which did not support the use of MVMMs for the primary prevention of cancer or CVD (18). The greater frequency of multivitamin use has also been related to longer telomere length (58). Telomeres are the protein-DNA structures at the ends of chromosomes and have been implicated in human aging and longevity (59). However, our results suggest that these potential benefits of multivitamin use do not necessarily translate to increased longevity, or rather, reduced mortality.

The strengths of the current study include the rigorous approach to article searching, the assessment of trial bias according to Cochrane guidelines, the analysis of cause-specific in addition to all-cause mortality, and the large number of trials and participants for which data were available. Furthermore, all analyses were defined a priori, and all results were free from statistical heterogeneity and publication bias. Several caveats of this meta-analysis existed. Although this review does not indicate a protective role of MVMM treatment against mortality, it does not exclude the possibility of other health benefits of supplementation. A further limitation was that information on cause-specific mortality was not available for all of the trials included in our review. We identified 7 trials that were missing the appropriate mortality data, and these studies could not be included in our review (*see* Supplemental Table 1 under “Supplemental data” in the online issue). Nevertheless, the current analyses are still based on a substantial number of trials and participants. We were able to limit publication bias by obtaining mortality data through personal communication for 8 studies (*see* Supplemental Table 1 under “Supplemental data” in the online issue). A further limitation was the variation in the multivitamins used by the reviewed studies, in terms of constituents and dosages. This lack of equivalency is widespread in complementary medicine because products vary in quality, dosage, and efficacy. Our review focused on MVMM supplements administered in isolation,

without focusing on the addition of other concomitant therapies or medications. It would be interesting to examine whether multivitamins have additive effects with other medications or supplements.

In conclusion, current evidence on MVMM use and mortality has generally been sought from observational studies. By performing a meta-analysis of RCTs, the current study provides the highest level of evidence to indicate that MVMM supplementation has no significant effect on the risk of all-cause mortality, mortality of vascular etiology, or mortality due to cancer. MVMMs are used for the purpose of supplementing the diet and maintaining general health (5) and tend to be consumed over longer time periods than are individual vitamin constituents (2). In response to these indications and increasing popularity, ongoing scientific research into the effects of multivitamin use on health, in the context of primary prevention and habitual dietary patterns, is needed.

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