JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 71, NO. 22, 2018

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

David J.A. Jenkins, MD, PHD, DSC,[a,b,c,d,e] J. David Spence, MD,[f] Edward L. Giovannucci, MD, SCD,[g] Young-in Kim, MD,[a,h,i] Robert Josse, MD,[a,b,e] Reinhold Vieth, PHD,[a] Sonia Blanco Mejia, MD, MSC,[a,c,d] Effie Viguiliouk, MSC,[a,c,d] Stephanie Nishi, MSC, RD,[a,d] Sandhya Sahye-Pudaruth, MPH, RD,[a,d] Melanie Paquette, MSC, RD,[a,d] Darshna Patel, BA,[a,d] Sandy Mitchell, BASC, RD,[a,d] Meaghan Kavanagh, MSC,[a,d] Tom Tsirakis, BA,[d] Lina Bachiri, BSC,[j] Atherai Maran, BSC,[d] Narmada Umatheva, BSC,[d] Taylor McKay, MSC, BSCH,[d] Gelaine Trinidad, BASC,[d] Daniel Bernstein, BASC, BSC,[d] Awad Chowdhury, BSC,[d] Julieta Correa-Betanzo, PHD,[d] Gabriella Del Principe, BA,[d] Anisa Hajizadeh, BHSC,[d] Rohit Jayaraman, MD,[d] Amy Jenkins, MSC,[d] Wendy Jenkins, BSC,[d] Ruben Kalaichandran, BSCH,[d] Geithayini Kirupaharan, BASC,[d] Preveena Manisekaran, BASC,[d] Tina Qutta, BASC, BCOM, MBA,[d] Ramsha Shahid, BSC,[d] Alexis Silver, BASC,[d] Cleo Villegas,[d] Jessica White, BSC,[d] Cyril W.C. Kendall, PHD,[a,c,d,k] Sathish C. Pichika, MSC,[a,d,l] John L. Sievenpiper, MD, PHD[a,b,c,d,e]

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)

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

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the [a]Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; [b]Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada; [c]Toronto 3D Knowledge Synthesis and Clinical Trials Unit, St. Michael's Hospital, Toronto, Ontario, Canada; [d]Clinical Nutrition Risk Factor Modification Centre, St. Michael's Hospital, Toronto, Ontario, Canada; [e]Division of Endocrinology and Metabolism, St. Michael's Hospital, Toronto, Ontario, Canada; [f]Stroke Prevention & Atherosclerosis Research Centre, Robarts Research Institute, Western University, London, Ontario, Canada; [g]Departments of Nutrition and Epidemiology, Harvard TH Chan School of Public Health, Boston, Massachusetts; [h]Keenan Research Centre for Biomedical Science, St. Michael's Hospital, Toronto, Ontario, Canada; [i]Division of Gastroenterology, St. Michael's Hospital, Toronto, Ontario, Canada; [j]AgroParisTech, Paris Institute of Technology for Life, Food and Environmental Sciences, Paris, France; [k]College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, Saskatchewan, Canada; and the [l]Department of Mathematics and Statistics, University of Windsor, Windsor, Ontario, Canada. This work was supported by the Canada Research Chair Endorsement, Loblaw Cos. Ltd., and the Canadian Institutes for Health Research (CIHR). Dr. Jenkins is funded by the government of Canada through the Canada Research Chair Endowment; has received research grants from Saskatchewan Pulse Growers, the Agricultural Bioproducts Innovation Program through the Pulse Research Network, the Advanced Foods and Material Network (Loblaw Companies Ltd.), Unilever, Barilla, the Almond Board of California, Agriculture and Agri-food

ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2018.04.020

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).

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

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

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, Orafti, 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), Verywell, True Health Initiative, Institute of Food Technologists, Saskatchewan Pulse Growers, Sanitarium Company, Orafti, 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).

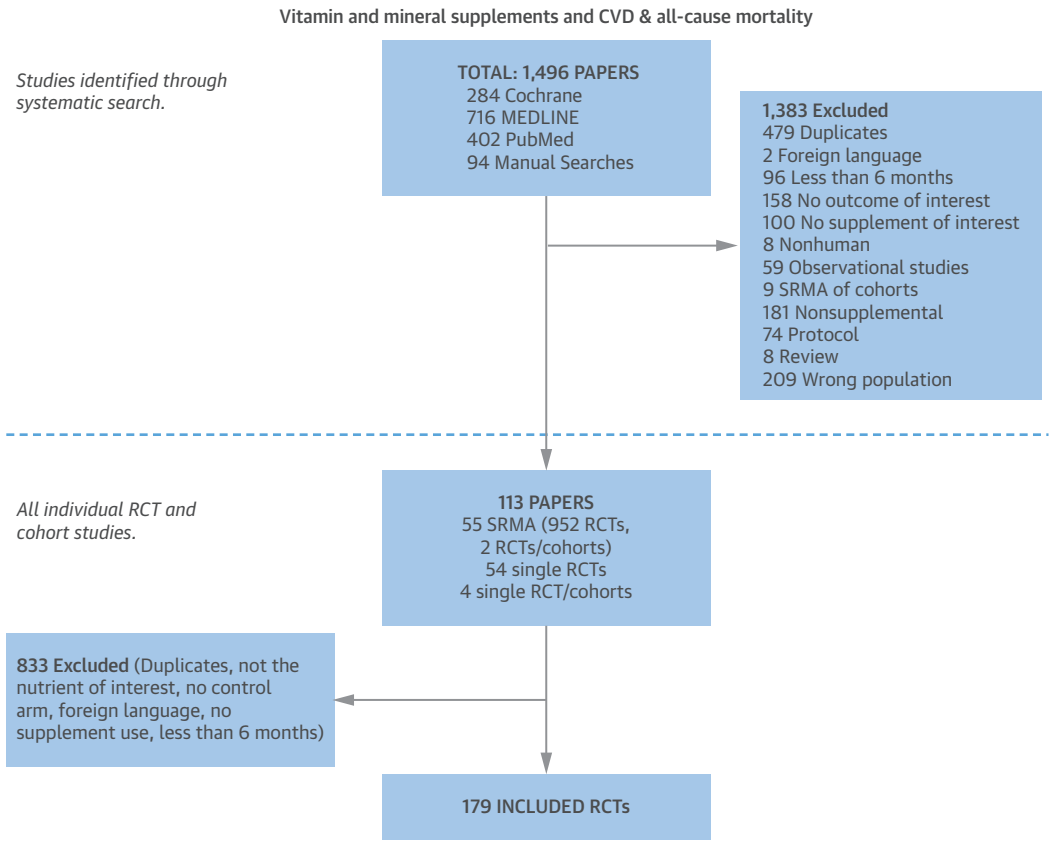
Where ≥2 meta-analyses with forest plots on the same topic were identified, we identified the unique studies and excluded duplicates, studies that were not relevant, and studies that did not provide data. Full paper review and data extraction were conducted by 2 independent investigators, with all disagreements 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 ≥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, B_1, B_2, B_3 (niacin), B_6, B_9 (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.

Manuscript received December 11, 2017; revised manuscript received March 26, 2018, accepted April 17, 2018.

FIGURE 1 Search Summary



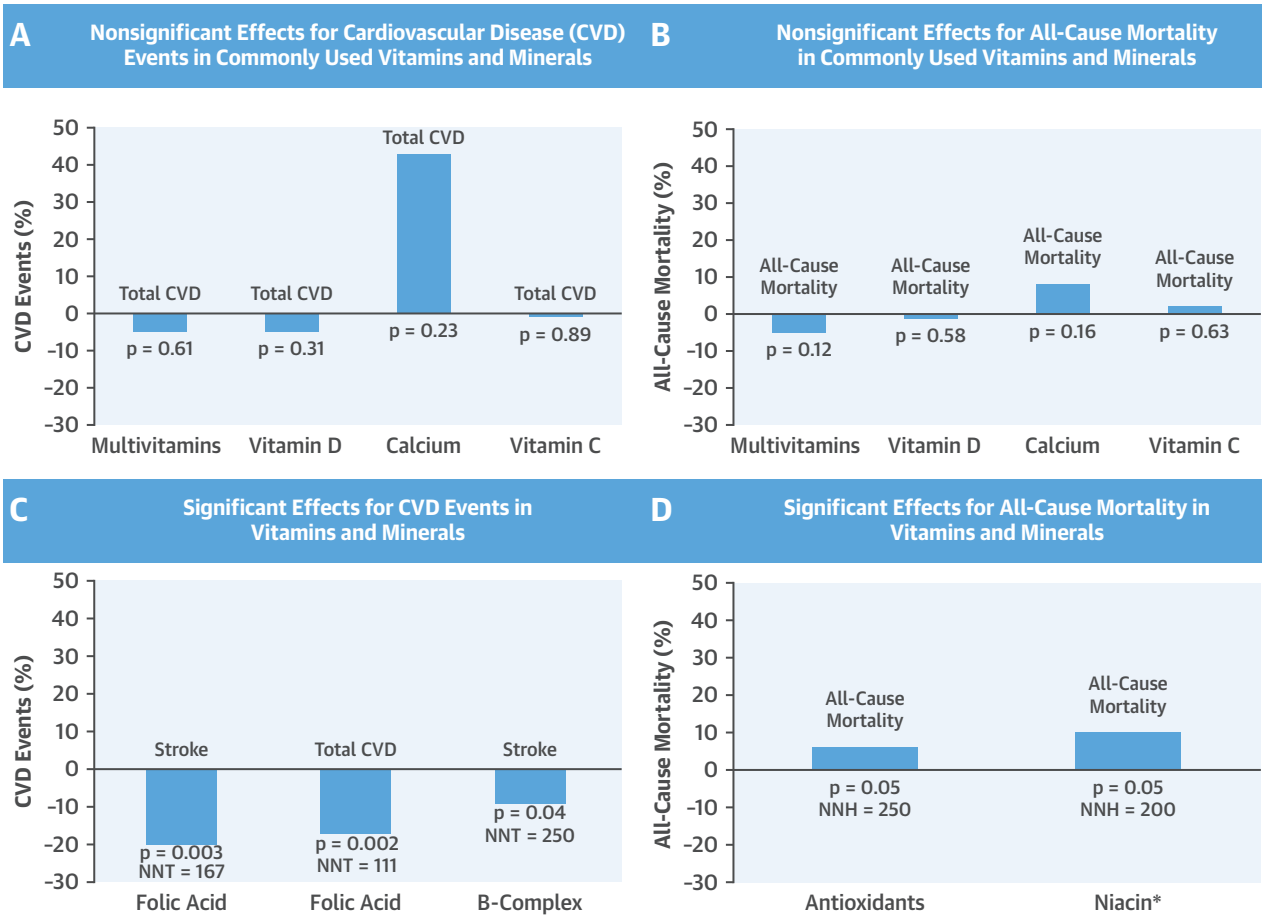
The search strategy used to identify publications that reported randomized control trial (RCT) data on vitamins and minerals with cardiovascular disease (CVD), CVD components, and all-cause mortality. The publications are from 2012 to 2017 and focus on meta-analysis of RCTs and single RCTs identified by searching Cochrane, MEDLINE, and PubMed, and by manual searches. The reasons for exclusion are given. There were 179 single RCTs included, of which 15 were new since the U.S. Preventive Services Task Force (USPSTF) meta-analysis. The capture rate of 113 of 1,496 at <10% indicates the general interest in this area, but a relative lack of usable data. SRMA = systematic review and meta-analysis.

(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: B_6, B_9 [folic acid], and B_{12}) 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.

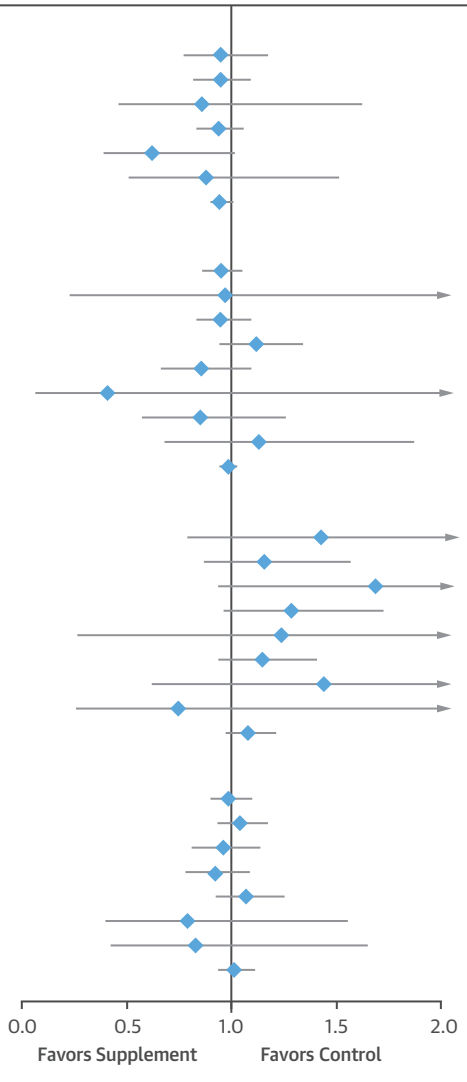
Attention was drawn to outcomes of meta-analyses that showed significance with moderate- to high-quality evidence (with >1 RCT). In this way, we reduced the risk of type 1 errors in the multiple comparison undertaken and avoided the use of corrections, such as the Bonferroni correction, which might have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

Comparison	RCTs	N	Events	Pooled Effect Estimates RR (95% CIs)	I^2	*p*-value
Multivitamins						
Total CVD	2	16,349	1,941	0.95 [0.77, 1.17]	62%	0.61
MI	3	16,414	772	0.95 [0.82, 1.09]	0%	0.43
Stroke	2	16,349	666	0.86 [0.46, 1.62]	59%	0.64
Total CVD mortality	3	17,351	984	0.94 [0.83, 1.06]	0%	0.30
MI mortality	1	14,641	70	0.63 [0.39, 1.02]	N/A	0.06
Stroke mortality	3	18,055	233	0.88 [0.51, 1.51]	55%	0.63
All-cause mortality	10	22,869	3,633	0.95 [0.90, 1.01]	0%	0.12
Vitamin D						
Total CVD	6	6,546	1,037	0.95 [0.86, 1.05]	0%	0.31
Total CHD	3	434	6	0.97 [0.22, 4.22]	0%	0.97
MI	12	11,081	643	0.95 [0.83, 1.10]	0%	0.52
Stroke	11	11,173	479	1.12 [0.94, 1.34]	0%	0.20
Total CVD mortality	2	3,907	219	0.86 [0.66, 1.10]	0%	0.23
Total CHD mortality	2	225	4	0.41 [0.06, 2.72]	0%	0.35
MI mortality	4	2,873	94	0.85 [0.57, 1.26]	0%	0.41
Stroke mortality	2	2,773	60	1.13 [0.68, 1.87]	0%	0.63
All-cause mortality	43	37,550	5,876	0.99 [0.95, 1.03]	0%	0.58
Calcium						
Total CVD	3	3,328	364	1.43 [0.79, 2.59]	80%	0.23
Total CHD	2	3,171	166	1.16 [0.87, 1.56]	0%	0.32
MI	4	5,387	231	1.69 [0.94, 3.04]	69%	0.08
Stroke	3	3,861	178	1.29 [0.96, 1.72]	0%	0.09
Total CVD mortality	2	2,931	47	1.24 [0.27, 5.65]	53%	0.78
Total CHD mortality	1	5,292	338	1.15 [0.94, 1.41]	N/A	0.18
MI mortality	1	1,460	22	1.44 [0.62, 3.36]	N/A	0.39
Stroke mortality	1	1,460	14	0.75 [0.26, 2.15]	N/A	0.59
All-cause mortality	6	9,765	1,084	1.08 [0.97, 1.21]	0%	0.16
Vitamin C						
Total CVD	2	15,497	1,459	0.99 [0.90, 1.10]	0%	0.89
Total CHD	1	8,171	999	1.04 [0.93, 1.17]	N/A	0.49
MI	2	15,497	545	0.96 [0.81, 1.14]	6%	0.62
Stroke	2	15,497	525	0.92 [0.78, 1.09]	0%	0.33
Total CVD mortality	2	15,497	646	1.07 [0.92, 1.25]	0%	0.35
MI mortality	1	8,171	34	0.79 [0.40, 1.55]	N/A	0.49
Stroke mortality	1	8,171	33	0.83 [0.42, 1.65]	N/A	0.60
All-cause mortality	4	16,004	1,819	1.02 [0.94, 1.11]	0%	0.63

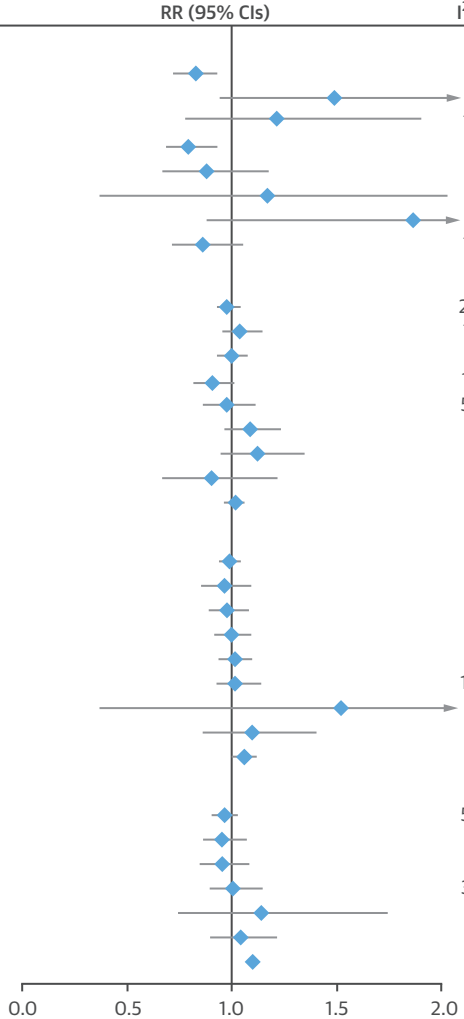


Summary data showing the risk ratios derived from meta-analyses of RCTs of the 4 most commonly consumed vitamins and mineral supplements (multivitamins, vitamin D, calcium, and vitamin C) on the components of CVD and all-cause mortality. Of note, none of these popular supplements had an effect on CVD 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 (I^2 = 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

Comparison	RCTs	N	Events	Pooled Effect Estimates RR (95% CIs)	I^2	*p*-value
Folic Acid						
Total CVD	5	21,567	960	0.83 [0.73, 0.93]	0%	<0.01
Total CHD	2	2,197	77	1.47 [0.95, 2.28]	0%	0.08
MI	6	24,210	106	1.21 [0.78, 1.88]	12%	0.41
Stroke	7	24,525	694	0.80 [0.69, 0.93]	0%	<0.01
Total CVD mortality	5	22,468	188	0.89 [0.68, 1.17]	0%	0.41
MI mortality	2	20,985	13	1.17 [0.39, 3.49]	0%	0.77
Stroke mortality	2	20,985	29	1.85 [0.88, 3.93]	0%	0.11
All-cause mortality	10	25,580	877	0.87 [0.72, 1.05]	17%	0.14
B-Complex						
Total CVD	9	39,756	6,888	0.98 [0.93, 1.04]	29%	0.58
Total CHD	5	20,886	3,197	1.04 [0.96, 1.14]	12%	0.32
MI	13	44,285	2,875	1.00 [0.93, 1.07]	0%	1.00
Stroke	12	43,339	2,067	0.90 [0.81, 1.00]	16%	0.04
Total CVD mortality	5	33,693	2,642	0.98 [0.87, 1.11]	52%	0.74
Total CHD mortality	3	13,267	964	1.09 [0.97, 1.23]	0%	0.16
MI mortality	2	13,944	482	1.11 [0.93, 1.32]	0%	0.26
Stroke mortality	2	17,586	181	0.91 [0.68, 1.21]	0%	0.50
All-cause mortality	16	45,424	6,245	1.02 [0.97, 1.06]	0%	0.41
Antioxidants						
Total CVD	7	60,826	7,726	0.99 [0.95, 1.04]	0%	0.77
Total CHD	1	13,630	1,045	0.97 [0.86, 1.09]	N/A	0.57
MI	6	42,134	1,815	0.98 [0.90, 1.08]	0%	0.73
Stroke	7	60,589	1,986	1.00 [0.92, 1.09]	0%	0.98
Total CVD mortality	7	49,729	2,263	1.02 [0.94, 1.10]	0%	0.65
Total CHD mortality	2	34,166	1,754	1.02 [0.93, 1.13]	10%	0.68
MI mortality	3	947	8	1.51 [0.39, 5.93]	0%	0.55
Stroke mortality	5	56,352	342	1.10 [0.87, 1.39]	7%	0.43
All-cause mortality	21	105,780	8,472	1.06 [1.00, 1.12]	0%	0.05
Vitamin B3 (Niacin)						
Total CVD	3	29,254	3,798	0.97 [0.91, 1.03]	55%	0.30
Total CHD	2	26,615	1.363	0.96 [0.87, 1.07]	0%	0.88
MI	4	30,196	1.036	0.96 [0.85, 1.08]	0%	0.53
Stroke	4	30,196	1,047	1.01 [0.90, 1.14]	37%	0.81
Total CVD mortality	2	3,581	86	1.14 [0.75, 1.73]	0%	0.56
Total CHD mortality	2	29,087	665	1.04 [0.90, 1.21]	0%	0.57
All-cause mortality	3	29,195	1,709	1.10 [1.00, 1.20]	0%	0.05



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).

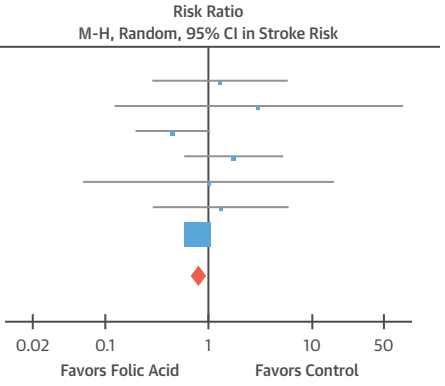
Niacin (nicotinic acid) or vitamin B_3, taken at pharmacological doses (1 to 3 g/day) in 3 RCTs, and when assessed against a background in which a statin was taken in both the test and control groups (all with extended-release niacin), was associated with increased all-cause mortality by 10% (p = 0.05), 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

Subgroup and Study, Year [Ref.]	Folic Acid Events	Folic Acid Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
RCTs						
Liem et al., 2003 [27]	4	300	3	293	1.0%	1.30 [0.29, 5.77]
Liem et al., 2004 [28]	1	140	0	143	0.2%	3.06 [0.13, 74.58]
Zoungas et al., 2006 - ASFAST [29]	8	156	18	159	3.4%	0.45 [0.20, 1.01]
Cole et al., 2007 - AFPPS [30]	9	516	5	505	1.9%	1.76 [0.59, 5.22]
Logan et al., 2008 - ukCAP [31]	1	470	1	469	0.3%	1.00 [0.06, 15.91]
Wu et al., 2009 - NHS/HPFS [32]	4	338	3	334	1.0%	1.32 [0.30, 5.84]
Huo et al., 2015 - CSPPT [33]	282	10,348	355	10,354	92.3%	0.79 [0.68, 0.93]
Total (95% CI)		12,268		12,257	100%	0.80 [0.69, 0.93]
Total events	309		385			

Heterogeneity: Tau^2 = 0.00; Chi^2= 5.51, df = 6 (P = 0.48); I^2 = 0%
Test for overall effect: Z = 2.92 (P = 0.003)



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 = Manthel-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, B_6, and E; β-carotene; zinc; iron; magnesium; selenium; and multivitamins.

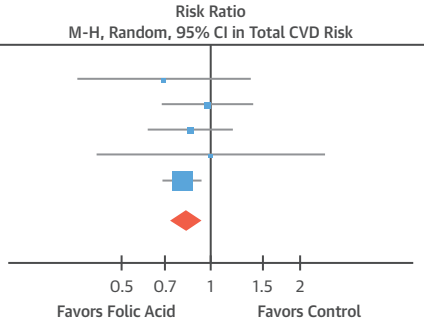
DISCUSSION

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, B_6, and B_{12} 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

Subgroup and Study, Year [Ref.]	Folic Acid Events	Folic Acid Total	Control Events	Control Total	Weight	Risk Ratio
RCTs						
Righetti et al., 2003 [34]	13	51	11	30	3.2%	0.70 [0.36, 1.35]
Liem et al., 2004 [28]	43	140	45	143	11.9%	0.98 [0.69, 1.38]
Zoungas et al., 2006 - ASFAST [29]	46	156	55	159	13.7%	0.85 [0.62, 1.18]
Vianna et al., 2007 [35]	9	93	9	93	1.9%	1.00 [0.42, 2.41]
Huo et al., 2015 - CSPPT [33]	324	10,348	405	10,354	69.4%	0.80 [0.69, 0.92]
Total (95% CI)		10,788		10,779	100%	0.83 [0.73, 0.93]
Total events	435		525			

Heterogeneity: Tau^2 = 0.00; Chi^2= 1.56, df = 4 (P = 0.82); I^2 = 0%
Test for overall effect: Z = 3.13 (P = 0.002)

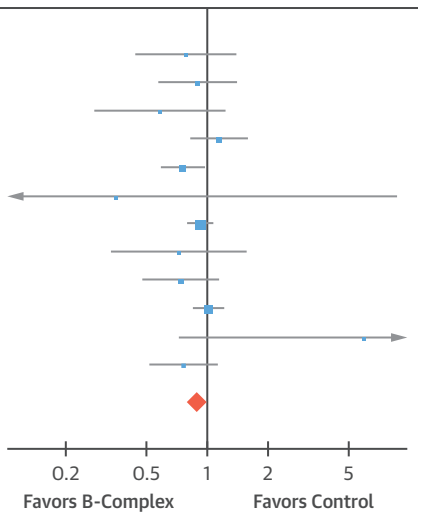


The **diamond** represents the pooled risk estimate. Interstudy heterogeneity was tested using the Cochran Q statistic (chi-square) at a significance level of $p < 0.10$ and quantified by the I^2 statistic. The results show a RR of 0.83 in favor of folic acid. This 17% reduction in CVD risk was driven 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

Subgroup and Study, Year [Ref.]	B-Complex Events	B-Complex Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
RCTs						
Bonaa et al., 2006 - NORVIT* [36]	21	937	27	943	3.3%	0.78 [0.45, 1.37]
Jamison et al., 2007 - HOST [37]	37	1,032	41	1,024	5.2%	0.90 [0.58, 1.38]
Ebbing et al., 2008 - WENBIT† [38]	11	772	19	780	2.0%	0.58 [0.28, 1.22]
Albert et al., 2008 - WAFACS [39]	79	2,721	69	2,721	9.1%	1.14 [0.83, 1.57]
Saposnik et al., 2009 - HOPE 2 [40]	111	2,758	147	2,764	14.2%	0.76 [0.59, 0.96]
Imasa et al., 2009 [41]	0	118	1	125	0.1%	0.35 [0.01, 8.58]
VITATOPS Trial Study Group 2010 [42]	360	4,089	388	4,075	28.7%	0.92 [0.81, 1.06]
Heinz et al., 2010 [43]	11	327	15	323	1.8%	0.72 [0.34, 1.55]
Galan et al., 2010 - SU.FOL.OM3 [44]	35	1,242	48	1,259	5.4%	0.74 [0.48, 1.13]
Armitage et al., 2010 - SEARCH [45]	269	6,033	265	6,031	23.3%	1.01 [0.86, 1.20]
House et al., 2010 - DIVINe [46]	6	119	1	119	0.2%	6.00 [0.73, 49.08]
Van Dijk et al., 2015 - B-PROOF [47]	46	1,516	60	1,511	7%	0.76 [0.52, 1.11]
Total (95% CI)		**21,664**		**21,675**	**100%**	**0.90 [0.81, 1.00]**
Total events	**986**		**1,081**			

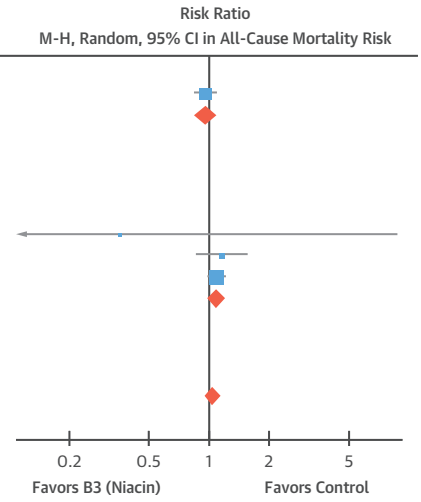
Heterogeneity: Tau² = 0.01; Chi² = 13.13, df = 11 (P = 0.28); I² = 16%
Test for overall effect: Z = 2.01 (P = 0.04)



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, B_6, and B_{12} versus placebo from Bønaa et al. (36). †Data for folic acid, B_6, and B_{12} versus placebo from Ebbing et al. (38). Abbreviations as in Figures 2 and 4.

FIGURE 7 Forest Plot of Niacin (B_3) Supplementation and All-Cause Mortality Risk in RCTs With and Without Background Statin Treatment

Subgroup and Study, Year [Ref.]	Vitamin B3 Events	Vitamin B3 Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
No Statins						
CDPRG 1975 [48]	273	1,119	709	2,789	38.8%	0.96 [0.85, 1.08]
Subtotal (95% CI)		**1,119**		**2,789**	**38.8%**	**0.96 [0.85, 1.08]**
Total events	273		709			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.51)						
Background Statin Treatment						
Sang et al., 2009* [49]	0	52	1	56	0.1%	0.36 [0.01, 8.61]
Boden et al., 2011 - AIM HIGH [50]	96	1,718	82	1,696	8.9%	1.16 [0.87, 1.54]
HPS2-THRIVE Collaborative Group 2014 [51]	798	12,838	732	12,835	52.3%	1.09 [0.99, 1.20]
Subtotal (95% CI)		**14,608**		**14,587**	**61.2%**	**1.10 [1.00, 1.20]**
Total events	894		815			
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 2 (P = 0.73); I² = 0%						
Test for overall effect: Z = 1.94 (P = 0.05)						
Total (95% CI)		**15,727**		**17,376**	**100.0%**	**1.04 [0.95, 1.14]**
Total events	**1,167**		**1,524**			
Heterogeneity: Tau² = 0.00; Chi² = 3.55, df = 3 (P = 0.31); I² = 16%						
Test for overall effect: Z = 0.91 (P = 0.36)						
Test for subgroup differences: Chi² = 2.90, df = 1 (P = 0.09), I² = 65.6%						

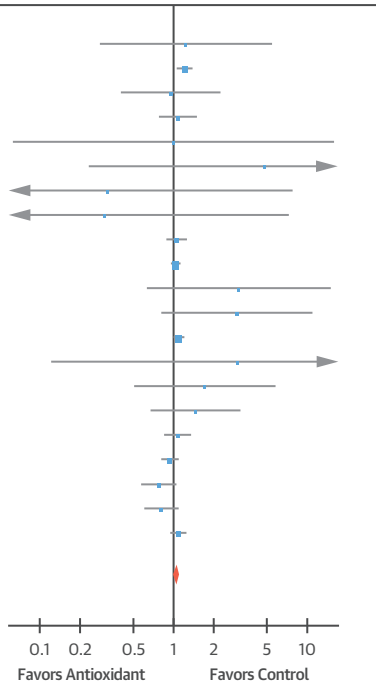


The **diamond** represents the pooled risk estimate. Interstudy heterogeneity was tested using the Cochran Q statistic (chi-square) at a significance level of $p < 0.10$ and quantified by the I^2 statistic. The data demonstrate that taking slow-release niacin to lower low-density lipoprotein cholesterol 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

Subgroup and Study, Year [Ref.]	Antioxidant Events	Antioxidant Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
RCTs						
McKeown-Eyssen et al., 1988 [52]	4	96	3	89	0.10%	1.24 [0.28, 5.37]
Omenn et al., 1996 - CARET [53]	544	9,420	424	8,894	12.50%	1.21 [1.07, 1.37]
Girodon et al., 1997* [54]	7	21	7	20	0.40%	0.95 [0.41, 2.23]
Girodon et al., 1999 - MIN.VIT.AOX† [55]	55	181	51	182	2.6%	1.08 [0.79, 1.49]
Salonen et al., 2000 - ASAP [56]	1	130	1	130	0.0%	1.00 [0.06, 15.82]
Correa et al., 2000 [57]	2	121	0	117	0.0%	4.84 [0.23, 99.67]
Jacobson et al., 2000 [58]	0	57	1	55	0.0%	0.32 [0.01, 7.74]
Brown et al., 2001 - HATS [59]	0	42	1	38	0.0%	0.30 [0.01, 7.21]
AREDS Research Group 2001 [60]	251	2,304	240	2,325	8.1%	1.06 [0.89, 1.25]
HPS Collaborative Group 2002 [61]	1,446	10,269	1,389	10,267	22.8%	1.04 [0.97, 1.11]
Waters et al., 2002 - WAVE [62]	6	105	2	108	0.1%	3.09 [0.64, 14.95]
Chylack et al., 2002- REACT [63]	9	149	3	148	0.2%	2.98 [0.82, 10.79]
Virtamo et al., 2003 - ATBC [64]	932	7,278	851	7,287	18.6%	1.10 [1.01, 1.20]
Mooney et al., 2005 [65]	1	142	0	142	0.0%	3.00 [0.12, 73.03]
CLIPS Group 2007 [66]	7	185	4	181	0.2%	1.71 [0.51, 5.75]
Plummer et al., 2007 [67]	16	990	11	990	0.5%	1.45 [0.68, 3.12]
Cook et al., 2007 - WAC [68]	133	1,020	124	1,022	4.8%	1.07 [0.85, 1.35]
Lippman et al., 2009 - SELECT [69]	359	8,904	382	8,910	10.4%	0.94 [0.82, 1.08]
Hercberg et al., 2010 - SU.VI.MAX [70]	77	6,377	99	6,364	3.1%	0.78 [0.58, 1.04]
Ma et al., 2012 - SIT [71]	82	1,706	101	1,705	3.3%	0.81 [0.61, 1.08]
Wang et al., 2014 - PHS II [72]	440	3,656	406	3,653	12.1%	1.08 [0.95, 1.23]
Total (95% CI)		53,153		52,627	100.0%	1.06 [1.00, 1.12]
Total events	4,372		4,100			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 24.05$, df = 20 (P = 0.24); $I^2 = 17\%$
Test for overall effect: Z = 2.00 (P = 0.05)



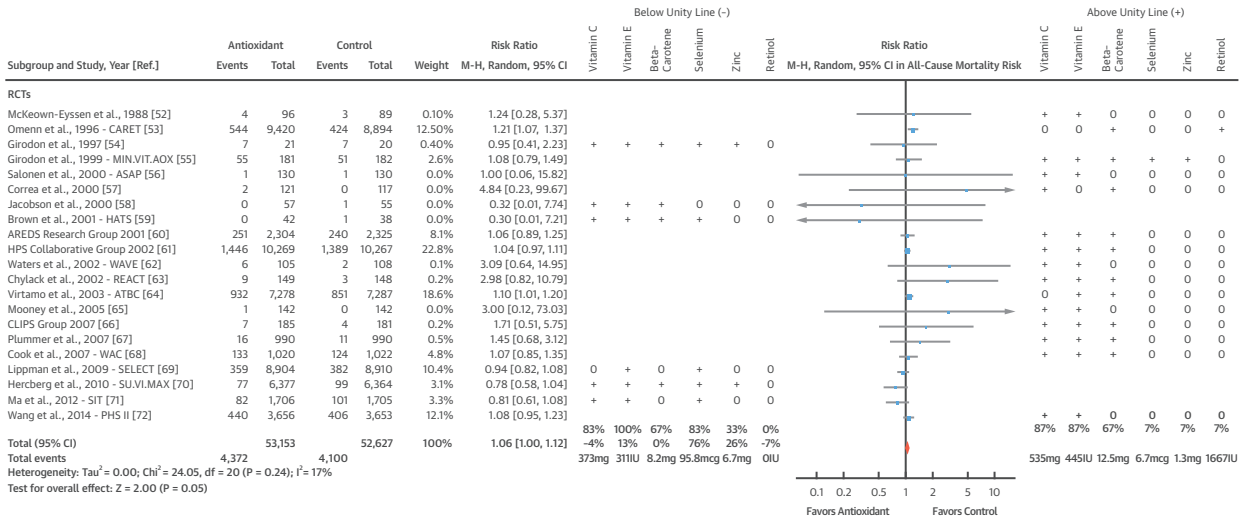
The **diamond** represents the pooled risk estimate. Interstudy heterogeneity was tested using the Cochran Q statistic (chi-square) at a significance level of $p < 0.10$ and quantified by the I^2 statistic. Antioxidant mixtures did not appear to benefit CVD outcomes, but many had marginally deleterious 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 B_{12} 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.

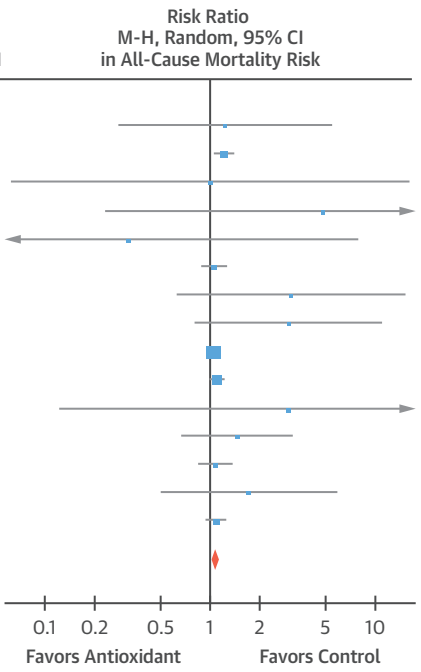
In the current statin era, the effect of niacin in increasing all-cause mortality by 10% (NNT = 200) in data for 3 RCTs (all of which used extended-release niacin) cautions against long-term use of extended-release (nonflush) niacin as an adjunct to statin therapy.

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

Subgroup and Study, Year [Ref.]	Antioxidant Events	Antioxidant Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
RCTs						
McKeown-Eyssen et al., 1988 [52]	4	96	3	89	0.10%	1.24 [0.28, 5.37]
Omenn et al., 1996 - CARET [53]	544	9,420	424	8,894	12.30%	1.21 [1.07, 1.37]
Salonen et al., 2000 - ASAP [56]	1	130	1	130	0.00%	1.00 [0.06, 15.82]
Correa et al., 2000 [57]	2	121	0	117	0.0%	4.84 [0.23, 99.67]
Jacobson et al., 2000 [58]	0	57	1	55	0.0%	0.32 [0.01, 7.74]
AREDS Research Group 2001 [60]	251	2,304	240	2,325	6.7%	1.06 [0.89, 1.25]
Waters et al., 2002 - WAVE [62]	6	105	2	108	0.1%	3.09 [0.64, 14.95]
Chylack et al., 2002 - REACT [63]	9	149	3	148	0.1%	2.98 [0.82, 10.79]
HPS Collaborative Group 2002 [61]	1,446	10,269	1,389	10,267	40.2%	1.04 [0.97, 1.11]
Virtamo et al., 2003 - ATBC [64]	932	7,278	851	7,287	24.8%	1.10 [1.01, 1.20]
Mooney et al., 2005 [65]	1	142	0	142	0.0%	3.00 [0.12, 73.03]
Plummer et al., 2007 [67]	16	990	11	990	0.3%	1.45 [0.68, 3.12]
Cook et al., 2007 - WAC [68]	133	1,020	124	1,022	3.6%	1.07 [0.85, 1.35]
CLIPS Group 2007 [66]	7	185	4	181	0.1%	1.71 [0.51, 5.75]
Wang et al., 2014 - PHS II [72]	440	3,656	406	3,653	11.7%	1.08 [0.95, 1.23]
Total (95% CI)		35,922		35,408	100.0%	1.09 [1.04, 1.13]
Total events	3,792		3,459			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 11.74$, df = 14 (P = 0.63); $I^2 = 0\%$
Test for overall effect: Z = 3.73 (P = 0.0002)



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 B_3 (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.

ADDRESS FOR CORRESPONDENCE: Dr. David J.A. Jenkins, Department of Nutritional Sciences, University of Toronto, 150 College Street, Fitzgerald Building, Toronto, Ontario M5S 3E2, Canada. E-mail: david.jenkins@utoronto.ca.

REFERENCES

1. Baron JH. Sailors' scurvy before and after James Lind–a reassessment. Nutr Rev 2009;67:315–32.

2. Kantor ED, Rehm CD, Du M, White E, Giovannucci EL. Trends in dietary supplement use among US adults from 1999–2012. JAMA 2016;316:1464–74.

3. Skeie G, Braaten T, Hjartåker A, et al. Use of dietary supplements in the European Prospective Investigation into Cancer and Nutrition calibration study. Eur J Clin Nutr 2009;63 Suppl 4:S226–38.

4. Canadian Cancer Society. Nutrition and Fitness (Healthy Eating, Vitamin D). 2018. Available at: http://www.cancer.ca/en/prevention-and-screening/reduce-cancer-risk/make-healthy-choices/eat-well/should-i-take-a-vitamin-d-supplement/?region=on. Accessed April 20, 2018.

5. Office of Disease Prevention and Health Promotion. Advisory Report. Report Index Available at: https://health.gov/dietaryguidelines/2015-scientific-report. Accessed April 17, 2018.

6. 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;159:824–34.

7. Moyer VA, U.S. Preventive Services Task Force. Vitamin, mineral, and multivitamin supplements for the primary prevention of cardiovascular disease and cancer: U.S. Preventive services Task Force recommendation statement. Ann Intern Med 2014;160:558–64.

8. Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2008. Available at: http://handbook-5-1.cochrane.org. Accessed April 17, 2018.

9. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.

10. Centre for Evidence-Based Medicine. Number needed to treat (NNT). Definition. Available at: https://www.cebm.net/2014/03/number-needed-to-treat-nnt. Accessed April 17, 2018.

11. Higgins JPT, Altman DG, Gøtzsche PC, et al., Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

12. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383–94.

13. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. J Clin Epidemiol 2011;64:395–400.

14. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64:401–6.

15. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence–study limitations (risk of bias). J Clin Epidemiol 2011;64:407–15.

16. Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence–publication bias. J Clin Epidemiol 2011;64:1277–82.

17. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence–imprecision. J Clin Epidemiol 2011;64:1283–93.

18. Guyatt GH, Oxman AD, Kunz R, et al., GRADE Working Group. GRADE guidelines: 7. Rating the quality of evidence–inconsistency. J Clin Epidemiol 2011;64:1294–302.

19. Guyatt GH, Oxman AD, Kunz R, et al., GRADE Working Group. GRADE guidelines: 8. Rating the quality of evidence–indirectness. J Clin Epidemiol 2011;64:1303–10.

20. Guyatt GH, Oxman AD, Sultan S, et al., GRADE Working Group. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol 2011;64:1311–6.

21. Brunetti M, Shemilt I, Pregno S, et al. GRADE guidelines: 10. Considering resource use and rating the quality of economic evidence. J Clin Epidemiol 2013;66:140–50.

22. Guyatt G, Oxman AD, Sultan S, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. J Clin Epidemiol 2013;66:151–7.

23. Guyatt GH, Oxman AD, Santesso N, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. J Clin Epidemiol 2013;66:158–72.

24. Guyatt GH, Thorlund K, Oxman AD, et al. GRADE guidelines: 13. Preparing summary of findings tables and evidence profiles-continuous outcomes. J Clin Epidemiol 2013;66:173–83.

25. Bender R, Lange S. Multiple test procedures other than Bonferroni's deserve wider use. BMJ 1999;318:600–1.

26. CONSORT Website. The Consort Statement. Available at: www.CONSORT-statement.org. Accessed April 17, 2018.

27. Liem A, Reynierse-Buitenwerf GH, Zwinderman AH, Jukema JW, van Veldhuisen DJ. Secondary prevention with folic acid: effects on

clinical outcomes. J Am Coll Cardiol 2003;41:2105–13.

28. Liem AH, van Boven AJ, Veeger NJ, et al., FOLic Acid on Risk Diminishment after Acute myocardial infarction (FOLARDA) study group. Efficacy of folic acid when added to statin therapy in patients with hypercholesterolemia following acute myocardial infarction: a randomised pilot trial. Int J Cardiol 2004;93:175–9.

29. Zoungas S, McGrath BP, Branley P, et al. Cardiovascular morbidity and mortality in the Atherosclerosis and Folic Acid Supplementation Trial (ASFAST) in chronic renal failure: a multicenter, randomized, controlled trial. J Am Coll Cardiol 2006;47:1108–16.

30. Cole BF, Baron JA, Sandler RS, et al., Polyp Prevention Study Group. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. JAMA 2007;297:2351–9.

31. Logan RF, Grainge MJ, Shepherd VC, Armitage NC, Muir KR. ukCAP Trial Group. Aspirin and folic acid for the prevention of recurrent colorectal adenomas. Gastroenterology 2008;134:29–38.

32. Wu K, Platz EA, Willett WC, et al. A randomized trial on folic acid supplementation and risk of recurrent colorectal adenoma. Am J Clin Nutr 2009;90:1623–31.

33. Huo Y, Li J, Qin X, et al., CSPPT Investigators. Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China: the CSPPT randomized clinical trial. JAMA 2015;313:1325–35.

34. Righetti M, Ferrario GM, Milani S, et al. Effects of folic acid treatment on homocysteine levels and vascular disease in hemodialysis patients. Med Sci Monit 2003;9:PI19–24.

35. Vianna AC, Mocelin AJ, Matsuo T, et al. Uremic hyperhomocysteinemia: a randomized trial of folate treatment for the prevention of cardiovascular events. Hemodial Int 2007;11:210–6.

36. Bønaa KH, Njølstad I, Ueland PM, et al., NORVIT Trial Investigators. Homocysteine lowering and cardiovascular events after acute myocardial infarction. N Engl J Med 2006;354:1578–88.

37. Jamison RL, Hartigan P, Kaufman JS, et al., Veterans Affairs Site Investigators. Effect of homocysteine lowering on mortality and vascular disease in advanced chronic kidney disease and end-stage renal disease: a randomized controlled trial. JAMA 2007;298:1163–70.

38. Ebbing M, Bleie Ø, Ueland PM, et al. Mortality and cardiovascular events in patients treated with homocysteine-lowering B vitamins after coronary angiography: a randomized controlled trial. JAMA 2008;300:795–804.

39. Albert CM, Cook NR, Gaziano JM, et al. Effect of folic acid and B vitamins on risk of cardiovascular events and total mortality among women at high risk for cardiovascular disease: a randomized trial. JAMA 2008;299:2027–36.

40. Saposnik G, Ray JG, Sheridan P, McQueen M, Lonn E, Heart Outcomes Prevention Evaluation 2 Investigators. Homocysteine-lowering therapy and stroke risk, severity, and disability: additional findings from the HOPE 2 trial. Stroke 2009;40:1365–72.

41. Imasa MS, Gomez NT, Nevado JB Jr.. Folic acid-based intervention in non-ST elevation acute coronary syndromes. Asian Cardiovasc Thorac Ann 2009;17:13–21.

42. VITATOPS Trial Study Group. B vitamins in patients with recent transient ischaemic attack or stroke in the VITAmins TO Prevent Stroke (VITATOPS) trial: a randomised, double-blind, parallel, placebo-controlled trial. Lancet Neurol 2010;9:855–65.

43. Heinz J, Kropf S, Domröse U, et al. B vitamins and the risk of total mortality and cardiovascular disease in end-stage renal disease: results of a randomized controlled trial. Circulation 2010;121:1432–8.

44. Galan P, Kesse-Guyot E, Czernichow S, Briancon S, Blacher J, Hercberg S, SU.FOL.OM3 Collaborative Group. Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases: a randomised placebo controlled trial. BMJ 2010;341:c6273.

45. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group. Effects of homocysteine-lowering with folic acid plus vitamin B12 vs placebo on mortality and major morbidity in myocardial infarction survivors: a randomized trial. JAMA 2010;303:2486–94.

46. House AA, Eliasziw M, Cattran DC, et al. Effect of B-vitamin therapy on progression of diabetic nephropathy: a randomized controlled trial. JAMA 2010;303:1603–9.

47. van Dijk SC, Enneman AW, Swart KM, et al. Effects of 2-year vitamin B12 and folic acid supplementation in hyperhomocysteinemic elderly on arterial stiffness and cardiovascular outcomes within the B-PROOF trial. J Hypertens 2015;33:1897–906; discussion 1906.

48. Clofibrate and niacin in coronary heart disease. JAMA 1975;231:360–81.

49. Sang ZC, Wang F, Zhou Q, et al. Combined use of extended-release niacin and atorvastatin: safety and effects on lipid modification. Chinese Med J (Engl) 2009;122:1615–20.

50. AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 2011;365:2255–67.

51. HPS2-THRIVE Collaborative Group. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med 2014;371:203–12.

52. McKeown-Eyssen G, Holloway C, Jazmaji V, Bright-See E, Dion P, Bruce WR. A randomized trial of vitamins C and E in the prevention of recurrence of colorectal polyps. Cancer Res 1988;48:4701–5.

53. Omenn GS, Goodman GE, Thornquist MD, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med 1996;334:1150–5.

54. Girodon F, Lombard M, Galan P, et al. Effect of micronutrient supplementation on infection in institutionalized elderly subjects: a controlled trial. Ann Nutr Metab 1997;41:98–107.

55. Girodon F, Galan P, Monget AL, et al., MIN. VIT. AOX. geriatric network. Impact of trace elements and vitamin supplementation on immunity and infections in institutionalized elderly patients: a randomized controlled trial. Arch Intern Med 1999;159:748–54.

56. Salonen JT, Nyyssönen K, Salonen R, et al. Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study: a randomized trial of the effect of vitamins E and C on 3-year progression of carotid atherosclerosis. J Intern Med 2000;248:377–86.

57. Correa P, Fontham ET, Bravo JC, et al. Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti-helicobacter pylori therapy. J Natl Cancer Inst 2000;92:1881–8.

58. Jacobson JS, Begg MD, Wang LW, et al. Effects of a 6-month vitamin intervention on DNA damage in heavy smokers. Cancer Epidemiol Biomarkers Prev 2000;9:1303–11.

59. Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med 2001;345:1583–92.

60. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9. Arch Ophthalmol 2001;119:1439–52; erratum Arch Ophthalmol 2008;126:1251.

61. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:23–33.

62. Waters DD, Alderman EL, Hsia J, et al. Effects of hormone replacement therapy and antioxidant vitamin supplements on coronary atherosclerosis in postmenopausal women: a randomized controlled trial. JAMA 2002;288:2432–40.

63. Chylack LT Jr., Brown NP, Bron A, et al. The Roche European American Cataract Trial (REACT): a randomized clinical trial to investigate the efficacy of an oral antioxidant micronutrient mixture to slow progression of age-related cataract. Ophthalmic Epidemiol 2002;9:49–80.

64. Virtamo J, Pietinen P, Huttunen JK, et al., ATBC Study Group. Incidence of cancer and mortality following alpha-tocopherol and beta-carotene supplementation: a postintervention follow-up. JAMA 2003;290:476–85.

65. Mooney LA, Madsen AM, Tang D, et al. Antioxidant vitamin supplementation reduces benzo(a)pyrene-DNA adducts and potential cancer risk in female smokers. Cancer Epidemiol Biomarkers Prevention 2005;14:237–42.

66. Critical Leg Ischaemia Prevention Study (CLIPS) Group. Prevention of serious vascular events by aspirin amongst patients with peripheral arterial disease: randomized, double-blind trial. J Intern Med 2007;261:276–84.

67. Plummer M, Vivas J, Lopez G, et al. Chemoprevention of precancerous gastric lesions with antioxidant vitamin supplementation: a randomized trial in a high-risk population. J Natl Cancer Inst 2007;99:137–46.

68. Cook NR, Albert CM, Gaziano JM, et al. A randomized factorial trial of vitamins C and E and beta carotene in the secondary prevention of cardiovascular events in women: results from the Women's Antioxidant Cardiovascular Study. Arch Intern Med 2007;167:1610–8.

69. Lippman SM, Klein EA, Goodman PJ, et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 2009;301:39–51.

70. Hercberg S, Kesse-Guyot E, Druesne-Pecollo N, et al. Incidence of cancers, ischemic cardiovascular diseases and mortality during 5-year follow-up after stopping antioxidant vitamins and minerals supplements: a post-intervention follow-up in the SU.VI.MAX Study. Int J Cancer 2010;127:1875–81.

71. Ma JL, Zhang L, Brown LM, et al. Fifteen-year effects of Helicobacter pylori, garlic, and vitamin treatments on gastric cancer incidence and mortality. J Natl Cancer Inst 2012;104:488–92.

72. Wang L, Sesso HD, Glynn RJ, et al. Vitamin E and C supplementation and risk of cancer in men: posttrial follow-up in the Physicians' Health Study II randomized trial. Am J Clin Nutr 2014;100:915–23.

73. Collin SM, Metcalfe C, Refsum H, et al. Circulating folate, vitamin B12, homocysteine, vitamin B12 transport proteins, and risk of prostate cancer: a case-control study, systematic review, and meta-analysis. Cancer Epidemiol Biomarkers Prev 2010;19:1632–42.

74. Stolzenberg-Solomon RZ, Chang SC, Leitzmann MF, et al. Folate intake, alcohol use, and postmenopausal breast cancer risk in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Am J Clin Nutr 2006;83:895–904.

75. Lawson KA, Wright ME, Subar A, et al. Multivitamin use and risk of prostate cancer in the National Institutes of Health-AARP Diet and Health Study. J Natl Cancer Inst 2007;99:754–64.

76. Chou R, Dana T, Blazina I, et al. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews. Statin Use for the Prevention of Cardiovascular Disease in Adults: A Systematic Review for the US Preventive Services Task Force. Evidence Synthesis No. 139. AHRQ Publication No. 14-05206-EF-2. Rockville, MD: Agency for Healthcare Research and Quality, 2016.

77. Zhang C, Wang ZY, Qin YY, Yu FF, Zhou YH. Association between B vitamins supplementation and risk of cardiovascular outcomes: a cumulative meta-analysis of randomized controlled trials. PloS One 2014;9:e107060.

78. Dong H, Pi F, Ding Z, et al. Efficacy of supplementation with B vitamins for stroke prevention: a network meta-analysis of randomized controlled trials. PloS One 2015;10:e0137533.

79. Klein EA, Thompson IM Jr., Tangen CM, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 2011;306:1549–56.

80. Spence JD. Metabolic vitamin B12 deficiency: a missed opportunity to prevent dementia and stroke. Nutr Res 2016;36:109–16.

81. Spence JD, Stampfer MJ. Understanding the complexity of homocysteine lowering with vitamins: the potential role of subgroup analyses. JAMA 2011;306:2610–1.

82. Spence JD, Urquhart BL, Bang H. Effect of renal impairment on atherosclerosis: only partially mediated by homocysteine. Nephrol Dial Transplant 2016;31:937–44.

83. Forouhi NG, Luan J, Cooper A, Boucher BJ, Wareham NJ. Baseline serum 25-hydroxy vitamin D is predictive of future glycemic status and insulin resistance: the Medical Research Council Ely Prospective Study 1990–2000. Diabetes 2008;57:2619–25.

84. Mattila C, Knekt P, Männistö S, et al. Serum 25-hydroxyvitamin D concentration and subsequent risk of type 2 diabetes. Diabetes Care 2007;30:2569–70.

85. Zheng W, Anderson KE, Kushi LH, et al. A prospective cohort study of intake of calcium, vitamin D, and other micronutrients in relation to incidence of rectal cancer among postmenopausal women. Cancer Epidemiol Biomarkers Prev 1998;7:221–5.

86. Park Y, Leitzmann MF, Subar AF, Hollenbeck A, Schatzkin A. Dairy food, calcium, and risk of cancer in the NIH-AARP Diet and Health Study. Arch Intern Med 2009;169:391–401.

87. Baron JA, Beach M, Mandel JS, et al., Calcium Polyp Prevention Study Group. Calcium supplements for the prevention of colorectal adenomas. N Engl J Med 1999;340:101–7.

88. Bonithon-Kopp C, Kronborg O, Giacosa A, Räth U, Faivre J. European Cancer Prevention Organisation Study Group. Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial. Lancet 2000;356:1300–6.

89. Willett WC. Take a multivitamin for insurance. In: Willit WC, Skerrit PJ, eds. Eat, Drink, and Be Healthy: the Harvard Medical School Guide to Healthy Eating. New York: Simon & Schuster Source, 2001:205–36.

90. Leung Yinko SS, Pelletier R, Behlouli H, et al., GENESIS-PRAXY Investigators. Potential factors associated with fruit and vegetable intake after premature acute coronary syndrome: a prospective cohort study. Int J Food Sci Nutr 2015;66:943–9.

91. Peto R, Awasthi S, Read S, Clark S, Bundy D. Vitamin A supplementation in Indian children - Authors' reply. Lancet 2013;382:594–6.

92. Anderson TJ, Boden WE, Desvigne-Nickens P, et al., AIM-HIGH Investigators. Safety profile of extended-release niacin in the AIM-HIGH trial. N Engl J Med 2014;371:288–90.

93. Health Canada. Summary of Guiding Principles and Recommendations. 2017. Available at: https://www.foodguideconsultation.ca/guiding-principles-summary. Accessed April 17, 2018.

94. Keene D, Price C, Shun-Shin MJ, Francis DP. Effect on cardiovascular risk of high density lipoprotein targeted drug treatments niacin, fibrates, and CETP inhibitors: meta-analysis of randomised controlled trials including 117,411 patients. BMJ 2014;349:g4379.

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

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