

SPECIAL FOCUS ISSUE: CARDIOVASCULAR HEALTH PROMOTION

THE PRESENT AND FUTURE: JACC STATE-OF-THE-ART REVIEW

Supplemental Vitamins and Minerals for CVD Prevention and Treatment



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ABSTRACT

The authors identified individual randomized controlled trials from previous meta-analyses and additional searches, and then performed meta-analyses on cardiovascular disease outcomes and all-cause mortality. The authors assessed publications from 2012, both before and including the U.S. Preventive Service Task Force review. Their systematic reviews and meta-analyses showed generally moderate- or low-quality evidence for preventive benefits (folic acid for total cardiovascular disease, folic acid and B-vitamins for stroke), no effect (multivitamins, vitamins C, D, β -carotene, calcium, and selenium), or increased risk (antioxidant mixtures and niacin [with a statin] for all-cause mortality). Conclusive evidence for the benefit of any supplement across all dietary backgrounds (including deficiency and sufficiency) was not demonstrated; therefore, any benefits seen must be balanced against possible risks. (J Am Coll Cardiol 2018;71:2570–84)
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Treatment and prevention of micronutrient deficiencies with vitamins and minerals in the last two-and-a-half centuries are among the most dramatic achievements in the history of nutritional science. The treatment of scurvy with citrus fruit (vitamin C) by the British Naval Surgeon James Lind in 1747 was, perhaps, the first clinical trial ever conducted (1), in which 12 sailors who had scurvy were (presumably randomly) selected to receive 1 of 6 treatments (2 sailors) per treatment. However, interest in micronutrients has shifted recently from prevention of classic deficiency states to prevention of possible



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subclinical deficiencies and promotion of overall health and longevity using supplemental vitamins and minerals (supplement use). Here, the data are less clear, but supplement use is widespread. Using the National Health and Nutrition Examination Survey data (1999 to 2012) on 37,958 adults, it was estimated that supplement use was high in 2012, with up to 52% of the population taking supplements. Multivitamins were taken by 31% of the population, vitamin D by 19%, calcium by 14%, and vitamin C by 12% (2). In Europe during this period, the European Prospective Investigation into Cancer and Nutrition (EPIC) data on 36,034 men and women indicated a wide range of supplement use, with a strong north-south gradient that was highest in the north (e.g., Denmark: 51% men, 65.8% women) and lowest in the south (e.g., Greece: 2.0% men, 6.7% women), and with higher supplement use by women (3). Despite high supplement use by the general public, there is no general agreement on whether individual vitamins and minerals or their combinations should be taken as supplements for cardiovascular disease (CVD) prevention or treatment. Only the Canadian Cancer Society recommends a supplement (1,000 IU vitamin D to be taken in fall and winter) (4). What is generally recommended internationally is consumption of a good diet as part of a healthy lifestyle. The recent science-based report of the U.S. Dietary Guidelines Advisory Committee, also

concerned with CVD risk reduction, recommended 3 dietary patterns: 1) a healthy American diet low in saturated fat, trans fat, and red meat, but high in fruit and vegetables; 2) a Mediterranean diet; and 3) a vegetarian diet (5). These diets, with their accompanying recommendations, continue the move toward more plant-based diets that are relatively rich in vitamins and minerals, which liberally satisfies requirements (Dietary Reference Intakes) but which are still below the tolerable upper levels of intake of the recommended range in which adverse effects may be seen. Thus, for the general public, the focus has been on meeting requirements through diet, rather than supplements.

Therefore, we reviewed the evidence for supplement use over the last 4 years since the publication of the evidence (6) and guidelines (7) for supplement use of the U.S. Preventive Services Task Force (USPSTF).

METHODS

We conducted a systematic review and meta-analysis of existing systematic reviews and meta-analyses and single randomized controlled trials (RCTs) published in English from January 2012 (1 year before the census, when this field was reviewed comprehensively by the

ABBREVIATIONS AND ACRONYMS

CI	= confidence interval
CVD	= cardiovascular disease
GRADE	= Grading of Recommendations Assessment, Development, and Evaluation
MI	= myocardial infarction
NNT	= number needed to treat
RCT	= randomized controlled trial
RR	= risk ratio
USPSTF	= U.S. Preventive Services Task Force

Canada, Pulse Canada, Kellogg's Company, Quaker Oats, Procter & Gamble Technical Centre Ltd., Bayer Consumer Care, Pepsi/Quaker, International Nut & Dried Fruit (INC), Soy Foods Association of North America, the Coca-Cola Company (investigator-initiated, unrestricted grant), Solae, Haine Celestial, the Sanitarium Company, Orafit, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, the Canola and Flax Councils of Canada, the Calorie Control Council, the CIHR, the Canada Foundation for Innovation, and the Ontario Research Fund; has received in-kind supplies for trials as a research support from the Almond Board of California, Walnut Council of California, American Peanut Council, Barilla, Unilever, Unico, Primo, Loblaw Companies, Quaker (Pepsico), Pristine Gourmet, Bunge Limited, Kellogg Canada, and WhiteWave Foods; has been on the speakers panel, served on the scientific advisory board, and/or received travel support and/or honoraria from the Almond Board of California, Canadian Agriculture Policy Institute, Loblaw Companies Ltd., the Griffin Hospital (for the development of the NuVal scoring system), the Coca-Cola Company, EPICURE, Danone, Diet Quality Photo Navigation, Better Therapeutics (FareWell), Verwywell, True Health Initiative, Institute of Food Technologists, Saskatchewan Pulse Growers, Sanitarium Company, Orafit, the American Peanut Council, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, Herbalife International, Pacific Health Laboratories, Nutritional Fundamental for Health, Barilla, Metagenics, Bayer Consumer Care, Unilever Canada and Netherlands, Solae, Kellogg, Quaker Oats, Procter & Gamble, the Coca-Cola Company, the Griffin Hospital, Abbott Laboratories, the Canola Council of Canada, Dean Foods, the California Strawberry Commission, Haine Celestial, PepsiCo, the Alpro Foundation, Pioneer Hi-Bred International, DuPont Nutrition and Health, Spherix Consulting and WhiteWave Foods, the Advanced Foods and Material Network, the Canola and Flax Councils of Canada, the Nutritional Fundamentals for Health, Agriculture and Agri-Food Canada, the Canadian Agri-Food Policy Institute, Pulse Canada, the Saskatchewan Pulse Growers, the Soy Foods Association of North America, the Nutrition Foundation of Italy, Nutra-Source Diagnostics, the McDougall Program, the Toronto Knowledge Translation Group (St. Michael's Hospital), the Canadian College of Naturopathic Medicine, The Hospital for Sick Children, the Canadian Nutrition Society (CNS), the American Society of Nutrition (ASN), Arizona State University, Paolo Sorbini Foundation, and the Institute of Nutrition, Metabolism and Diabetes; has received an honorarium from the United States Department of Agriculture to present the 2013 W.O. Atwater Memorial Lecture; has received funding and travel support from the Canadian Society of Endocrinology and Metabolism to produce mini-cases for the Canadian Diabetes Association; is a member of the International Carbohydrate Quality Consortium (ICQC); his wife is a director and partner of Glycemic Index Laboratories, Inc.; and his sister received funding through a grant from the St. Michael's Hospital Foundation to develop a cookbook for one of his studies. Dr. Spence is an officer of Vascularis, Inc.; and has received lecture fee from Bristol-Myers Squibb. Dr. Kendall has received grants or research support from the Advanced Food Materials Network, Agriculture and Agri-Foods Canada, Almond Board of California, American Pistachio Growers, Barilla, Calorie Control Council, CIHR, Canola Council of Canada, International Nut and Dried Fruit

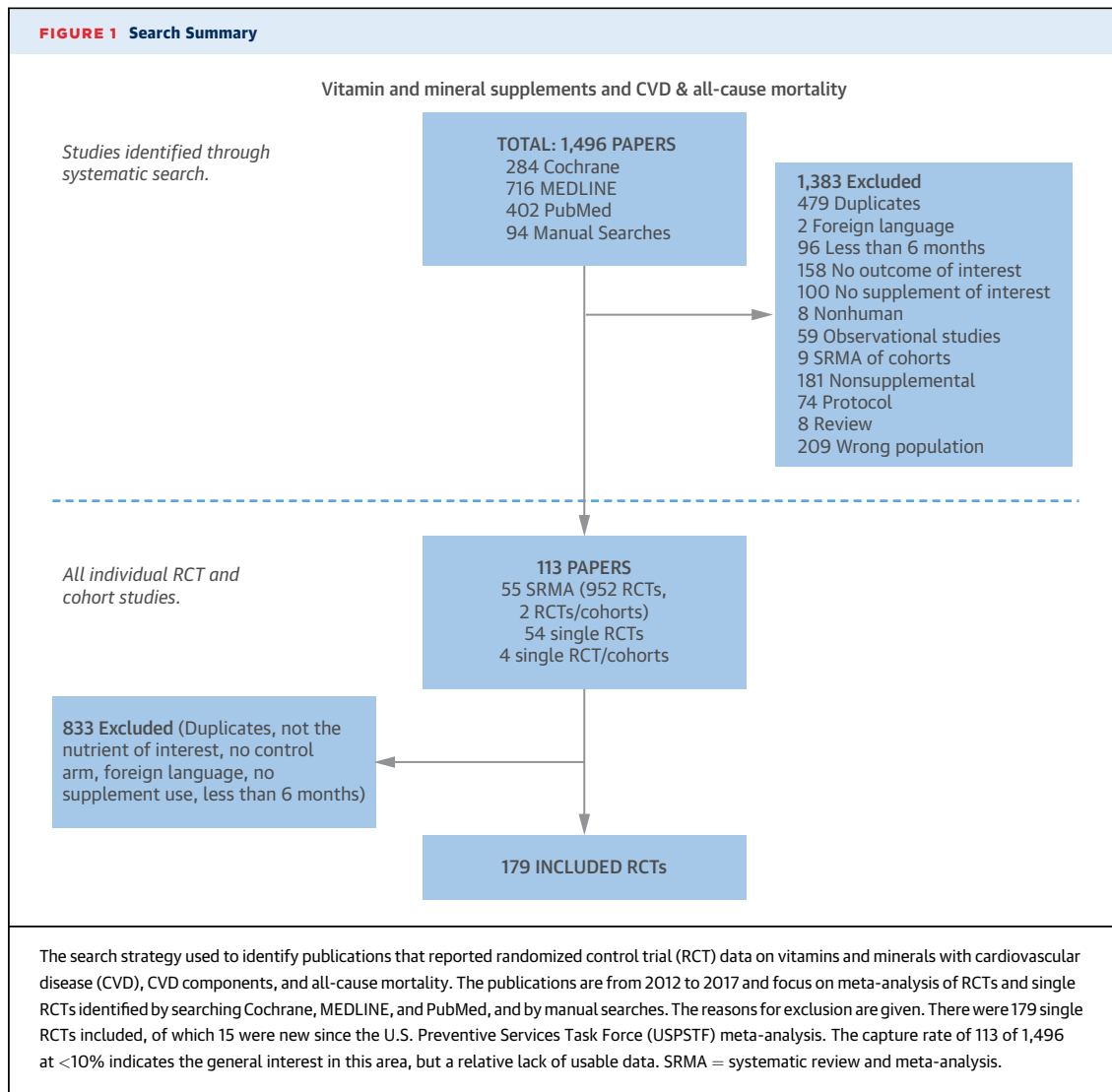
USPSTF) through October 2017 and including the studies reviewed by the USPSTF (6,7). We performed a search of published studies in the Cochrane Library, MEDLINE, and PubMed, and used the search terms: “dietary supplements or supplement*” and “cardiovascular disease or myocardial infarction or stroke or cardiovascular death or mortality or all-cause mortality or death or cancer death or cancer mortality.” Specific searches were conducted for individual supplements of the vitamins and minerals in the USPSTF report of 2013 for CVD outcomes and total mortality. The search was limited to meta-analyses, RCTs, and observational studies (data not reported).

Where ≥ 2 meta-analyses with forest plots on the same topic were identified, we identified the unique studies and excluded duplicates, studies that were not relevant, and studies that did not provide data. Full paper review and data extraction were conducted by 2 independent investigators, with all disagreements reconciled through consensus. The extracted data for RCTs included the number of cases and total participants per population for the intervention or exposed group, and also for the control group or nonexposed group. Data were analyzed using Review Manager (RevMan) version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark), and publication bias analysis was conducted using STATA software, version 13.0 (StataCorp, College

Station, Texas). To obtain summary estimates, data were pooled using the Mantel-Haenszel method, with data presented only for random effects models. Heterogeneity was assessed using the Cochran Q statistic at $p < 0.1$ and quantified by the I^2 statistic. An I^2 value $\geq 50\%$ indicated substantial heterogeneity (8). Publication bias was investigated by visual inspection of funnel plots and quantitative assessment using Begg’s and Egger’s tests, in which $p < 0.05$ was considered evidence of small study effects (9). If < 10 trials were available in a meta-analysis, publication bias analysis was not conducted due to insufficient power. The number needed to treat (NNT) and the number needed to harm (NNH) were calculated by the inverse of the absolute risk reduction (ARR) ($NNT = 1/ARR$, $NNH = 1/ARR$). The ARR equals control cases/control total minus experimental cases/experimental total (10).

VITAMINS AND MINERALS ASSESSED. Where both supplements and dietary intakes of nutrients in foods were combined as total intakes, data were not used unless supplement data were also presented separately. We assessed those supplements previously reported on by the USPSTF: vitamins A, B₁, B₂, B₃ (niacin), B₆, B₉ (folic acid), C, D, and E, as well as β -carotene, calcium, iron, zinc, magnesium, and selenium. The term multivitamin has been used to denote the use of supplements that include most vitamins and minerals

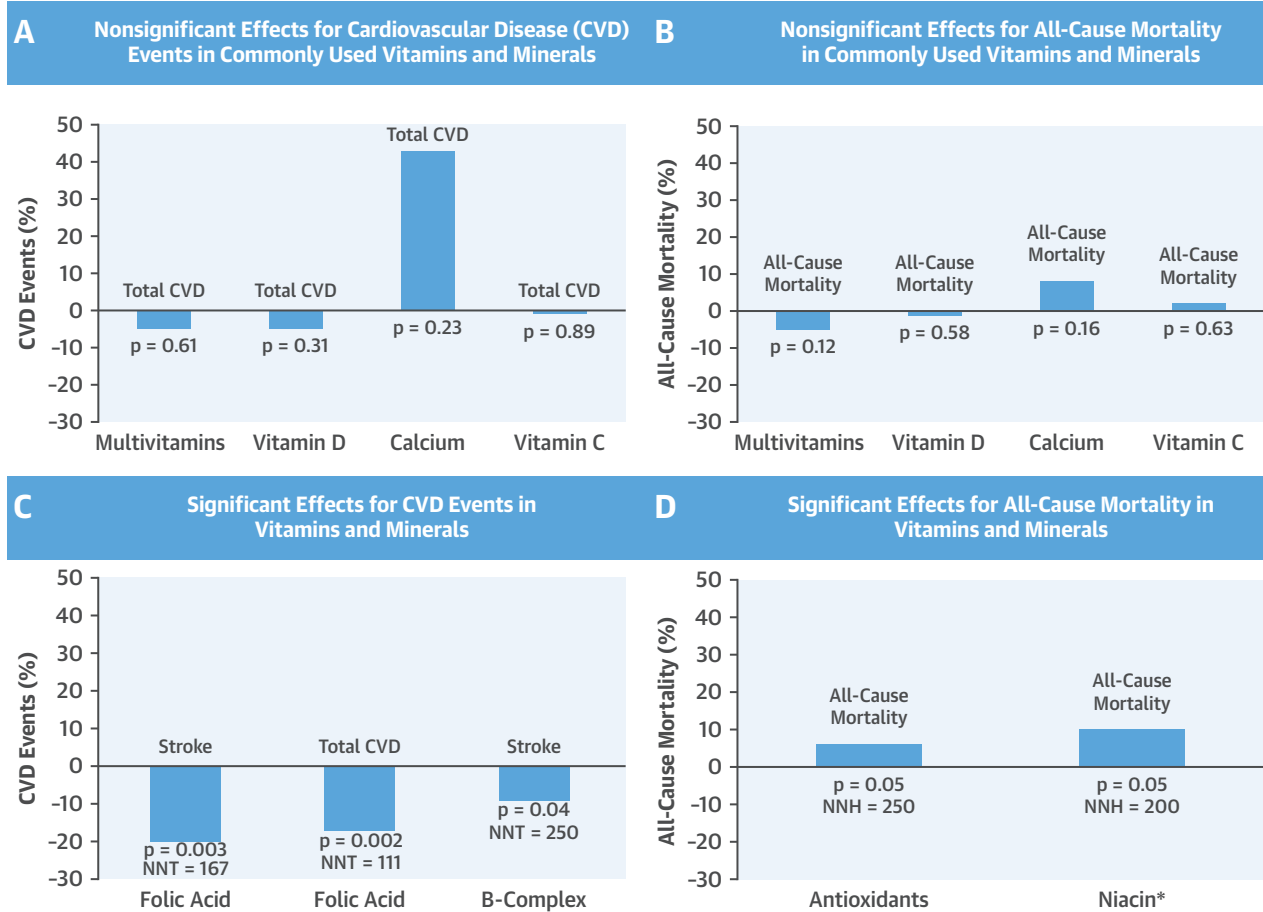
Council, International Tree Nut Council Research and Education Foundation, Loblaw Brands Ltd., Pulse Canada, Saskatchewan Pulse Growers, and Unilever; has received in-kind research support from the Almond Board of California, American Peanut Council, Barilla, California Walnut Commission, Kellogg Canada, Loblaw Companies, Quaker (Pepsico), Primo, Unico, Unilever, and WhiteWave Foods; has received travel support and/or honoraria from the American Peanut Council, American Pistachio Growers, Barilla, California Walnut Commission, Canola Council of Canada, General Mills, International Nut and Dried Fruit Council, International Pasta Organization, Loblaw Brands Ltd., Nutrition Foundation of Italy, Oldways Preservation Trust, Paramount Farms, Peanut Institute, Pulse Canada, Sabra Dipping Co., Saskatchewan Pulse Growers, Sun-Maid, Tate & Lyle, Unilever, and White Wave Foods; has served on the scientific advisory board for the International Tree Nut Council, International Pasta Organization, McCormick Science Institute, Oldways Preservation Trust, Paramount Farms, and Pulse Canada; and is a member of the International Carbohydrate Quality Consortium (ICQC), an executive board member of the Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD), is on the Clinical Practice Guidelines Expert Committee for Nutrition Therapy of the EASD, and is a director of the Toronto 3D Knowledge Synthesis and Clinical Trials Foundation. Dr. Sievenpiper has received research support from the CIHR, Diabetes Canada, PSI Foundation, Banting and Best Diabetes Centre (BBDC), CNS, ASN, Calorie Control Council, INC, National Dried Fruit Trade Association, The Tate and Lyle Nutritional Research Fund at the University of Toronto, and the Glycemic Control and Cardiovascular Disease in Type 2 Diabetes Fund at the University of Toronto (a fund established by the Alberta Pulse Growers); has received in-kind research support from the Almond Board of California, California Walnut Commission, American Peanut Council, Barilla, Unilever, Unico, Primo, Loblaw Companies, Quaker (Pepsico), Kellogg Canada, and WhiteWave Foods; has received travel support, speaker fees, and/or honoraria from Diabetes Canada, CNS, Mott’s LLP, Dairy Farmers of Canada, Sprim Brasil, WhiteWave Foods, Rippe Lifestyle, mdBriefcase, Alberta Milk, FoodMinds LLC, Memac Ogilvy & Mather LLC, PepsiCo, The Ginger Network LLC, International Sweeteners Association, Nestlé Nutrition Institute, Pulse Canada, Canadian Society for Endocrinology and Metabolism, Barilla Centre for Food and Nutrition Foundation, and the GI Foundation; has ad hoc consulting arrangements with Winston & Strawn LLP, Perkins Coie LLP, and Tate & Lyle; is a member of the European Fruit Juice Association Scientific Expert Panel; is a member of the Clinical Practice Guidelines Expert Committees of Diabetes Canada, EASD, Canadian Cardiovascular Society, and the Canadian Obesity Network; serves as an unpaid scientific advisor for the Food, Nutrition, and Safety Program and the Technical Committee on Carbohydrates of the International Life Science Institute North America; is a member of the ICQC, Executive Board Member of the DNSG of the EASD, and Director of the Toronto 3D Knowledge Synthesis and Clinical Trials Foundation; and his wife is an employee of Unilever Canada. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.



(e.g., the brand, Centrum, Pfizer Inc., New York, New York), rather than a select few. In addition, we included B-complex vitamins (a combination of ≥ 2 of the following: B₆, B₉ [folic acid], and B₁₂) and antioxidant mixtures (a combination of ≥ 2 of the following: vitamins A, C, E, β -carotene, selenium, zinc) as composite entities, because there were >10 RCTs with all-cause mortality data for both types of supplements. Summary plots were also undertaken as summaries of pooled effect estimates to include all cardiovascular outcomes, and cumulative plots were undertaken to illustrate what was already significant or had become significant since the USPSTF 2013 assessment.

RISK OF BIAS. The Cochrane Risk of Bias Tool, which is based on randomization, allocation concealment, blinding, completeness of follow-up, and intention-to-treat was used to assess eligible RCTs (11).

GRADING OF THE EVIDENCE. The quality and strength of the evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool (12-24). Using the GRADE tool, evidence was graded as high-quality, moderate-quality, low-quality, or very low-quality evidence. By default, RCTs were graded as high-quality evidence. Criteria used to downgrade evidence included: study limitations (as assessed by the Cochrane Risk of Bias Tool), inconsistency (substantial) unexplained by interstudy heterogeneity, $I^2 > 50\%$, and $p < 0.10$; indirectness (presence of factors that limited the generalizability of the results); imprecision (the 95% confidence interval [CI] for effect estimates crossed a minimally important difference of 5% [risk ratio (RR): 0.95 to 1.05] from the line of unity); and publication bias (significant evidence of small study effects).

CENTRAL ILLUSTRATION Supplemental Vitamins and Minerals: Micronutrient Risks and Benefits

Jenkins, D.J.A. et al. *J Am Coll Cardiol.* 2018;71(22):2570-84.

(A and B) Effects of commonly used vitamins and minerals and (C and D) vitamins with significant effects derived from summary plot estimates of risk ratios expressed as percentages. Popular supplements were without demonstrable effects on cardiovascular disease (CVD) or all-cause mortality. Both folic acid and B-vitamins showed benefits for stroke, whereas antioxidants and niacin showed a marginally significant increase in all-cause mortality. These data highlight the lack of effect of popular supplements on CVD and all-cause mortality but demonstrate potential benefits of folic acid supplementation for stroke. *Slow-release niacin with background statins. NNH = number needed to harm; NNT = number needed to treat.

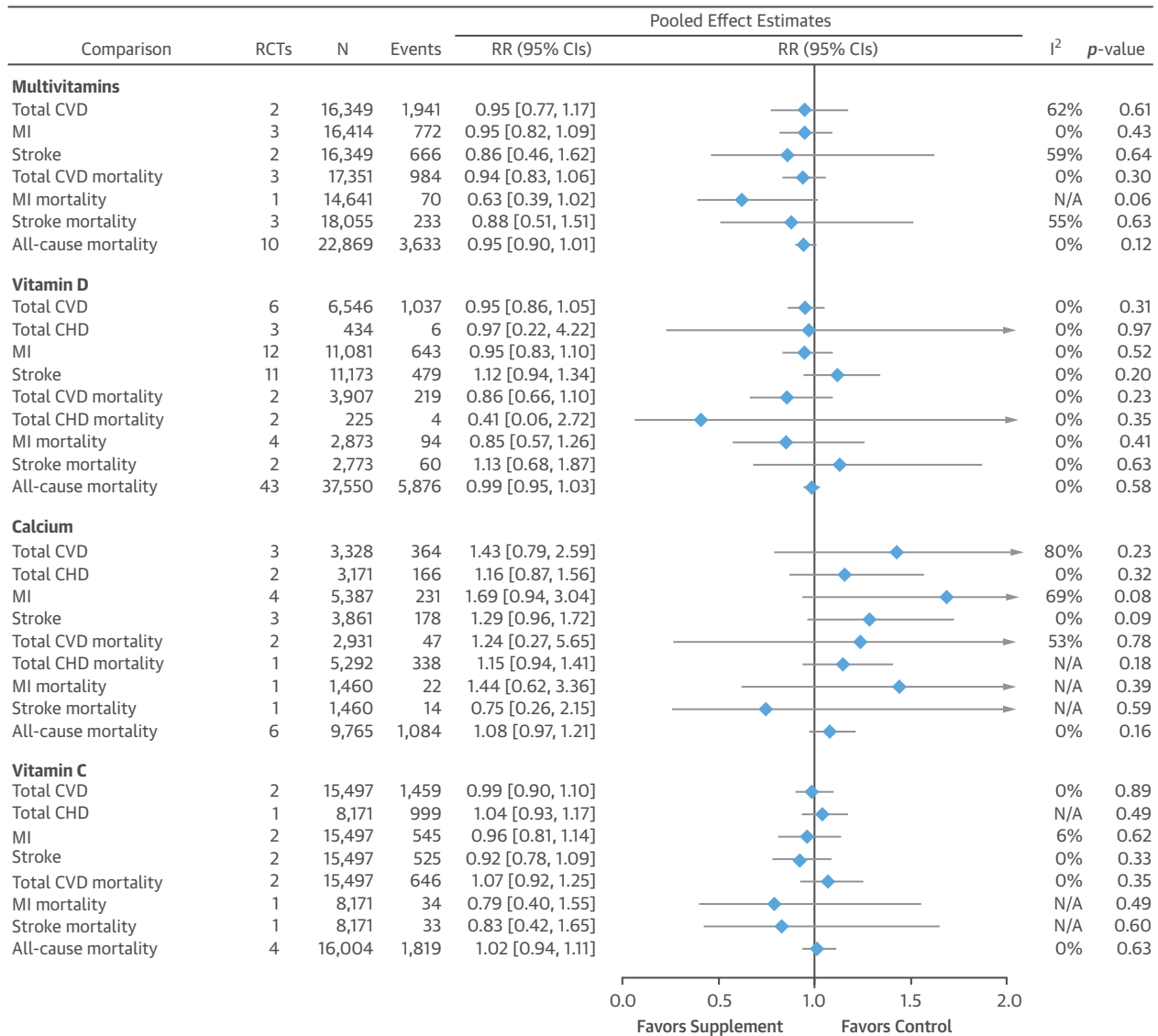
Attention was drawn to outcomes of meta-analyses that showed significance with moderate- to high-quality evidence (with >1 RCT). In this way, we reduced the risk of type 1 errors in the multiple comparison undertaken and avoided the use of corrections, such as the Bonferroni correction, which might have been too conservative (25).

RESULTS

Assessment of the meta-analyses and single studies of RCTs provided 179 individual studies, 15 of which were published after the USPSTF assessment (6,7). A

flow diagram is presented in [Figure 1](#) (26). Study characteristics and the Cochrane Risk of Bias were carried at each trial, and GRADE assessments were made on all meta-analyses ([Online Appendix](#)). Data are provided for the 4 common supplements taken (multivitamins, vitamin D, calcium, and vitamin C) and also for those that were significant for any of the following: all-cause mortality, CVD mortality, and total CVD risk or related outcomes (e.g., myocardial infarction [MI], stroke), provided that GRADE was more than low-quality evidence, and that >1 RCT was available for assessment ([Central Illustration](#)).

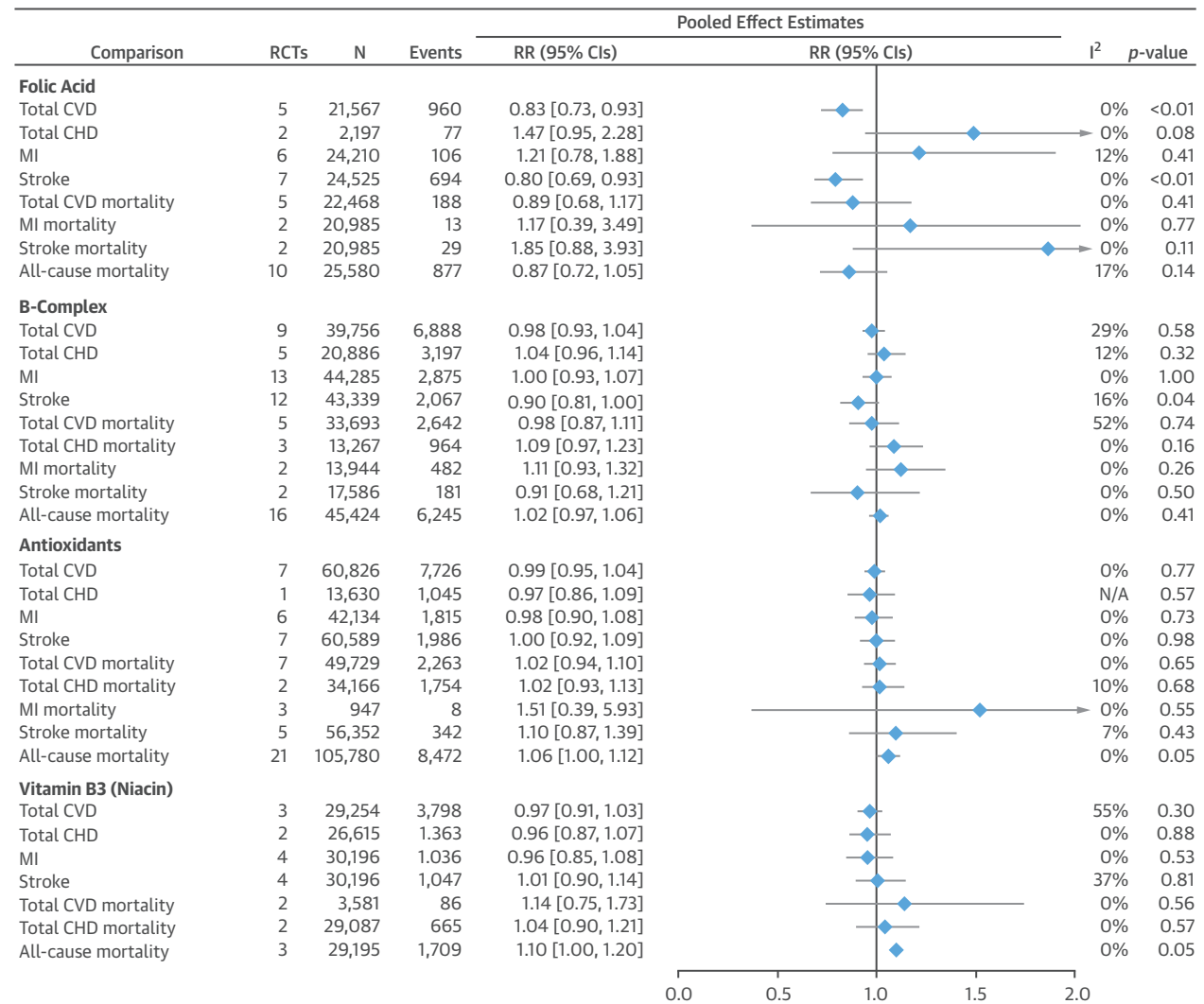
FIGURE 2 Summary Plots of Commonly Used Vitamins and Minerals



Summary data showing the risk ratios derived from meta-analyses of RCTs of the 4 most commonly consumed vitamins and mineral supplements (multivitamins, vitamin D, calcium, and vitamin C) on the components of CVD and all-cause mortality. Of note, none of these popular supplements had an effect on CVD or all-cause mortality. CHD = coronary heart disease; CI = confidence interval; MI = myocardial infarction; RR = risk ratio; other abbreviations as in Figure 1.

Of the 4 most commonly used supplements (multivitamins, vitamin D, calcium, and vitamin C), none had a significant effect on cardiovascular outcomes. The summary plots are shown in Figure 2. Furthermore, none had an effect on all-cause mortality (Figure 2). The forest plot for vitamin D, the most studied nutrient, with 43 RCTs, illustrates the lack of harm or benefit, with 2,908 deaths in 18,719 test subjects and 2,968 deaths in 18,831 control subjects. The point

estimates were divided evenly in favor of vitamin D (16 trials) and in favor of control treatment (17 trials), with 10 trials on the unity line. The overall RR was 0.99 (95% CI: 0.95 to 1.03; p = 0.58), with no heterogeneity (I² = 0), high-quality evidence, and convincingly demonstrated a null effect. Nutrients with significant effects included folic acid and B-complex vitamins for stroke reduction, and niacin and antioxidants, which increased all-cause mortality (Figure 3).

FIGURE 3 Summary Plots of Vitamins and Minerals With Significant Effects

Summary data derived from forest plot meta-analyses of RCTs that demonstrate positive effects of folic acid and B-vitamin supplements (of which folic acid is a component) on stroke and marginally significant adverse effects of antioxidants on stroke and niacin and all-cause mortality. Folic acid and stroke prevention (especially in areas without folic acid fortification) is one of the most conclusive findings in this area over the last 6 years. Abbreviations as in [Figures 1 and 2](#).

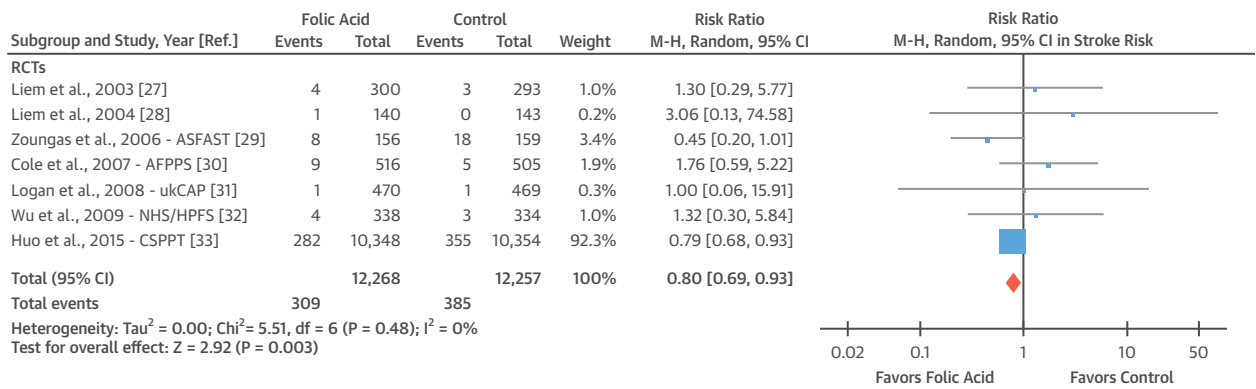
Folic acid in 2 of 7 RCTs reduced stroke risks (RR: 0.80; $p = 0.003$) ([Figure 4](#)) (27-33), with no heterogeneity and moderate quality evidence. The total meta-analysis of the 7 studies showed a benefit for folic acid driven by the CSPPT (China Stroke Primary Prevention Trial) study. CVD was also reduced in the meta-analysis of 5 trials (RR: 0.83; $p = 0.002$) ([Figure 5](#)) (28,29,33-35).

B-complex vitamins reduced the risk of stroke in 9 of 12 studies in the meta-analysis of 12 RCTs (RR: 0.90; $p = 0.04$), with no heterogeneity ($I^2 = 16%$; $p = 0.28$), and moderate-quality evidence ([Figure 6](#)) (36-47).

Niacin (nicotinic acid) or vitamin B₃, taken at pharmacological doses (1 to 3 g/day) in 3 RCTs, and when assessed against a background in which a statin was taken in both the test and control groups (all with extended-release niacin), was associated with increased all-cause mortality by 10% ($p = 0.05$), with no heterogeneity and moderate-quality evidence ([Figure 7](#)) (48-51).

Antioxidant mixtures had no effect on CVD outcomes, but resulted in an increase in all-cause mortality in the 21 RCT meta-analysis ([Figure 8](#)) (52-72), with a small but significant increase in RRs (1.06;

FIGURE 4 Forest Plot of Folic Acid Supplementation and Stroke Risk



The **diamond** represents the pooled risk estimate. Interstudy heterogeneity was tested using the Cochran Q statistic (chi-square) at a significance level of $p < 0.10$ and quantified by the I^2 statistic. The results show a RR of 0.80 in favor of folic acid. This 20% reduction in stroke risk was driven by the highly influential Chinese folic acid supplementation study, made in a community without folic acid fortification, but is the major supplement finding of the last 6 years. The number needed to treat (NNT) for folic acid supplementation and stroke risk is 167. df = degree of freedom; M-H = Mantel-Haenszel; other abbreviations as in [Figure 2](#).

$p = 0.05$), no heterogeneity, and with moderate-quality evidence for the RCTs. Studies containing selenium were removed from the meta-analysis of antioxidants due to the high percentage of these studies on the left side of the unity line versus the right side of the unity line in the antioxidant forest plot (83% vs. 7%) compared with the other components of antioxidant mixtures ([Figure 9](#)). Removal of the selenium studies resulted in a significant increase in all-cause mortality (RR: 1.09; 95% CI: 1.04 to 1.13; $p = 0.0002$; $I^2 = 0\%$) ([Figure 10](#)) (52,53,56-58,60-68,72).

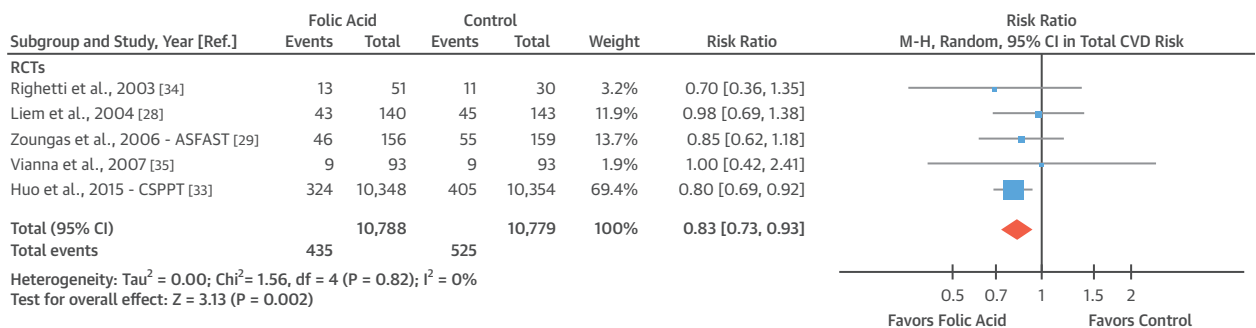
The following supplements were associated with no significant effect on CVD outcomes and all-cause

mortality: vitamins A, B₆, and E; β -carotene; zinc; iron; magnesium; selenium; and multivitamins.

DISCUSSION

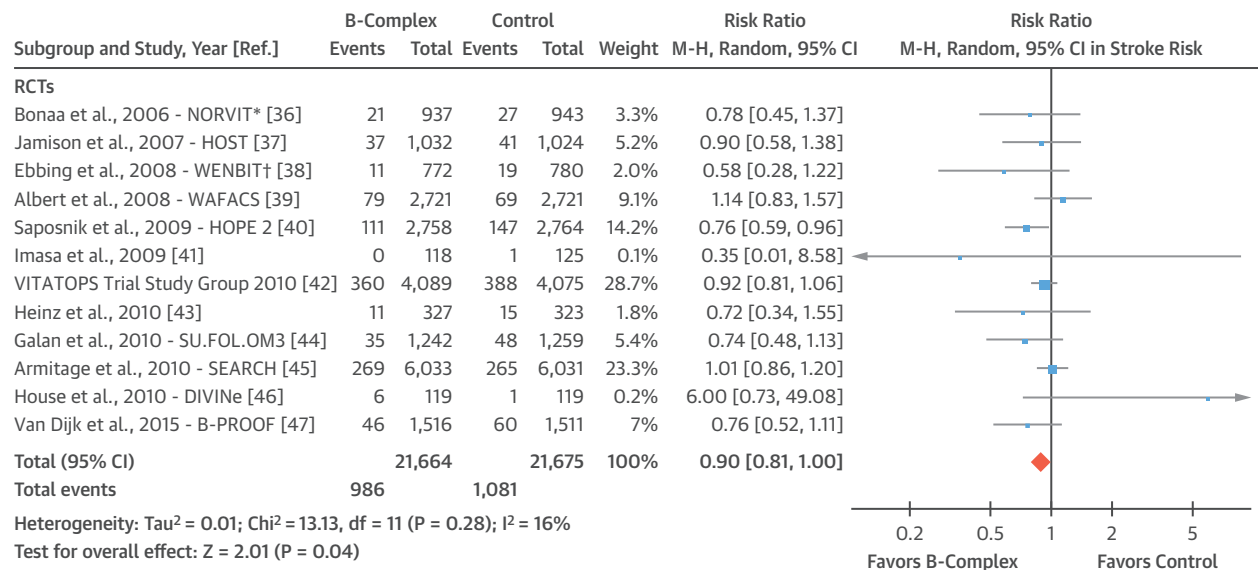
In general, the data on the popular supplements (multivitamins, vitamin D, calcium, and vitamin C) show no consistent benefit for the prevention of CVD, MI, or stroke, nor was there a benefit for all-cause mortality to support their continued use. At the same time, folic acid alone and B-vitamins with folic acid, B₆, and B₁₂ reduced stroke, whereas niacin and antioxidants were associated with an increased risk of all-cause mortality. Overall, the

FIGURE 5 Forest Plot of Folic Acid Supplementation and CVD Risk



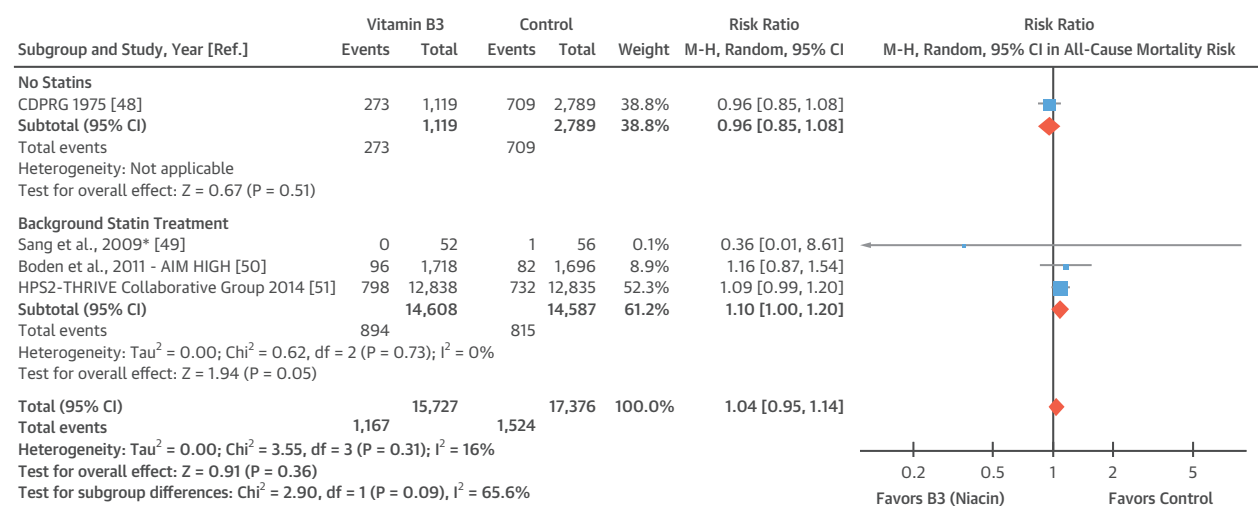
The **diamond** represents the pooled risk estimate. Interstudy heterogeneity was tested using the Cochran Q statistic (chi-square) at a significance level of $p < 0.10$ and quantified by the I^2 statistic. The results show a RR of 0.83 in favor of folic acid. This 17% reduction in CVD risk was driven by the highly influential Chinese folic acid supplementation study, made in a community without folic acid fortification, but is the major supplement finding of the last 6 years. NNT for folic acid supplementation and CVD risk is 111. Abbreviations as in [Figures 1, 2, and 4](#).

FIGURE 6 Forest Plot of Vitamin B Complex Supplementation and Stroke Risk



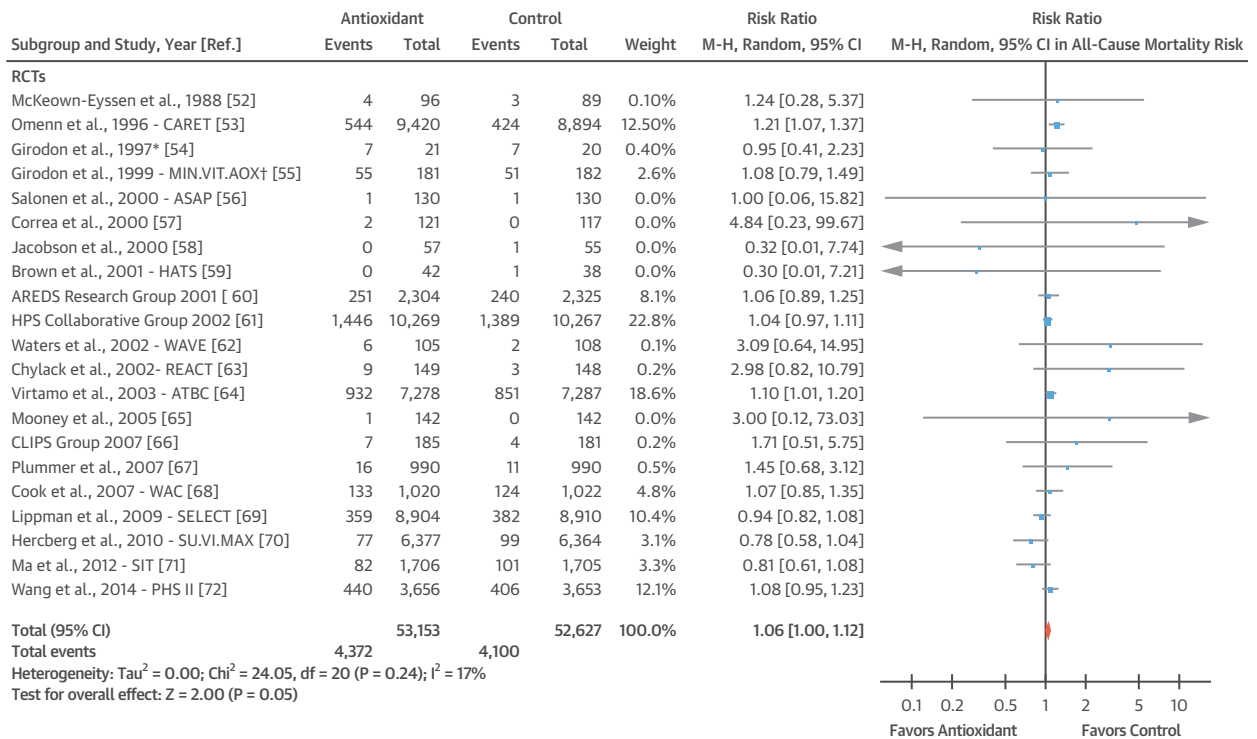
The **diamond** represents the pooled risk estimate. Interstudy heterogeneity was tested using the Cochran Q statistic (chi-square) at a significance level of $p < 0.10$ and quantified by the I^2 statistic. This 10% stroke reduction comes from trials that also include folic acid and from areas with folic acid fortification. These results also support not only B-complex supplementation but also the positive effect of folic acid in stroke prevention. The NNT for vitamin B complex supplementation and stroke risk is 250. *Data for folic acid, B₆, and B₁₂ versus placebo from Bønaa et al. (36). †Data for folic acid, B₆, and B₁₂ versus placebo from Ebbing et al. (38). Abbreviations as in Figures 2 and 4.

FIGURE 7 Forest Plot of Niacin (B₃) Supplementation and All-Cause Mortality Risk in RCTs With and Without Background Statin Treatment



The **diamond** represents the pooled risk estimate. Interstudy heterogeneity was tested using the Cochran Q statistic (chi-square) at a significance level of $p < 0.10$ and quantified by the I^2 statistic. The data demonstrate that taking slow-release niacin to lower low-density lipoprotein cholesterol further in those already taking a statin appears not to benefit CVD outcomes but has a marginally adverse effect on all-cause mortality. NNT for niacin without background statin use and all-cause mortality is 100; number needed to harm (NNH) with background statin use and all-cause mortality is 200. *Sang et al. (49); data taken from the meta-analysis in Keene et al. (94). Abbreviations as in Figures 2 and 4.

FIGURE 8 Forest Plot of Antioxidants Supplementation and All-Cause Mortality Risk in RCTs



The **diamond** represents the pooled risk estimate. Interstudy heterogeneity was tested using the Cochran Q statistic (chi-square) at a significance level of $p < 0.10$ and quantified by the I^2 statistic. Antioxidant mixtures did not appear to benefit CVD outcomes, but many had marginally deleterious effect on all-cause mortality. Therefore, these supplements cannot be advised for CVD risk reduction. NNH for antioxidants supplementation and all-cause mortality risk for is 250. *Data for vitamin C, vitamin E, β -carotene, selenium, and zinc versus placebo from Girodon et al. (54). †Data for vitamin C, vitamin E, β -carotene, selenium, and zinc versus placebo from Girodon et al. (55). Abbreviations as in Figures 1, 2, 4, and 7.

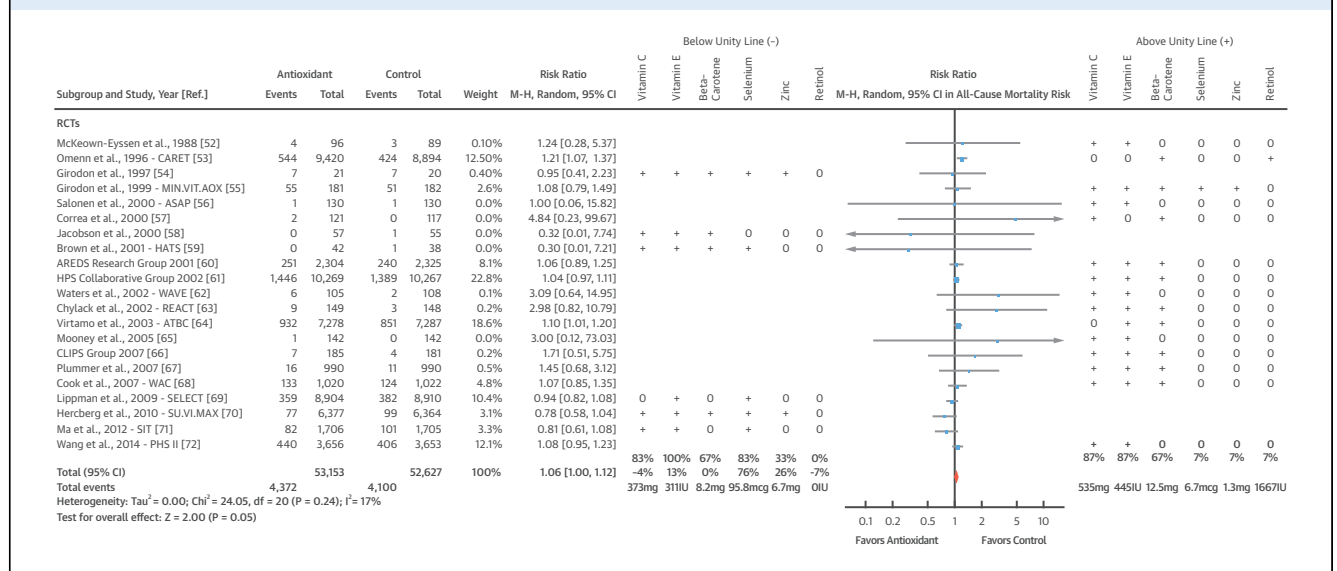
effects were small; the convincing lack of benefit of vitamin D on all-cause mortality is probably the reason for the lack of further studies published since 2013. However, a number of trials with high doses (2,000 IU/day) are underway (e.g., VITAL [Vitamin D and Omega-3 Trial]; NCT01169259). The effects of folic acid in reducing stroke is also convincing, with a 20% reduction.

WHAT WAS ALREADY KNOWN? After the latest update of the USPSTF in 2013 (6), their 2014 recommendation statement (7) concluded, “that the current evidence is insufficient to assess the balance of benefits and harms of single or paired nutrient supplements (except for β -carotene and vitamin E) [that were recommended against] for the prevention of cardiovascular disease and cancer.” The USPSTF 2014 report also drew attention to rare but severe harms seen in some trials, including hip fracture with vitamin A supplementation and an increased rate of prostate cancer with folic acid (73-75). None of these

concerns were addressed directly by studies reported in the past 5 years.

WHAT IS NEW? Since the USPSTF report, the 2015 publication from the large Chinese CSPPT demonstrated that folic acid supplementation may reduce CVD, and specifically, stroke (33). This folic acid effect was the substantial new positive finding on supplement use. Its demonstration in the CSPPT might be related to the lack of folic acid fortification in China. Its application to jurisdictions in which there is folic acid fortification was less certain, and stroke mortality was not reduced. Nevertheless, inclusion of the CSPPT in the meta-analysis of folic acid and CVD risk resulted in a 22% reduction in CVD risk with an NNT of 111. For comparative purposes, the NNT for statin use was 72 in the 2016 report of the USPSTF (76). Furthermore, supplementation with B-complex vitamins that included folic acid was also reported to reduce stroke in RCTs as far back as 2010, with the publication of the VITATOPS (Vitamins to Prevent

FIGURE 9 Forest Plot of Antioxidants Supplementation and All-Cause Mortality Risk



The forest plots show whether the antioxidant mixture contained a specific antioxidant (+) or not (0), with data on the right or left side of the forest plot depending on whether the point estimate lies to the right (harm) or left (benefit) side of the unity line. The first line at the bottom shows the percentage of studies with point estimates on the right and left sides of the unity line for the antioxidant component, and the next line on the left is the difference between the left and right sides. The line at the bottom shows the average dosage of the antioxidant used on that side of the unity line (milligrams, micrograms, or international units). Abbreviations as in Figures 2 and 4.

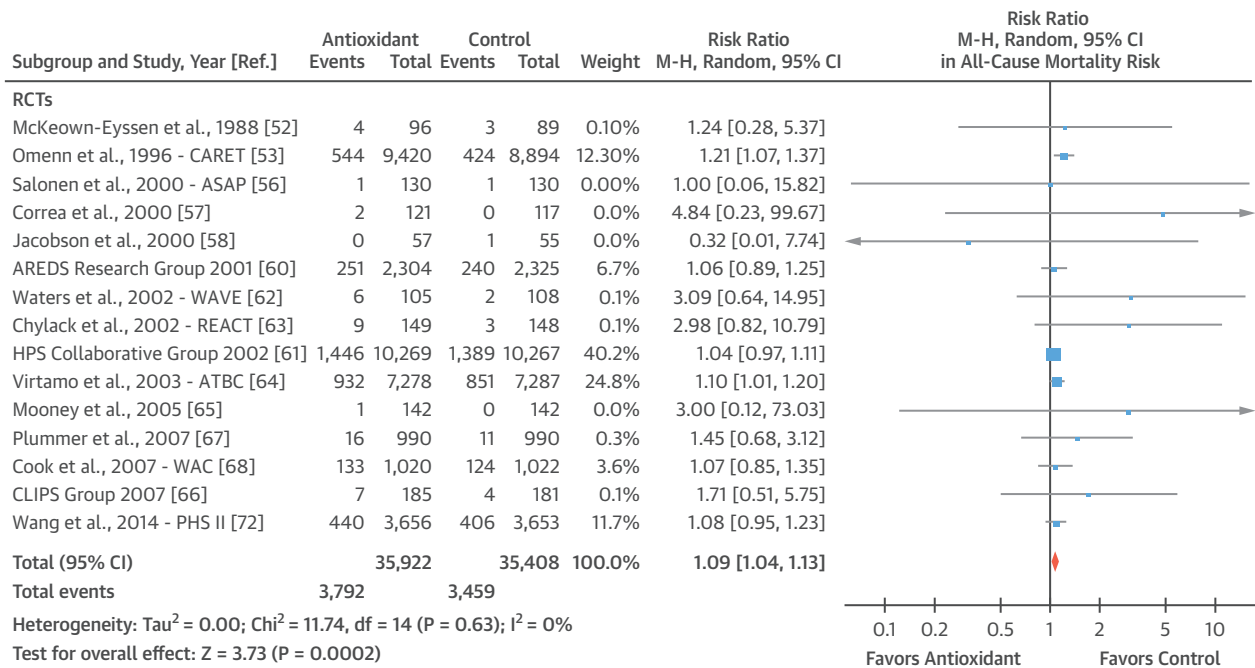
Stroke) trial (42). Nevertheless, folic acid did not reduce all-cause mortality, nor was all-cause mortality reduced by B-complex supplementation in our large meta-analysis of 16 RCTs. The USPSTF did not assess B-complex vitamins as such. The original mechanism proposed by which B-complex vitamins might reduce stroke was through the reduction of blood homocysteine levels. However, the reduction of homocysteine, when achieved, was not associated with stroke reduction (77,78). In addition, there was concern that high folic acid intake might increase the risk of cancer, as seen for prostate cancer in the long-term follow-up of the SELECT (Selenium and Vitamin E Cancer Prevention Trial) study (79). Nevertheless, folic acid administration and the reduction of CVD through stroke seen in the Chinese CSPPT trial provided the only example of CVD risk reduction by supplement use in the period following the Preventive Services Task Recommendations. Whether these data are sufficient to change clinical practice in areas of the world where folic acid food fortification is already in place is still a matter for discussion. In this respect, the B-complex benefit for stroke offered support, in that the 12 studies in the meta-analysis were derived from a variety of jurisdictions. There is now a call that using B-vitamins collectively for stroke prevention be reconsidered (80). In addition, the use of methyl and hydroxocobalamin has been

recommended to replace cyanocobalamin as the B₁₂ source due to the potential buildup of cyanide in those with renal failure (81,82). Furthermore, it has been speculated that use of cyanocobalamin may have obscured the potential benefit of B-vitamin supplementation in some previous studies (81). However, before folic acid and B-vitamin supplementation enters guidelines as part of the strategy for the prevention of CVD, large trials of folic acid and B-vitamins are required. This caution is relevant to jurisdictions (e.g., North America) where there is folic acid supplementation, to assess the effects, not only on CVD, but more importantly, on all-cause mortality.

In the current statin era, the effect of niacin in increasing all-cause mortality by 10% (NNT = 200) in data for 3 RCTs (all of which used extended-release niacin) cautions against long-term use of extended-release (nonflush) niacin as an adjunct to statin therapy.

Of particular interest was the lack of a clear effect of supplements in general on CVD outcomes and all-cause mortality. This lack of effect was particularly notable when large numbers of studies were available, such as for vitamin D with or without calcium. In view of the potential benefits of vitamin D for diabetes (83,84) and calcium for colon cancer (85-88), it was expected that these potential benefits would reflect changes in all-cause mortality. In contrast to this

FIGURE 10 Forest Plot of Antioxidants Supplementation and All-Cause Mortality Risk in RCTs With Removal of Studies Using Selenium



The **diamond** represents the pooled risk estimate. Interstudy heterogeneity was tested using the Cochran Q statistic (chi-square) at a significance level of $p < 0.10$ and quantified by the I^2 statistic. Antioxidant mixtures did not appear to benefit CVD outcomes, but many had a marginally deleterious effect on all-cause mortality. Therefore, these supplements cannot be advised for CVD risk reduction. The NNH for antioxidant supplementation and all-cause mortality risk is 127. Abbreviations as in Figures 1, 2, 4, and 7.

expectation was the fact that long-term studies might be required to detect changes in reduced incidence. In addition, the impact of a reduction in these diseases might be too low to be reflected in all-cause mortality.

Furthermore, overall health benefits were expected for multivitamin and multimineral use that also might have been reflected in reduced CVD risk. It has often been noted that a significant proportion of Western diets are not optimal, and it has been reasoned that supplementation could rectify potential deficiencies (89,90). If there are no potential adverse effects to supplementation, then it can be argued that some benefits might have been seen, but as yet, they have not.

STRENGTHS AND WEAKNESSES. The strength of this review was that it provided an update on the USPSTF assessment but focused on the components of CVD: MI, stroke, and their associated mortalities.

The weaknesses included our lack of consideration of data from the fixed-effects model and from the results from cohort studies. RCTs are often of shorter duration, whereas cohorts of longer duration might be required to fully capture chronic disease risk. Participants in RCTs are often more health-conscious,

and therefore, they were not representative of the general population. Supplement differences might also have influenced outcomes. Adherence to and persistence with supplement use were also an issue. Furthermore, dose-response data were not usually available. However, cohorts might be larger and longer than many RCTs, which would allow the effects of the dose to be assessed. This might require multiple assessments over time and might be confounded by many lifestyle and dietary factors in supplement users that might be difficult to adjust for adequately. Finally, combining different types of antioxidants might be suboptimal, because their mechanisms of action might also be different. Nevertheless, when studies containing selenium were removed from the meta-analysis, the significance level favoring control increased from $p = 0.05$ to $p = 0.0002$ (Figure 10), although the risk ratio only increased from 6% to 9% with a number needed to harm reduction of 250 to 127.

We used a random effect model for our meta-analyses. However, the random effects approach might be unsatisfactory when there is heterogeneity among studies because it gives undue weight to

smaller studies at the extremes, whereas a fixed-effect model reduces this false irregularity (91). Random effects models assess no fixed or “true” treatment effect, but assess a distribution of effects. The random effects model therefore provided a more conservative summary effect estimate, although in the absence of heterogeneity ($I^2 = 0\%$) both approaches provided the same results.

CONCLUSIONS

Since the 2013 to 2014 assessment and report of the USPSTF (7), the most notable finding was the effect of folic acid in reducing stroke and CVD, with significance driven by the 5-year 20,000 Chinese CSPPT RCT, which was supported by the reduction in stroke seen in RCTs of B-complex vitamins in which folic acid was a component. Vitamin B₃ (or niacin) might increase all-cause mortality, which was possibly related to its adverse effects on glycemic response (51,92). Antioxidant mixtures did not appear to

benefit CVD but might increase all-cause mortality. Although sufficient studies on vitamin D exist, to be confident that there is no all-cause mortality effect, further studies on multivitamins, the most commonly used supplement, may still be useful, because of the marginal benefit seen in our analysis. In the absence of further studies, the current data on supplement use reinforce advice to focus on healthy dietary patterns, with an increased proportion of plant foods in which many of these required vitamins and minerals can be found (5,93).

The authors are happy to share their database with those who request it, either for verification or for collaborative purposes.

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KEY WORDS all-cause mortality, meta-analysis, supplements

APPENDIX For supplemental tables and figures, please see the online version of this paper.