Selenium, antioxidants, cardiovascular disease, and all-cause mortality: a systematic review and meta-analysis of randomized controlled trials

David JA Jenkins,[1,2,3,4,5] David Kitts,[6] Edward L Giovannucci,[7] Sandhya Sahye-Pudaruth,[1,4] Melanie Paquette,[1,4] Sonia Blanco Mejia,[1,3,4] Darshna Patel,[1,4] Meaghan Kavanagh,[1,4] Tom Tsirakis,[4] Cyril WC Kendall,[1,3,4,8] Sathish C Pichika,[1,9] and John L Sievenpiper[1,2,3,4,5]

[1]Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; [2]Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada; [3]Toronto 3D Knowledge Synthesis and Clinical Trials Unit, Toronto, Ontario, Canada; [4]Clinical Nutrition Risk Factor Modification Centre, St. Michael's Hospital, Toronto, Ontario, Canada; [5]Division of Endocrinology and Metabolism, St. Michael's Hospital, Toronto, Ontario, Canada; [6]Food Nutrition and Health, Faculty of Land and Food Systems, University of British Columbia, Vancouver, British Columbia, Canada; [7]Department of Nutrition and Epidemiology, Harvard TH Chan School of Public Health, Boston, MA, USA; [8]College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, Saskatchewan, Canada; and [9]Department of Mathematics and Statistics, University of Windsor, Windsor, Canada

ABSTRACT

Background: Antioxidants have been promoted for cardiovascular disease (CVD) risk reduction and for the prevention of cancer. Our preliminary analysis suggested that only when selenium was present were antioxidant mixtures associated with reduced all-cause mortality.

Objective: We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to determine the effect of selenium supplementation alone and of antioxidant mixtures with or without selenium on the risk of CVD, cancer, and mortality.

Methods: We identified studies using the Cochrane Library, Medline, and Embase for potential CVD outcomes, cancer, and all-cause mortality following selenium supplementation alone or after antioxidant supplement mixtures with and without selenium up to June 5, 2020. RCTs of ≥24 wk were included and data were analyzed using random-effects models and classified by the Grading of Recommendations, Assessment, Development, and Evaluation approach.

Results: The meta-analysis identified 9423 studies, of which 43 were used in the final analysis. Overall, no association of selenium alone or antioxidants was seen with CVD and all-cause mortality. However, a decreased risk with antioxidant mixtures was seen for CVD mortality when selenium was part of the mix (RR: 0.77; 95% CI: 0.62, 0.97; $P = 0.02$), with no association when selenium was absent. Similarly, when selenium was part of the antioxidant mixture, a decreased risk was seen for all-cause mortality (RR: 0.90; 95% CI: 0.82, 0.98; $P = 0.02$) as opposed to an increased risk when selenium was absent (RR: 1.09; 95% CI: 1.04, 1.13; $P = 0.0002$).

Conclusion: The addition of selenium should be considered for supplements containing antioxidant mixtures if they are to be associated with CVD and all-cause mortality risk reduction. This trial was registered at https://www.crd.york.ac.uk/PROSPERO/ as CRD42019138268. *Am J Clin Nutr* 2020;112:1642–1652.

Keywords: supplements, antioxidants, selenium, cardiovascular disease, all-cause mortality, meta-analysis

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Supplemental Tables 1–5 and Supplemental Figures 1–114 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

Address correspondence to DJAJ (e-mail: david.jenkins@utoronto.ca).

Abbreviations used: ARR, absolute risk reduction; CVD, cardiovascular disease; CER, control event rate; CHD, coronary heart disease; EER, experimental event rate; GPx, glutathione peroxidase; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; MI, myocardial infarction; NNH, number needed to harm; NNT, number needed to treat; RCT, randomized controlled trial; RRR, relative risk reduction; SOD, superoxide dismutase; USPSTF, US Preventive Services Task Force.

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Introduction

The US Preventive Service Task Force (USPSTF) has warned against the use of vitamin E and β-carotene as single or paired nutrient supplements (1). Yet these vitamins are included in significant quantities in multivitamin supplements that are taken by 33–39% (2) of Western populations. These vitamins have antioxidant properties, and there has been a longstanding interest in antioxidants to reduce the oxidative stress that promotes the aging process (3). Chronic diseases such as cardiovascular disease (CVD), diabetes, and cancer are closely related to aging, but studies using antioxidant supplements have not produced clear evidence of their benefit for these diseases (4–6) and show they may be associated with harm, especially in smokers (7, 8).

However, evidence is emerging that maintaining an active endogenous antioxidant system may be important, including adequate concentrations of selenium-dependent glutathione peroxidase (GPx) (9), which appears to support healthy aging (10). This selenium-dependent GPx reduces lipid hydroperoxides to their corresponding alcohols and water and so maintains intracellular redox status (11).

Selenium is required as a cofactor for the synthesis of this enzyme, and data suggest that reduced blood selenium concentrations are associated with an increased CVD incidence (12), certain cancers (13), and all-cause mortality (14).

We have therefore assessed the effect of selenium alone and in antioxidant supplement mixtures to determine whether its presence, with the potential to maintain endogenous antioxidant activity, resulted in a reduced risk rather than an increased risk of antioxidants for CVD and all-cause mortality, as suggested in a previous more general supplement meta-analysis (15).

Methods

We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) and of existing systematic reviews and meta-analyses up to June 5, 2020. We performed a literature search in the Cochrane Library, Medline, and Embase using search terms for dietary supplements (as well as the individual vitamin or mineral antioxidants of interest—as described in the "Vitamins and minerals assessed" section below), CVD and its components, cancer, and mortality. See **Supplementary Table 1** for our full search terms. The search was limited to meta-analyses of RCTs and single RCTs. Meta-analyses were reviewed to identify any further studies not identified from the search. We included RCT studies in human adult populations where oral supplementation (selenium alone and antioxidant mixtures with and without selenium) was provided for a duration of at least 24 wk and where there was a comparable placebo with no other unmatched confounding interventions in either the supplementation or the control group. Only published data on CVD, cancer, and all-cause mortality outcomes were used. Excluded were studies conducted in laboratory animals, children, pregnant and breast-feeding women, and those with chronic infections (e.g., HIV and hepatitis C). Interventions combining other supplements than those specified were excluded as well as studies that were observational, supplements provided intravenously, and studies lasting <24 wk.

Full-article review and data extraction were conducted by 2 independent investigators (MP, SS-P), with all disagreements reconciled through consensus. The extracted data included number of cases and total number of participants for the intervention and the control groups. Where multiple intervention groups existed (e.g., factorial design studies), data from all control groups and all supplement groups were extracted and combined. Data were analyzed using Review Manager (RevMan) version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration), and publication bias analysis was conducted using STATA software, version 16.1 (StataCorp). The methods have been described in detail elsewhere (15). To obtain summary estimates, data were pooled using the Mantel-Haenszel method with data presented using 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 (16). Publication bias was investigated by visual inspection of funnel plots and quantitative assessment using Begg's and Egger's tests where $P < 0.05$ was considered evidence of a significant small study effect (17, 18). 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 or absolute risk increase, respectively (ARR) (NNT = 1/ARR, NNH = 1/ARR) (19). ARR can be calculated either as the difference between the control event rate (CER) and experimental event rate (EER) (ARR = CER – EER) (19) or by multiplying the CER by the relative risk reduction (RRR) (ARR = CER × RRR); RRR is calculated as 1 – RR (20). The latter approach was used in this analysis to avoid infinite NNT values in some situations (**Supplementary Table 2**, Method A).

Vitamins and minerals assessed

We confined our assessment to combinations of antioxidants (antioxidant mixtures) rather than single antioxidants with the exception of selenium, which was also assessed as a single supplement. The supplements of antioxidant mixtures consisted of combinations of 2 or more of the following: vitamin A, retinol, β-carotene, vitamin C, vitamin E, selenium, zinc, and copper as composite entities. These antioxidants were selected because they were included in the 2012 Cochrane Review (21), to which we added retinol as part of vitamin A as well as zinc and copper as metals associated with the synthesis or activity of the endogenous antioxidant system (22, 23). The antioxidants used in specific studies included in this analysis are shown in **Supplementary Table 3**.

Outcomes

The primary outcomes of the review are total CVD, CVD mortality, total cancer, cancer mortality, and all-cause mortality. The secondary outcomes of the review are coronary heart disease (CHD), CHD mortality, myocardial infarction (MI), MI mortality, stroke, and stroke mortality.

Dose-response analysis

Post hoc dose-response analysis was completed for all-cause mortality by categories of selenium doses. Linear dose response for selenium use in trials of antioxidants on risk of all-cause mortality was assessed by using random-effects meta-regression. Nonlinear dose-response analysis in the same trials was assessed using a 2-stage multivariate random-effects method with restricted cubic splines and a knot at 50 mcg/d of selenium.

Exploratory analyses

A prespecified exploratory analysis was conducted to determine whether geographic locations affected the outcome, and a further post hoc analysis was conducted stratified by participants' health or risk status.

Risk of bias

The Cochrane Risk of Bias Tool, which is based on randomization, allocation concealment, blinding, completeness of follow-up, and an intention-to-treat analysis, was used to assess eligible RCTs (24).

Grading of the evidence

The quality and strength of the evidence was assessed as described previously using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool (25, 26). Using the GRADE tool, evidence was graded as high-, moderate-, low-, or very low-quality evidence. By default, RCTs are 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 interstudy heterogeneity, $I^2 > 50\%$ and $P < 0.10$; indirectness (presence of factors that limit the generalizability of the results); imprecision [the 95% CI for effect estimates crosses a minimally important difference of 5% (RR, 0.95–1.05) from the line of unity]; and publication bias (significant evidence of small study effects).

Results

Assessment of the search results identified a total number of 43 single RCTs (27–69). The study flow diagram is presented in **Figure 1**. Study characteristics, GRADE assessments, search results, and the Cochrane risk of bias are also reported (**Supplementary Tables 3–5**; **Supplementary Figures 1–3**).

Selenium alone and antioxidant mixtures with and without selenium

Selenium taken alone (**Supplementary Figures 4–15**) and combined antioxidants (**Supplementary Figures 16–27**) were not associated with CVD outcomes, CVD mortality, cancer, cancer mortality, or all-cause mortality. However, when the antioxidant trials were separated into those that included selenium as part of the antioxidant supplement mix compared with those that did not (**Supplementary Figures 28–38**), a decreased risk was seen for CVD mortality when selenium was part of the antioxidant mix (RR: 0.77; 95% CI: 0.62, 0.97; $P = 0.02$; $I^2 = 0\%$), which was not observed when selenium was not part of the mix (RR: 1.05; 95% CI: 0.97, 1.15; $P = 0.23$; $I^2 = 0\%$). Furthermore, these 2 antioxidant groups (with and without selenium) were significantly different ($P = 0.01$; $I^2 = 84.3\%$; **Figure 2**). Opposite responses between these 2 antioxidant groups were also observed for all-cause mortality (**Figure 3**), in which a decreased risk was seen for all-cause mortality when selenium was included (RR: 0.90; 95% CI: 0.82, 0.98; $P = 0.02$; $I^2 = 0\%$), while for antioxidant mixtures without selenium, there was evidence for increased risk (RR: 1.09; 95% CI: 1.04, 1.13; $P = 0.0002$; $I^2 = 0\%$). These 2 antioxidant groups were also significantly different ($P = 0.0002$; $I^2 = 92.8\%$). There was no effect on cancer incidence and mortality. The quality of the evidence was considered moderate for antioxidants and low for selenium supplementation only by GRADE assessment.

Dose-response analysis

Dose-response analysis by category of doses showed no significant findings for selenium-only trials and antioxidant trials containing selenium (**Supplementary Figures 39–40**). **Supplementary Figures 41** and **42** show the linear and nonlinear dose-response relation between selenium and all-cause mortality risk in trials with antioxidants. There was a significant linear ($P = 0.004$) and nonlinear ($P = 0.013$) dose response seen for the addition of selenium to antioxidants on all-cause mortality. The addition of selenium to the antioxidant mix was associated with a decrease in the risk for all-cause mortality. However, a dose greater than 50 mcg/d did not seem to reduce the risk further (Supplementary Figure 42).

Exploratory analyses by health or risk status

Studies stratified by health or risk status of the population **(Supplementary Figures 43–45)** showed significant findings for all-cause mortality only. Six trials were identified of healthy individuals who had no preexisting disease or were considered at increased risk (**Figure 4**). Of those 6 trials, the 4 with selenium in the antioxidant mix showed a decreased risk for all-cause mortality (RR: 0.89; 95% CI: 0.81, 0.98; $P = 0.02$; $I^2 = 0\%$), with no effect seen in the 2 trials without selenium (RR: 1.08; 95% CI: 0.96, 1.23; $P = 0.21$; $I^2 = 0\%$). The difference between the 2 antioxidant groups was significant ($P = 0.01$; $I^2 = 83\%$).

Seventeen trials were identified in higher-risk individuals (e.g., history of CVD, cancer, precancerous lesions, pulmonary artery disease, hypercholesterolemia, institutionalized). In the 4 studies with selenium in the antioxidant mix, there was no association with all-cause mortality, but in the 13 trials without selenium, a possible borderline significant increased risk was seen (RR: 1.05, 95% CI: 0.99, 1.12; $P = 0.08$; $I^2 = 0\%$; Figure 4). The difference between these 2 antioxidant groups was not significant ($P = 0.54$; $I^2 = 0\%$).

Four trials were identified in smokers (possibly the highest risk group) (Figure 4). Unfortunately, no trials were identified

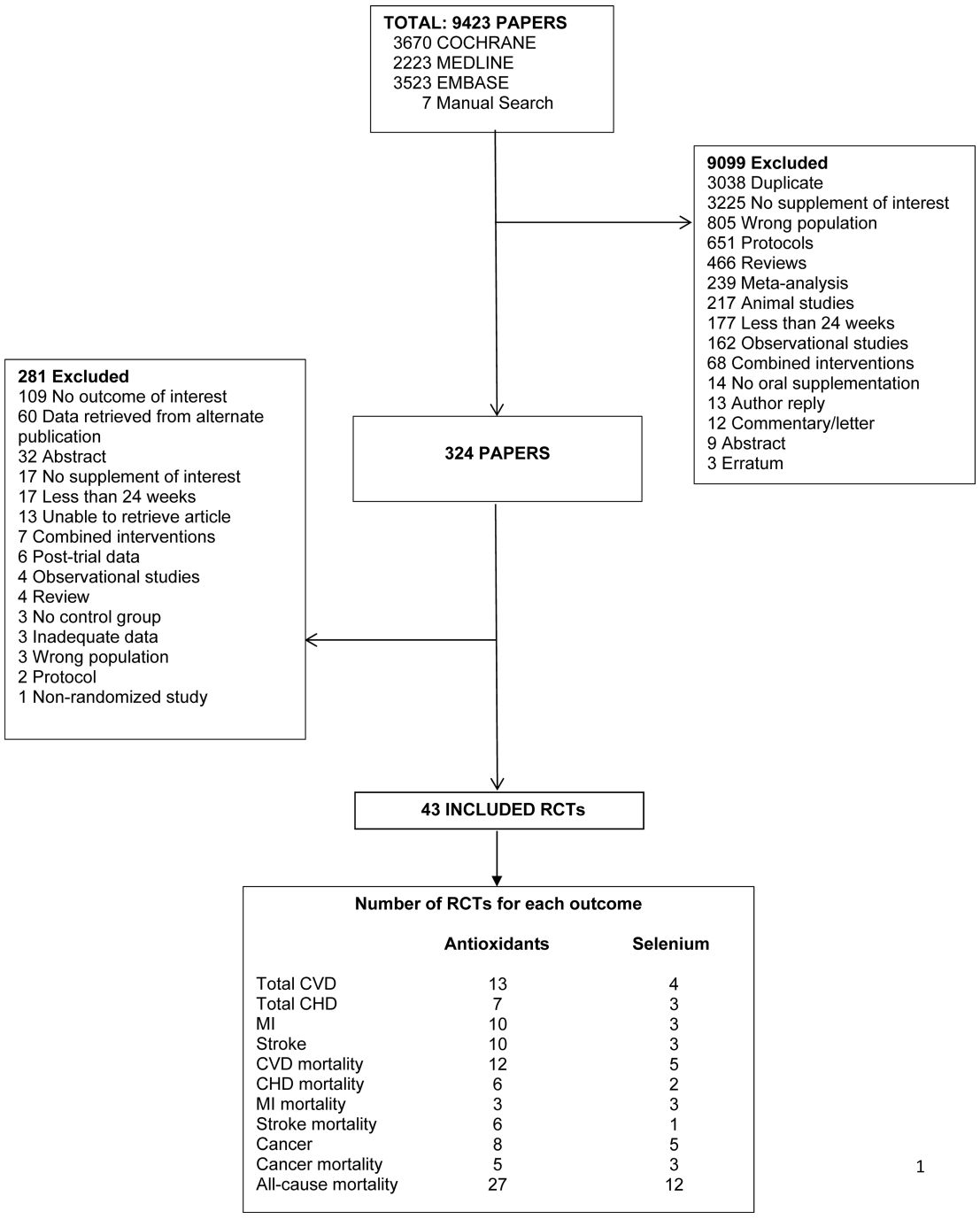

FIGURE 1 Search summary. Flow diagram outlining the search strategy used to identify publications that report RCT data on antioxidant supplementation and risk of CVD, cancer, and all-cause mortality. The publications are from database inceptions to June 5, 2020, of single RCTs identified by searching Cochrane, Medline, and Embase and by manual searches. Titles and abstracts were reviewed in the first stage of screening while full-manuscript review was done in the second stage. CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction, RCT, randomized controlled trial.

with selenium in the antioxidant mix, but the 4 trials without selenium were associated with the greatest increase in risk for all-cause mortality (RR: 1.13, 95% CI: 1.04, 1.21; $P = 0.002$; $I^2 = 0\%$).

These assessments yielded no significant effects for CVD or CVD mortality probably due to the limited numbers in each group (Supplementary Figures 43–44).

Sequential removal of nonselenium antioxidants

Removal of other specific antioxidants (e.g., vitamins A, C, and E; β-carotene; retinol; and zinc) singly did not influence the outcomes (**Supplementary Figures 46–111**) at the significance level $P < 0.05$, with the exception of zinc. Although studies with zinc were not associated with any change in all-cause mortality (RR: 0.94; 95% CI: 0.85, 1.04; $P = 0.25$; $I^2 = 0\%$),

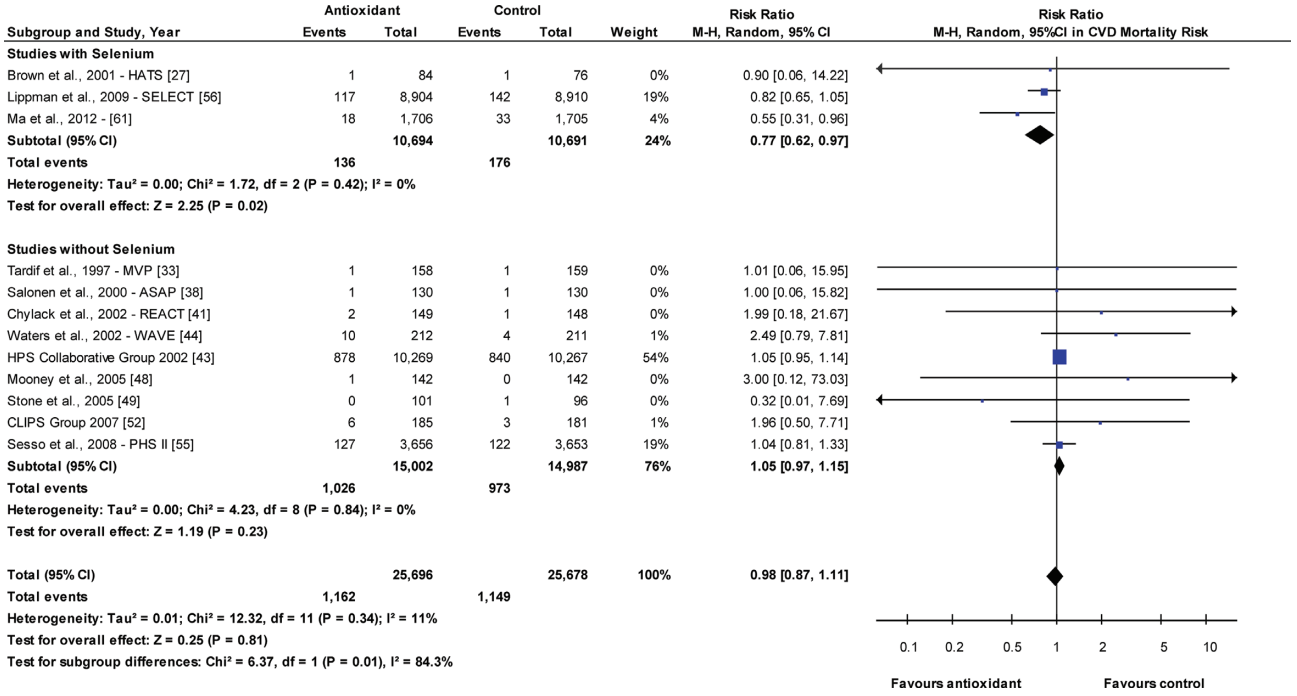

FIGURE 2 Sensitivity analysis of antioxidant supplementation and CVD mortality risk for studies with and without selenium. The diamond represents the pooled risk estimate. Interstudy heterogeneity was tested using the Cochran Q statistic (χ^2) at a significance level of $P < 0.10$ and quantified by the I^2 statistic. An I^2 value $\geq$50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% confidence intervals, using the Mantel-Haenszel method with a random-effects model. NNT for antioxidant supplementation and CVD mortality risk for studies with selenium is 264. The 2 antioxidant groups are significantly different ($P = 0.01$; $I^2 = 84.3\%$). ASAP, Antioxidant Supplementation in Atherosclerosis Prevention; CLIPS, Critical Leg Ischaemia Prevention Study; CVD, cardiovascular disease; HATS, HDL-Atherosclerosis Treatment Study; HPS, Heart Protection Study Collaborative Group; M-H, Mantel-Haenszel; MVP, Multivitamins and Probucol Study Group; NNT, number needed to treat; PHS, Physicians' Health Study; REACT, Roche European American Cataract Trial; SELECT, Selenium and Vitamin E Cancer Prevention; SIT, Shadong Intervention Trial; WAVE, Women's Angiographic Vitamin and Estrogen.

antioxidant mixtures that lacked zinc increased the risk of all-cause mortality (RR: 1.07; 95% CI: 1.01, 1.13; $P = 0.02$; $I^2 = 14\%$; Supplementary Figure 100) with a significant difference between these antioxidant groups ($P = 0.03$; $I^2 = 78.6\%$). In addition the Blot trial (30) in Linxian, China, which included zinc, showed a borderline reduction in risk for stroke mortality (RR: 0.71; 95% CI: 0.5, 1.00; $P = 0.05$; Supplementary Figure 97).

Retinol was borderline significant for reducing risk from stroke mortality (RR: 0.71; 95% CI: 0.5, 1.00; $P = 0.05$) and cancer mortality (RR: 0.75, 95% CI: 0.57, 1.00; $P = 0.05$) (Supplementary Figures 108 and 110). The caveat is that these associations are based on a single Chinese trial, the Linxian trial, with different baseline vitamin intake concentrations from North American and European trials (30).

Antioxidants trials from areas with high or low soil selenium

Dividing the studies into areas of higher soil selenium content (the Americas) and lower soil selenium content (Europe and Asia) (70), the 2 studies with higher soil selenium content showed no significant risk reduction when selenium was included in the antioxidant mix, but for the 14 studies in which there was no selenium in the antioxidant supplement, this antioxidant mix was associated with a significantly increased risk of all-cause mortality (RR: 1.13, 95% CI: 1.05, 1.22; $P = 0.0006$; $I^2 = 0\%$; **Supplementary Figure 112**). A similar pattern was seen in studies with low soil selenium; studies with selenium in the antioxidant mix were associated with a decreased risk (RR: 0.88; 95% CI: 0.78, 0.98; $P = 0.02$; $I^2 = 0$) while those without selenium were associated with an increased risk of all-cause mortality (RR: 1.06, 95% CI: 1.01, 1.12; $P = 0.03$; $I^2 = 0\%$; Supplementary Figure 112). Again, no differences between antioxidant groups were seen for CVD or CVD mortality due to the limited data (**Supplementary Figures 113–114**).

Discussion

Our findings suggest that inclusion of selenium, as part of the antioxidant mix, is important to allow the associated decreased risk of antioxidants on CVD and all-cause mortality to be seen. Although definitive benefits of antioxidants have proved elusive (71), there is a long history of interest in mechanisms by which antioxidants might reduce the risk of chronic diseases, especially CVD and cancer—for example, reducing concentrations of oxidized LDL (4) and reducing oxidative damage to DNA (and the formation of 8-OH-2 deoxyguanosine) (72). Our analysis of trials that have included selenium in the antioxidant mix support continued interest in the relation between antioxidant activity and disease. However, our demonstration of significantly increased CVD and all-cause mortality risk when selenium was absent

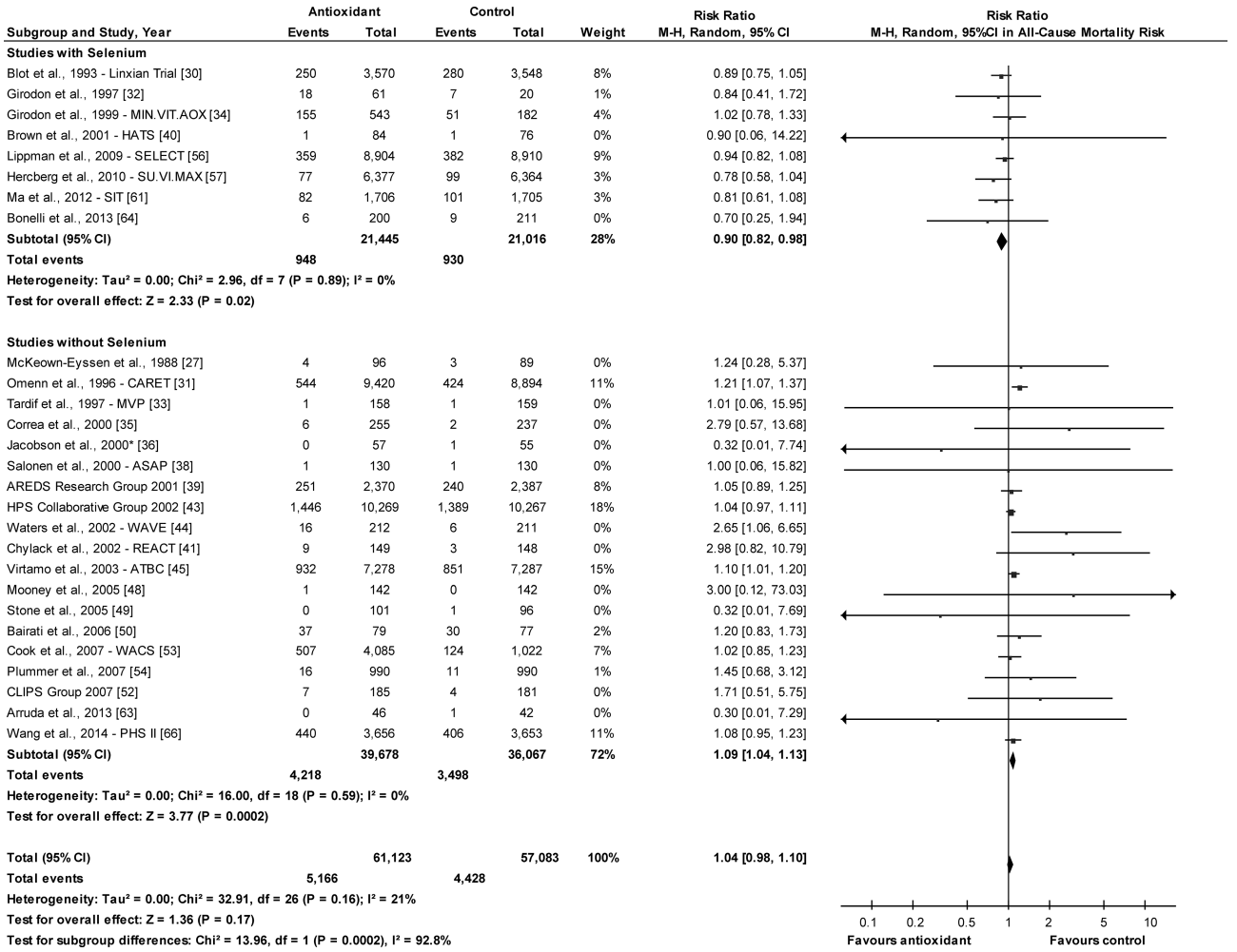

FIGURE 3 Sensitivity analysis of antioxidant supplementation and all-cause mortality risk for studies with and without selenium. The diamond represents the pooled risk estimate. Interstudy heterogeneity was tested using the Cochran Q statistic (χ^2) at a significance level of $P < 0.10$ and quantified by the I^2 statistic. An I^2 value $\geq$50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% confidence intervals, using the Mantel-Haenszel method with random-effects model. *Jacobson et al., 2000—data retrieved from meta-analysis (21). NNT for antioxidant supplementation and all-cause mortality risk for studies with selenium is 226. NNH for antioxidant supplementation and all-cause mortality risk for studies without selenium is 115. The 2 antioxidant groups are significantly different ($P = 0.0002$; $I^2 = 92.8\%$). AREDS, Age-Related Eye Disease Study; ASAP, Antioxidant Supplementation in Atherosclerosis Prevention; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CARET, Carotene and Retinol Efficacy Trial; CLIPS, Critical Leg Ischaemia Prevention Study; HATS, HDL-Atherosclerosis Treatment Study; HPS, Heart Protection Study Collaborative Group; M-H, Mantel-Haenszel; MINVITOAX, Mineral Vitamin Antioxidant; MVP, Multivitamins and Probucol Study Group; NNH, number needed to harm; NNT, number needed to treat; PHS, Physicians' Health Study; REACT, Roche European American Cataract Trial; SELECT, Selenium and Vitamin E Cancer Prevention; SIT, Shadong Intervention Trial; SU.VI.MAX, Supplémentation en Vitamines et Minéraux AntioXydants study; WACS, Women's Antioxidant Cardiovascular Study; WAVE, Women's Angiographic Vitamin and Estrogen.

from the antioxidant mix suggests that this process is finely balanced and selenium should be added to any supplement mix that includes antioxidants.

This antioxidant selenium phenomenon did not appear to be influenced by differences in soil and therefore dietary selenium concentrations, although we have no studies from areas with truly low or high concentrations of soil selenium as found in China (73).

Of major relevance to the present study is the 2013 conclusion of the USPSTF (74) "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 are recommended against) for the prevention of CVD and cancer."

Sequential exclusion of antioxidants other than selenium failed to produce the same increased risk of health effects seen with the exclusion of selenium, emphasizing the unique antioxidant role of selenium. An exception to this conclusion may be zinc, which is also part of the endogenous antioxidant system as a component of superoxide dismutase (SOD) (75). However, trials of selenium or zinc taken in isolation have not shown any generally agreed-on CVD or total mortality benefit (15), although diet, blood, and toenail selenium concentrations have been associated with a reduced risk of both overall (76) and aggressive prostate cancer (77).

The possibly differing effects of antioxidants in individuals at different levels of chronic disease risk have been raised (71). Our analyses indicate a potential benefit of antioxidants with selenium in healthy trial participants, no effect in trial participants with

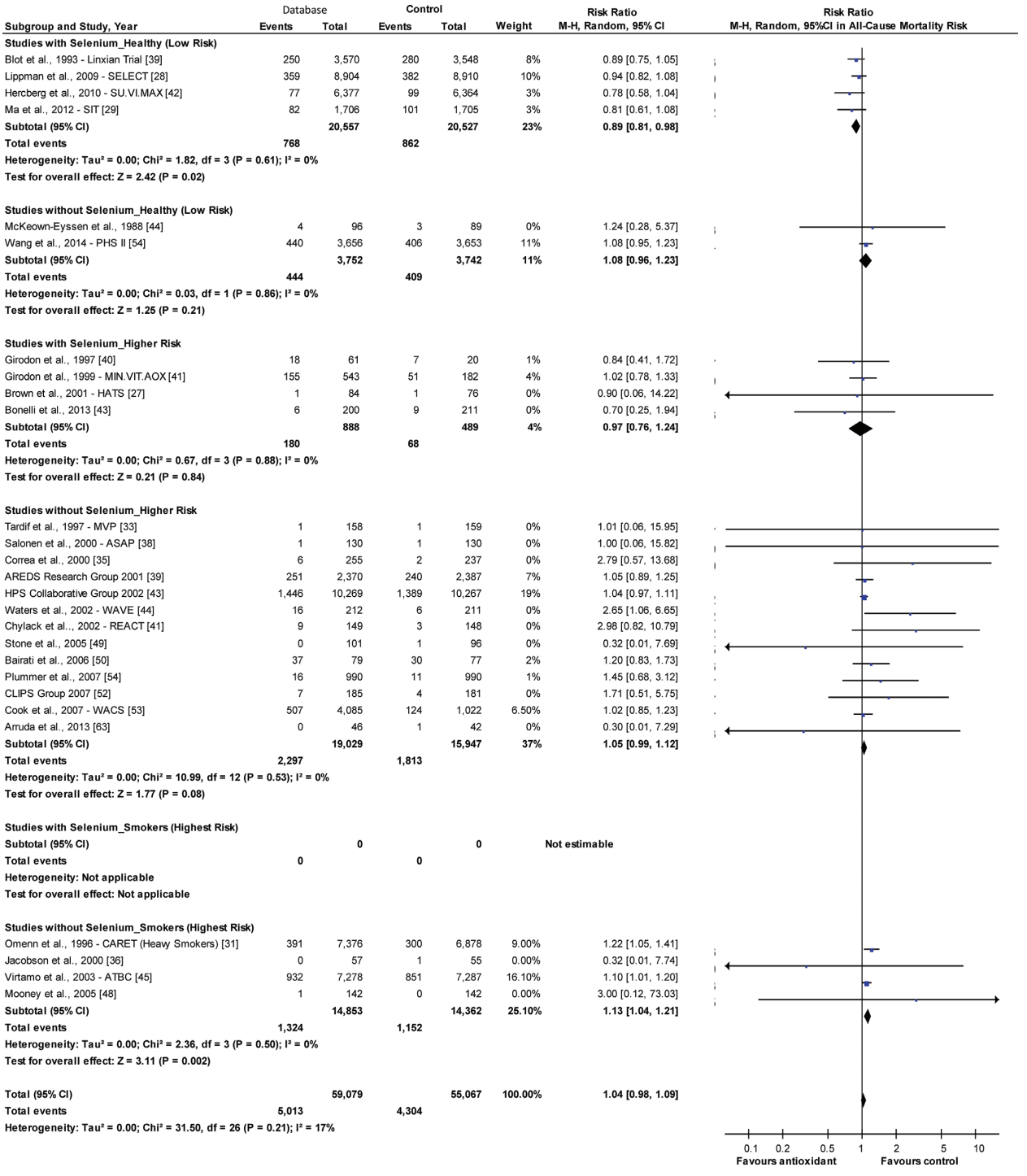

FIGURE 4 Forest plot showing antioxidants (with and without selenium) by smoking and health status and all-cause mortality. *Jacobson et al., 2000—data retrieved from meta-analysis (21). The diamond represents the pooled risk estimate. Interstudy heterogeneity was tested using the Cochran Q statistic (χ^2) at a significance level of $P < 0.10$ and quantified by the I^2 statistic. An I^2 value $\geq$50% is considered to indicate substantial heterogeneity. All results are presented as risk ratios with 95% confidence intervals, using the Mantel-Haenszel method with random-effects model. The difference between studies with and without selenium among the healthy (low-risk) group was significant ($P = 0.01$; $I^2 = 83.4\%$) while the difference within the higher risk group was not significant ($P = 0.54$; $I^2 = 0\%$), and there were no studies in the highest risk category (smokers) with selenium in the antioxidant mix. AREDS, Age-Related Eye Disease Study; ASAP, Antioxidant Supplementation in Atherosclerosis Prevention; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CARET, Carotene and Retinol Efficacy Trial; CLIPS, Critical Leg Ischaemia Prevention Study; HATS, HDL-Atherosclerosis Treatment Study; HPS, Heart Protection Study Collaborative Group; M-H, Mantel-Haenszel; MINVITOAX, Mineral Vitamin Antioxidant; MVP, Multivitamins and Probucol Study Group; PHS, Physicians' Health Study; REACT, Roche European American Cataract Trial; SELECT, Selenium and Vitamin E Cancer Prevention; SIT, Shadong Intervention Trial; SU.VI.MAX, Supplémentation en Vitamines et Minéraux AntioXydants study; WACS, Women's Antioxidant Cardiovascular Study; WAVE, Women's Angiographic Vitamin and Estrogen.

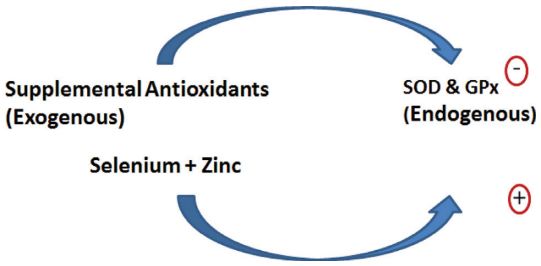

FIGURE 5 The opposing activity of supplemental antioxidants and selenium and zinc on the endogenous antioxidant system. GPx, glutathione peroxidase; SOD, superoxide dismutase.

a range of conditions or risk factors, and an increased risk of antioxidants without selenium with total mortality in smokers, as perhaps the highest risk group. These data support the concept that antioxidant supplementation may affect those with different levels of risk differently (71).

The antioxidant effects of selenium, zinc, and copper are not direct. They act through the endogenous antioxidant system that also involves SOD, GPx, and catalase. Selenium is essential for the synthesis of GPx and is part of the molecular structure (78) of GPx and other seleno-proteins (79). Likewise, zinc and copper are part of the structure of copper, zinc, and SOD (80, 81). These metals are therefore essential for the activity of the endogenous antioxidant system responsible for quenching the free radicals generated by metabolic processes. The system is finely balanced since the creation of oxidative damage by WBCs is the mechanism by which invading pathogens are destroyed and abnormal or transformed cells removed as part of immune surveillance (80). It therefore appears that a balancing process may exist such that when dietary antioxidants are provided in excess amounts as supplements, the large rise in serum antioxidant activity will suppress the expression of the endogenous antioxidant system (e.g., SOD and GPx) (**Figure 5**). The presence of higher concentrations of selenium and zinc may promote the rapid and necessary rebound in the endogenous antioxidant system to reverse the suppression of endogenous antioxidant activity that would otherwise leave tissues vulnerable to pro-oxidant stresses, such as postprandial events and smoking (82, 83) (Figure 5). Over time, vulnerable populations such as the elderly and those with preexisting CVD or transformed cells in precancerous lesions may be more vulnerable to the effects of oxidative stress. The adverse effects of antioxidants in smokers, for example, in the Carotene and Retinol Efficacy Trial and Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study that resulted in increased rather than reduced lung cancer incidence (7, 8) might have been due to suppression of the endogenous antioxidant system by the antioxidant supplements provided and may have made trial populations of smokers more vulnerable to the pro-oxidant activity of tobacco smoke (83).

There is a non-CVD caveat for the use of selenium with antioxidants from the Selenium and Vitamin E Cancer Prevention trial ($n = 35{,}533$) that demonstrated possible increased risk for high-grade prostate cancer and type 2 diabetes in participants taking vitamin E and selenium (56, 84). Weak evidence for this association was also found in a large Mendelian randomization study (85). Our data suggest that selenium and zinc supplementation should be part of any antioxidant supplement mixture aimed at reducing CVD risk. However, until we clarify the long-term selenium effect on antioxidant supplement use, a balanced diet rich in antioxidant foods, fruit, vegetables, legumes, whole-grain cereals, and nuts and seeds (86, 87) may be the safer approach (88), as selenium and zinc will come naturally as components of antioxidant-rich foods.

Strengths and Limitations. The study strength lies in having a sufficient number of trials with and without selenium to allow the effect on CVD and all-cause mortality to be determined and the ability to assess all-cause mortality in different geographic areas with different soil selenium contents and in individuals with differing risk factors for chronic disease, especially smokers.

The weaknesses of this study include the inclusion of trials with low event rates and where CVD and all-cause mortality were not the primary outcomes. A major deficiency was the lack of trials in smokers with selenium in the antioxidant mix that might have more clearly demonstrated the potential value of selenium addition. Finally, for selenium taken alone, there is a lack of consistency in the few long-term studies (42, 51, 56) and a relative lack of long-term dose-response studies. However, 1 study demonstrated that selenium consumed alone at doses of 300 μg had adverse effects on all-cause mortality in the 10-y follow-up after a 5-y supplementation. However, the nonsignificant increase in CVD and cancer mortality was not seen at 100-μg and 200-μg doses (89). These data may help inform the safe upper level for selenium inclusion in antioxidant mixtures, especially as our dose-response data show no added benefit above 50 μg/d.

Conclusion. We conclude that if antioxidant supplements are to have a benefit in reducing CVD and all-cause mortality, then inclusion of selenium and possibly zinc may be important to maintain endogenous antioxidant activity.

The authors' responsibilities were as follows——DJAJ: conceptualized the meta-analysis and designed the overall research plan; MP and SS-P: conducted the database search, screened studies for inclusion, extracted and analyzed the data, and revised the manuscript; DJAJ, DK, ELG, and JLS: drafted and revised the manuscript; SBM and TT: analyzed the data and revised the manuscript; DP, MK, CK, and SCP: revised the manuscript; DJAJ: is the study guarantor; and all authors: reviewed and approved the final version of the manuscript.

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for the Food Industry; his 2 daughters, Wendy Jenkins and Amy Jenkins, have published a vegetarian book that promotes the use of the plant foods advocated here, The Portfolio Diet for Cardiovascular Risk Reduction; and his sister, Caroline Brydson, received funding through a grant from the St. Michael's Hospital Foundation to develop a cookbook for one of his studies. CWCK has received grants or research support from the Advanced Food Materials Network, Agriculture and Agri-Foods Canada (AAFC), Almond Board of California, American Peanut Council, Barilla, Canadian Institutes of Health Research (CIHR), Canola Council of Canada, International Nut and Dried Fruit Council, International Tree Nut Council Research and Education Foundation, Loblaw Brands Ltd, Pulse Canada, and Unilever. He 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/Danone. He has received travel support and/or honoraria from the American Peanut Council, 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, Sun-Maid, Tate & Lyle, Unilever, and White Wave Foods/Danone. He has served on the scientific advisory board for the International Tree Nut Council, International Pasta Organization, McCormick Science Institute, and Oldways Preservation Trust. He is a member of the International Carbohydrate Quality Consortium (ICQC), is 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 a director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. JLS has received research support from the Canadian Foundation for Innovation, Ontario Research Fund, Province of Ontario Ministry of Research and Innovation and Science, Canadian Institutes of Health Research (CIHR), Diabetes Canada, PSI Foundation, Banting and Best Diabetes Centre (BBDC), American Society for Nutrition (ASN), INC International Nut and Dried Fruit Council Foundation, National Dried Fruit Trade Association, The Tate and Lyle Nutritional Research Fund at the University of Toronto, The Glycemic Control and Cardiovascular Disease in Type 2 Diabetes Fund at the University of Toronto (a fund established by the Alberta Pulse Growers), and the Nutrition Trialists Fund at the University of Toronto (a fund established by an inaugural donation from the Calorie Control Council). He has received in-kind food donations to support a randomized controlled trial from the Almond Board of California, California Walnut Commission, American Peanut Council, Barilla, Unilever, Upfield, Unico/Primo, Loblaw Companies, Quaker, Kellogg Canada, WhiteWave Foods, and Nutrartis. He has received travel support, speaker fees, and/or honoraria from Diabetes Canada, Dairy Farmers of Canada, FoodMinds LLC, International Sweeteners Association, Nestlé, Pulse Canada, Canadian Society for Endocrinology and Metabolism (CSEM), GI Foundation, Abbott, Biofortis, ASN, Northern Ontario School of Medicine, INC Nutrition Research & Education Foundation, European Food Safety Authority (EFSA), Comité Européen des Fabricants de Sucre (CEFS), and Physicians Committee for Responsible Medicine. He has or has had ad hoc consulting arrangements with Perkins Coie LLP, Tate & Lyle, Wirtschaftliche Vereinigung Zucker e.V., and Inquis Clinical Research. He is a member of the European Fruit Juice Association Scientific Expert Panel and Soy Nutrition Institute (SNI) Scientific Advisory Committee. He is on the Clinical Practice Guidelines Expert Committees of Diabetes Canada, European Association for the Study of Diabetes (EASD), Canadian Cardiovascular Society (CCS), and Obesity Canada. He serves or has served as an unpaid scientific advisor for the Food, Nutrition, and Safety Program (FNSP) and the Technical Committee on Carbohydrates of the International Life Science Institute (ILSI) North America. He is a member of the International Carbohydrate Quality Consortium (ICQC), executive board member of the Diabetes and Nutrition Study Group (DNSG) of the EASD, and director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. His wife is an employee of AB InBev. DK, ELG, SS-P, MP, SBM, DP, MK, TT, and SCP have no conflicts of interest to declare.

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