REVIEW

Evaluating Concordance of Bodies of Evidence from Randomized Controlled Trials, Dietary Intake, and Biomarkers of Intake in Cohort Studies: A Meta-Epidemiological Study

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ABSTRACT

We aimed to identify and compare empirical data to determine the concordance of diet–disease effect estimates of bodies of evidence (BoE) from randomized controlled trials (RCTs), dietary intake, and biomarkers of dietary intake in cohort studies (CSs). The Cochrane Database of Systematic Reviews and MEDLINE were searched for systematic reviews (SRs) of RCTs and SRs of CSs that investigated both dietary intake and biomarkers of intake published between 1 January 2010 and 31 December 2019. For matched diet–disease associations, the concordance between results from the 3 different BoE was analyzed using 2 definitions: qualitative (e.g., 95% CI within a predefined range) and quantitative (test hypothesis on the *z* score). Moreover, the differences in the results coming from BoE_{RCTs}, $BoE_{CSs\ dietary\ intake}$, and $BoE_{CSs\ biomarkers}$ were synthesized to get a pooled ratio of risk ratio (RRR) across all eligible diet–disease associations, so as to compare the 3 BoE. Overall, 49 diet–disease associations derived from 41 SRs were identified and included in the analysis. Twenty-four percent, 10%, and 39% of the diet–disease associations were qualitatively concordant comparing BoE_{RCTs} with $BoE_{CSs\ dietary\ intake}$, BoE_{RCTs} with $BoE_{CSs\ biomarkers}$, and comparing both BoE from CSs, respectively; 88%, 69%, and 90% of the diet–disease associations were quantitatively concordant comparing BoE_{RCTs} with $BoE_{CSs\ dietary\ intake}$, BoE_{RCTs} with $BoE_{CSs\ biomarkers}$, and comparing both BoE from CSs, respectively. The pooled RRRs comparing effects from BoE_{RCTs} with effects from $BoE_{CSs\ dietary\ intake}$ were 1.09 (95% CI: 1.06, 1.13) and 1.18 (95% CI: 1.10, 1.25) compared with $BoE_{CSs\ biomarkers}$. Comparing both BoE from CSs, the difference in the results was also small (RRR: 0.92; 95% CI: 0.88, 0.96). Our findings suggest that BoE from RCTs and CSs are often quantitatively concordant. Prospective SRs in nutrition research should include, whenever possible, BoE from RCTs and CSs on dietary intake and biomarkers of intake to provide the whole picture for an investigated diet–disease association. *Adv Nutr* 2022;13:48–65.

Statement of Significance: Our findings suggest that bodies of evidence from randomized controlled trials and cohort studies are often concordant.

Keywords: meta-epidemiological, dietary intake, biomarkers of intake, concordance, randomized controlled trials, cohort studies

Introduction

The Global Burden of Disease (GBD) Study Group showed that noncommunicable diseases (NCDs) accounted for nearly 75% of deaths worldwide (1), and evidence from prospective cohort studies (CSs) showed that suboptimal diet accounted for 22% of all deaths worldwide (2). Bodies of evidence (BoE) from CSs with clinical outcomes provide valuable insights into diet–disease relations and are the most important evidence source of GBD reports and dietary guidelines (2, 3). However, nutritional epidemiology has been criticized for providing potentially less trustworthy findings (4). Therefore, limitations of CSs, such as residual confounding and measurement error, need to be considered (4). In CSs, self-reported dietary assessment methods are often used, but have limitations impacting validity and reliability. Dietary biomarkers provide objective verification of self-reported dietary intakes, and can complement and strengthen credibility of diet–disease associations (5). On

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TABLE 1 Detailed description of inclusion criteria

	Inclusion criteria
Population	Generally healthy participants (adults).
Intervention/exposure (dietary intake and biomarkers of dietary intake)	1. Dietary pattern: e.g., Mediterranean diet, Dietary Approaches to Stop Hypertension (DASH), low-carbohydrate diet. 2. Food groups: the following food groups (macro-level) and foods (micro-level) were considered: e.g., grains, vegetables, fruit, milk and dairy products, meat, processed meat, fish, eggs, nuts, chocolate, oils. 3. Macronutrients: carbohydrate (starch, fructose, glucose, sucrose); fat: e.g., n–3 fatty acids (EPA, DHA, α-linolenic acid); n–6 fatty acids (linoleic acid); monounsaturated fat; protein (e.g., amino acids).. 4. Micronutrients: vitamins: B-carotene; vitamins A, E, C (ascorbic acid), and D (cholecalciferol, ergocalciferol); B vitamins (thiamin, riboflavin, niacin, pyridoxine, cobalamin, folic acid); minerals: magnesium, calcium, selenium, sodium, potassium, iron, zinc, copper, iodine. 5. Other: fiber (psyllium, inulin, cellulose); probiotics; prebiotics; and synbiotics.
Control/comparison	1. Low (no) intake and status level of the above interventions/exposure. 2. Placebo/usual care.
Outcomes	For example, all-cause mortality, cardiovascular disease, coronary heart disease (myocardial infarction, ischemic heart disease, and acute coronary syndrome), stroke, cancer, type 2 diabetes, dementia, fractures, age-related macular degeneration, anthropometric outcomes; important intermediate disease markers such systolic blood pressure and diastolic blood pressure, fasting glucose, and LDL cholesterol.
Study design	1. Systematic reviews of randomized controlled trials. 2. Matching systematic reviews of cohort studies investigating both dietary intake and biomarkers of dietary intake: cohort studies (if available, prospective cohorts were preferred).

the other hand, RCTs, if well designed and well conducted, give robust answers to the research questions they address and are widely accepted as the ideal methodology for causal inference (6). However, dietary RCTs often suffer from inherent methodological limitations. In the past, several RCTs comparing dietary interventions with placebo or control interventions have failed to replicate the inverse associations between dietary intake/biomarkers of dietary intake and risk for NCDs found in large-scale CSs (7–10). For example, RCTs found no evidence for a beneficial effect of vitamin E and cardiovascular disease (11). On the contrary, some consistent findings between CSs and RCTs have been reported as well (e.g., omega-3 and stroke risk) (12), but to the best of our knowledge, no systematic evaluation of concordance between the 3 BoE has been conducted so far. This meta-epidemiological study aims to do exactly this, to identify and compare empirical data to determine the extent to which diet–disease effect estimates of BoE from RCTs, CSs on dietary intake, and CSs on biomarkers of dietary intake are concordant or discordant.

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Supplemental Appendixes 1 and 2, Supplemental Figures 1–10, Supplemental Tables 1–5, and Supplemental References are available from the "Supplemental 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/advances/.
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Abbreviations used: ACR, assumed control risk; BoE, bodies of evidence; CS, cohort study; GBD, Global Burden of Disease; NCD, noncommunicable disease; PI, prediction interval; PI/ECO, patients/population, intervention/exposure, comparator, and outcome; RCT, randomized controlled trial; RR, risk ratio; RRR, ratio of risk ratio; SR, systematic review.

Methods

This meta-epidemiological study was planned, written, and reported in adherence to guidelines for reporting meta-epidemiological methodology research (13). Inclusion criteria [patients/population, intervention/exposure, comparator, and outcome (PI/ECO)] are described in **Table 1**.

Identification of systematic reviews of RCTs

Search strategy.

We searched for systematic reviews (SRs) of RCTs, considering the inclusion criteria, in the Cochrane Database of Systematic Reviews (**Supplemental Appendix 1**) and MEDLINE (hand search), published within 1 January 2010 and 31 December 2019 (**Supplemental Figure 1**). Screening of titles/abstracts was done by 1 reviewer (LS), and then in the second stage, all potentially relevant full papers were screened for inclusion by 2 reviewers independently (JB, LS) using an inclusion/exclusion form specifically developed for the present study. By hand-searching, 17 additional SRs of RCTs were identified [12 of them were included (12, 14–24) and one of them was published in 2020 (16)]. Discrepancies were resolved by an additional reviewer.

Identification of matching SRs of CSs

Search strategy.

After all potentially relevant SRs of RCTs were identified, we searched for matching SRs of CSs. First, we screened all eligible SRs of RCTs, whether or not they also included CSs. Second, we conducted searches for matching SRs of CSs (only SRs of CSs were included, which investigated diet–disease associations on both dietary intake and biomarkers of intake for the same outcome) in MEDLINE, published within the last 10 y (**Supplemental Appendix 2** and **Supplemental**

Figure 2). We selected a time period of 10 y to ensure comparability between the 3 BoE. No language restriction was used. Screening of titles/abstracts was conducted by 1 reviewer (LS), and then, in the second stage, all potentially relevant full papers were screened for inclusion by 2 reviewers (LS, JB). By hand-searching, an additional 3 matching SRs of CSs were identified (24–26) [one of them was published in 2020 (26)]. The most appropriate (investigating similar PI/ECO) and comprehensive (most recent) matching SRs of CSs were selected for inclusion. For each eligible SR of RCTs we matched a maximum of 3 outcomes for a given intervention/exposure. Furthermore, in the Cochrane Reviews, the selection of outcomes was based on the ranking in the Summary of Findings tables (from top to bottom).

Data extraction

We extracted the following data for each included diet–disease association of a BoE_{RCTs}, $BoE_{CSs\ dietary\ intake}$, and $BoE_{CSs\ biomarkers}$: name of first author, year of publication, intervention/exposure, outcome, effect estimates [risk ratio (RR), HR, OR, 95% CI], type of comparison (e.g., high vs. low, dose-response), number of studies, number of participants, and number of cases included. The data were extracted by 2 reviewers (LS, JB) using a piloted data extraction form.

In cases where a BoE reported effect estimates based on a pool of studies of variable design (i.e., case-control, cross-sectional studies, retrospective cohort studies, or quasi-RCTs), we recalculated the pooled effect estimates by excluding non-cohort/non-RCT studies, while retaining the CSs/RCTs fulfilling our inclusion criteria. The meta-analyses were recalculated by combining the RRs of the corresponding study designs based on a random-effects model using the DerSimonian-Laird method (27). Using an inverse-variance method, the SE for the log-transformed RRs was calculated and interpreted as an estimated variance of log-transformed RR to weight each study. Also, if an intervention in a BoE of RCTs (e.g., low vs. high sodium) and an exposure in a BoE of CSs (e.g., high vs. low sodium) investigated opposite comparisons, we recalculated the risk estimates, respectively (e.g., low vs. high sodium). The analyses were conducted using the Review Manager by the Cochrane Collaboration (version 5.4) (28).

Methodological quality

The methodological quality of eligible SRs was evaluated using AMSTAR 2 (A Measurement Tool to Assess systematic Reviews, version 2) (29). Each SR was assessed based on 16 predefined items and rated in 1 of 4 categories (high, moderate, low, or critically low) according to the presence of critical and noncritical weaknesses. This assessment was done by 1 reviewer (JS).

Statistical analysis

The concordance between results from the eligible BoE_{RCTs}, $BoE_{CSs\ dietary\ intake}$, and $BoE_{CSs\ biomarkers}$ was assessed using 2 definitions (qualitative, quantitative). We defined as qualitatively concordant effect estimates of the outcome-specific BoE_{RCTs}, $BoE_{CSs\ dietary\ intake}$, and $BoE_{CSs\ biomarkers}$ that were statistically significant (at the 0.05 level) and were in the same direction (e.g., all RRs suggesting lower risk of disease). We defined qualitative concordant also effect estimates that were both not statistically significant with the 95% CI fully within the range of 0.80 to 1.25 (30). We also performed a secondary qualitative concordance analysis, considering a wider range for the CI (i.e., 0.70 to 1.30). If the effect estimate of the BoE_{RCTs} was expressed with a different measure than the effect estimate of a $BoE_{CSs\ dietary\ intake}$, or $BoE_{CSs\ biomarkers}$, the appropriate conversion formulas were used to have the estimates expressed in the same measure [e.g., RR and OR: the relevant formula requires an assumed control risk (ACR): $RR = \frac{OR}{1-ACR\ x\ (1-OR)}$] (31). The measure of quantitative concordance between effects estimates of the outcome-specific BoE_{RCTs}, $BoE_{CSs\ dietary\ intake}$, and $BoE_{CSs\ biomarkers}$ was calculated as follows (32, 33):

$$z = \frac{\text{effect BoE(RCTs)} - \text{effect BoE(CSs dietary intake)}}{\sqrt{\text{variance BoE(RCTs)} + \text{variance BoE(CSs dietary intake)}}} \sim N\ (0, 1) \quad (1)$$

$$z = \frac{\text{effect BoE(RCTs)} - \text{effect BoE(CSs biomarkers)}}{\sqrt{\text{variance BoE(RCTs)} + \text{variance BoE(CSs biomarkers)}}} \sim N\ (0, 1) \quad (2)$$

$$z = \frac{\text{effect BoE(CSs biomarkers)} - \text{effect BoE(CSs dietary intake)}}{\sqrt{\text{variance BoE(CSs biomarkers)} + \text{variance BoE(CSs dietary intake)}}} \sim N\ (0, 1) \quad (3)$$

We defined quantitative concordant results if the *P* value associated to the *z* was ≥0.017—that is, 0.5/3 (i.e., applying a Bonferroni correction). Moreover, we synthesized the differences in the results coming from BoE_{RCTs}, $BoE_{CSs\ dietary\ intake}$, and $BoE_{CSs\ biomarkers}$ to get a pooled difference across all eligible outcome pairs and compare the 3 BoE. These were expressed as ratio of risk ratios (RRRs) (33). By using $BoE_{CSs\ dietary\ intake}$ as the reference group, we examined the pooled estimate to see whether there was a relative larger (effect BoE_{RCTs} > effect $BoE_{CSs\ dietary\ intake}$) or smaller (effect BoE_{RCTs} < effect $BoE_{CSs\ dietary\ intake}$) estimate coming from BoE of RCTs. This procedure was adopted for the other 2 comparisons: BoE_{RCTs} vs. $BoE_{CSs\ biomarkers}$, and $BoE_{CSs\ biomarkers}$ vs. $BoE_{CSs\ dietary\ intake}$, respectively. We conducted a priori planned subgroup analyses: type of intervention/exposure, outcome. Finally, we also conducted a sensitivity analysis by using risk estimates for BoE from RCTs from SRs of CSs that included also RCTs. The pooled estimates were obtained through a random-effects meta-analysis model. We assessed heterogeneity through the I^2 and τ^2 statistics (34, 35). The τ^2 was estimated by the Paule and Mandel method (36, 37). Furthermore, the 95% prediction intervals (PIs) were obtained in order to show the range of possible values for the difference in the results between the different BoE that might be observed in future comparisons. These meta-analyses were performed using the R package meta (38).

Results

Overall, 20 SRs of RCTs (12, 14–24, 39–46) and 25 matching SRs of CSs were included in this study (12, 19, 24–26, 39, 47–65). One Cochrane Review and 3 SRs of RCTs also included CSs (12, 19, 24, 39). Forty-nine diet–disease

associations were included. Ten pooled estimates from 6 SRs were recalculated (24, 39, 49, 51, 60, 62). The number of primary studies contributing to the 49 diet–disease outcome pairs ranged from 1 to 64 (median: 5) for BoE from RCTs, and between 1 and 16 (median: 7) for BoE from CSs. The total number of participants ranged from 122 to 211,957 for BoE from RCTs, and from 1414 to 1,012,099 for BoE from CSs.

The interventions/exposures investigated in the identified SRs can be categorized into micronutrients ($n = 33$), fatty acids ($n = 15$), and phytonutrients ($n = 1$) and the outcomes cluster included the following: cancer ($n = 19$), cardiovascular disease ($n = 19$), overall mortality ($n = 7$), diabetes ($n = 2$), neurodegenerative disease ($n = 1$), and pregnancy outcomes (n = 1).

Tables 2 and **3** show the concordance between the summary effects of the 3 BoE using the 2 definitions. **Supplemental Tables 2–4** shows the general study characteristics.

Methodological quality of the included SRs

Of the 42 identified SRs, 27 studies (66%) were classified as critically low and 7 (17%) as low, whereas 2 (5%) were classified as moderate and 5 (12%) as high quality. Nine of the SRs including RCTs (45%) and 21 of the SRs including CSs (84%) were rated as critically low. Most SRs did not provide a list of excluded studies ($n = 29$; 71%) and did not report the presence or registration of a review protocol ($n = 25$; 61%). Moreover, 31 SRs (76%) did not provide funding information of the original studies, and 20 (49%) did not account for risk of bias in individual studies when discussing the results. Results of the quality assessment are presented in detail in **Supplemental Table 5**.

Qualitative concordance

In 98% (48/49) of the BoE_{RCTs} no statistically significant effect was observed, whereas 65% (32/49) from $BoE_{CSs\ dietary\ intake}$ and 53% (26/49) from $BoE_{CSs\ biomarkers}$ showed no statistically significant effect. Using the first definition of concordance, 12 (24%), 5 (10%), and 19 (39%) out of 49 eligible of the diet–disease associations were qualitatively concordant comparing BoE_{RCTs} with $BoE_{CSs\ dietary\ intake}$, BoE_{RCTs} with $BoE_{CSs\ biomarkers}$, and comparing both BoE from CSs, respectively (Table 2). Eight percent (4/49) of the diet–disease associations were qualitatively concordant considering all 3 BoE simultaneously. Considering a wider range for the CIs (i.e., 0.70 to 1.30), 35%, 20%, and 47% of the diet–disease associations were qualitatively concordant comparing BoE_{RCTs} with $BoE_{CSs\ dietary\ intake}$, BoE_{RCTs} with $BoE_{CSs\ biomarkers}$, and comparing both BoE from CSs, respectively.

Quantitative concordance

Using the second definition (calculated as z score), 88%, 69%, and 90% of the diet–disease associations were quantitatively concordant comparing BoE_{RCTs} with $BoE_{CSs\ dietary\ intake}$, BoE_{RCTs} with $BoE_{CSs\ biomarkers}$, and comparing both BoE from CSs, respectively (Table 3). Sixty-five percent (32/49) of the diet–disease associations were quantitatively concordant considering all 3 BoE simultaneously.

Pooled estimate

In order to compare overall effect estimates between the RCTs and CSs we calculated the pooled estimates using $BoE_{CSs\ dietary\ intake}$ and $BoE_{CSs\ biomarkers}$ as the reference group, which showed that overall BoE_{RCTs} had larger estimates compared with that of CSs (RRR: 1.09; 95% CI: 1.06, 1.13; $I^2 = 44\%$; PI: 0.96 to 1.24; and RRR: 1.18; 95% CI: 1.10, 1.25; $I^2 = 60\%$; PI: 0.83 to 1.66) (**Figures 1** and **2**). By using $BoE_{CSs\ dietary\ intake}$ as the reference group, we showed that the pooled estimate was a relative smaller estimate (RRR: 0.92; 95% CI: 0.88, 0.96; $I^2 = 58\%$; PI: 0.74 to 1.14) coming from $BoE_{CSs\ biomarkers}$ (**Figure 3**).

In subgroup analyses stratified by intervention type, the relative larger estimate was driven by micronutrient comparisons (BoE_{RCTs} vs. $BoE_{CSs\ dietary\ intake}$ RRR: 1.09; 95% CI: 1.05, 1.14; $I^2 = 56\%$; PI: 0.93 to 1.28; BoE_{RCTs} vs. $BoE_{CSs\ biomarkers}$ RRR: 1.19; 95% CI: 1.10, 1.30; $I^2 = 67\%$; PI: 0.79 to 1.81; $BoE_{CSs\ biomarkers}$ vs. $BoE_{CSs\ dietary\ intake}$ RRR: 0.89; 95% CI: 0.84, 0.95; $I^2 = 67\%$; PI: 0.69 to 1.15) (**Supplemental Figures 3–5**). Stratifying by outcome type, the estimates coming from the 3 BoE were relatively more different for overall mortality (BoE_{RCTs} vs. $BoE_{CSs\ dietary\ intake}$ RRR: 1.14; 95% CI: 1.08, 1.21; $I^2 = 67\%$; PI: 0.97 to 1.33; BoE_{RCTs} vs. $BoE_{CSs\ biomarkers}$ RRR: 1.29; 95% CI: 1.15, 1.46; $I^2 = 62\%$; PI: 0.91 to 1.84; $BoE_{CSs\ biomarkers}$ vs. $BoE_{CSs\ dietary\ intake}$ RRR: 0.87; 95% CI: 0.81, 0.94; $I^2 = 9\%$; PI: 0.77 to 0.98) (**Supplemental Figures 6–8**).

The sensitivity analysis confirmed the findings of the primary analysis (**Supplemental Figures 9** and **10**).

Discussion

Summary of findings

This is the first meta-epidemiological study to identify and compare empirical data to determine the extent to which diet–disease association estimates of BoE from RCTs and CSs on dietary intake and biomarkers of intake are concordant. Of the 49 eligible diet–disease associations included, few were qualitatively concordant; this might be related to the fact that most of the BoE of RCTs reported not statistically significant results, whereas one-third and one-half of the BoE from CSs on dietary and biomarkers of intake, respectively, showed no statistically significant effect. More than 70% of the diet–disease associations were quantitatively concordant. By using both BoE from CSs as the reference category, the pooled estimate showed small relative larger estimates coming from BoE of RCTs, and comparing both BoE from CSs yielded also similar effects. The relative larger estimate in BoE of RCTs was mainly driven by comparing micronutrient comparisons. The majority of the eligible SRs (66%) were classified as critically low, whereas only 17% were moderate- or high-quality evidence based on the AMSTAR 2 criteria.

TABLE 2 Analysis of qualitative concordance of the 49 included diet–disease outcomes[1]

Study (reference)	Intervention /exposure category	Outcome category	Summary measure	Direction of effect (RCTs)	Significance (RCTs)	Direction of association: CS dietary intake	Significance (CSs)	Direction of association: CS biomarkers	Significance (CSs)	Qualitative concordance			
										RCTs vs. CSs: dietary intake	RCTs vs. CSs: biomarker	CS biomarker vs. CS dietary intake	Overall
Abdelhamid et al. 2018 (40) + Chowdhury et al. 2014 (47)	Omega-3	Cardiovascular disease	RR	Decreasing	Not sign	Decreasing	Sign	Decreasing	Not sign	Not concordant	Not concordant	Not concordant	Not concordant
Abdelhamid et al. 2018 (40) + Chowdhury et al. 2014 (47)	Omega-3	Cardiovascular mortality	RR	Decreasing	Not sign	Decreasing	Not sign	Decreasing	Sign	Not concordant	Not concordant	Not concordant	Not concordant
Abdelhamid et al. 2018 (40) + Pan et al. 2012 (48)	α-Linolenic acid	Cardiovascular disease	RR	Decreasing	Not sign	Decreasing	Not sign	Decreasing	Not sign	Concordant	Not concordant	Not concordant	Not concordant
Adler et al. 2014 (41) + Aburto et al. 2013 (49)	Low sodium	All-cause mortality	RR	Decreasing	Not sign	Decreasing	Not sign	Decreasing	Not sign	Not concordant	Concordant	Not concordant	Not concordant
Adler et al. 2014 (41) + Aburto et al. 2013 (49)	Low sodium	Cardiovascular disease	RR	Decreasing	Not sign	Decreasing	Not sign	Decreasing	Not sign	Not concordant	Not concordant	Not concordant	Not concordant
Adler et al. 2014 (41) + Aburto et al. 2013 (49)	Low sodium	Cardiovascular mortality	RR	Decreasing	Not sign	Decreasing	Not sign	Decreasing	Not sign	Not concordant	Not concordant	Not concordant	Not concordant
Bjelakovic et al. 2012 (42) + Aune et al. 2018 (50)	Vitamin C	All-cause mortality	RR	Increasing	Not sign	Decreasing	Sign	Decreasing	Sign	Not concordant	Not concordant	Concordant	Not concordant
Bjelakovic et al. 2012 (42) + Aune et al. 2018 (50)	Vitamin E	All-cause mortality	RR	Increasing	Not sign	Decreasing	Not sign	Decreasing	Not sign	Concordant	Not concordant	Not concordant	Not concordant
Bjelakovic et al. 2012 (42) + Aune et al. 2018 (50)	β-Carotene	All-cause mortality	RR	Increasing	Not sign	Decreasing	Sign	Decreasing	Sign	Not concordant	Not concordant	Concordant	Not concordant
Bjelakovic et al. 2014 (46) + Hossain et al. 2019 (51)	Vitamin D	Breast cancer	RR	Decreasing	Not sign	Decreasing	Not sign	Increasing	Not sign	Concordant	Not concordant	Not concordant	Not concordant
Bjelakovic et al. 2014 (46) + Touvier et al. 2011 (52)	Vitamin D	Colorectal cancer	RR	Increasing	Not sign	Decreasing	Sign	Decreasing	Sign	Not concordant	Not concordant	Concordant	Not concordant
Bjelakovic et al. 2014 (46) + Zhang et al. 2015 (53)	Vitamin D	Lung cancer	RR	Decreasing	Not sign	Decreasing	Not sign	Decreasing	Sign	Not concordant	Not concordant	Not concordant	Not concordant

(*Continued*)

TABLE 2 (*Continued*)

Study (reference)	Intervention /exposure category	Outcome category	Summary measure	Direction of effect (RCTs)	Significance (RCTs)	Direction of association: CS dietary intake	Significance (CSs)	Direction of association: CS biomarkers	Significance (CSs)	Qualitative concordance			
										RCTs vs. CSs: dietary intake	RCTs vs. CSs: biomarker	CS biomarker vs. CS dietary intake	Overall
Brown et al. 2019 (14) + Wu et al. 2012 (54)	Omega-3	Type 2 diabetes	RR	Same effect	Not sign	Increasing	Not sign	Decreasing	Not sign	Concordant	Concordant	Concordant	Concordant
Brown et al. 2019 (14) + Wu et al. 2012 (54)	α-Linolenic acid	Type 2 diabetes	RR	Decreasing	Not sign	Decreasing	Not sign	Decreasing	Not sign	Not concordant	Not concordant	Not concordant	Not concordant
Chowdhury et al. 2012 (12) + Chowdhury et al. 2012 (12)	Omega-3	Stroke	RR	Increasing	Not sign	Decreasing	Not sign	Increasing	Not sign	Concordant	Concordant	Concordant	Concordant
Druesne-Pecollo et al. 2010 (15) + Aune et al. 2012 (55)	β-Carotene	Breast cancer	RR	Decreasing	Not sign	Decreasing	Sign	Decreasing	Not sign	Not concordant	Not concordant	Not concordant	Not concordant
Druesne-Pecollo et al. 2010 (15) + Aune et al. 2018 (50)	β-Carotene	Cancer	RR	Increasing	Not sign	Decreasing	Not sign	Decreasing	Sign	Concordant	Not concordant	Not concordant	Not concordant
Hanson et al. 2020 (16) + Alexander et al. 2015 (56)	Omega-3	Prostate cancer	RR	Increasing	Not sign	Same effect	Not sign	Increasing	Not sign	Concordant	Not concordant	Concordant	Not concordant
Hanson et al. 2020 (16) + Cao et al. 2016 (57)	Omega-6	Breast cancer	RR	Same effect	Not sign	Increasing	Not sign	Decreasing	Not sign	Not concordant	Not concordant	Not concordant	Not concordant
Hanson et al. 2020 (16) + Cao et al. 2016 (57)	PUFA	Breast cancer	RR	Increasing	Not sign	Increasing	Not sign	Decreasing	Not sign	Not concordant	Not concordant	Not concordant	Not concordant
Hanson et al. 2020 (16) + Fu et al. 2015 (58)	α-Linolenic acid	Prostate cancer	RR	Increasing	Not sign	Decreasing	Not sign	Same effect	Not sign	Not concordant	Not concordant	Concordant	Not concordant
Hanson et al. 2020 (16) + Zheng et al. 2013 (59)	Omega-3	Breast cancer	RR	Increasing	Not sign	Decreasing	Sign	Decreasing	Not sign	Not concordant	Not concordant	Not concordant	Not concordant
Hooper et al. 2018 (43) + Chowdhury et al. 2014 (47)	Omega-6	Cardiovascular disease	RR	Decreasing	Not sign	Decreasing	Not sign	Decreasing	Not sign	Concordant	Concordant	Concordant	Concordant
Hooper et al. 2018 (43) + Li et al. 2020 (26)	Omega-6	All-cause mortality	RR	Same effect	Not sign	Decreasing	Sign	Decreasing	Sign	Not concordant	Not concordant	Concordant	Not concordant
Hooper et al. 2018 (43) + Li et al. 2020 (26)	Omega-6	Cardiovascular mortality	RR	Increasing	Not sign	Decreasing	Sign	Decreasing	Sign	Not concordant	Not concordant	Concordant	Not concordant
Jenkins et al. 2018 (18) + Aune et al. 2018 (50)	Vitamin C	Cardiovascular disease	RR	Decreasing	Not sign	Decreasing	Sign	Decreasing	Sign	Not concordant	Not concordant	Concordant	Not concordant
Jenkins et al. 2018 (18) + Aune et al. 2018 (50)	Vitamin C	Cardiovascular mortality	RR	Increasing	Not sign	Decreasing	Sign	Decreasing	Sign	Not concordant	Not concordant	Concordant	Not concordant

(*Continued*)

TABLE 2 (*Continued*)

Study (reference)	Intervention /exposure category	Outcome category	Summary measure	Direction of effect (RCTs)	Significance (RCTs)	Direction of association: CS dietary intake	Significance (CSs)	Direction of association: CS biomarkers	Significance (CSs)	Qualitative concordance			
										RCTs vs. CSs: dietary intake	RCTs vs. CSs: biomarker	CS biomarker vs. CS dietary intake	Overall
Jenkins et al. 2018 (18) + Aune et al. 2018 (50)	Vitamin C	Stroke	RR	Decreasing	Not sign	Decreasing	Sign	Decreasing	Sign	Not concordant	Not concordant	Concordant	Not concordant
Jenkins et al. 2018 (18) + Aune et al. 2018 (50)	Vitamin E	Cardiovascular disease	RR	Decreasing	Not sign	Decreasing	Not sign	Decreasing	Not sign	Not concordant	Not concordant	Not concordant	Not concordant
Jenkins et al. 2018 (18) + Aune et al. 2018 (50)	Vitamin E	Cardiovascular mortality	RR	Decreasing	Not sign	Same effect	Not sign	Decreasing	Not sign	Concordant	Concordant	Concordant	Concordant
Jenkins et al. 2018 (18) + Aune et al. 2018 (50)	Vitamin E	Stroke	RR	Decreasing	Not sign	Decreasing	Not sign	Decreasing	Sign	Not concordant	Not concordant	Not concordant	Not concordant
Jenkins et al. 2018 (18) + Aune et al. 2018 (50)	β-Carotene	Cardiovascular disease	RR	Increasing	Not sign	Decreasing	Not sign	Decreasing	Sign	Concordant	Not concordant	Not concordant	Not concordant
Jenkins et al. 2018 (18) + Aune et al. 2018 (50)	β-Carotene	Coronary heart disease	RR	Increasing	Not sign	Decreasing	Sign	Decreasing	Sign	Not concordant	Not concordant	Concordant	Not concordant
Jenkins et al. 2018 (18) + Aune et al. 2018 (50)	β-Carotene	Stroke	RR	Increasing	Not sign	Decreasing	Sign	Decreasing	Not sign	Not concordant	Not concordant	Not concordant	Not concordant
Jenkins et al. 2018 (18) + Hunnicutt et al. 2014 (60)	Iron	Cardiovascular mortality	RR	Decreasing	Not sign	Decreasing	Not sign	Same effect	Not sign	Not concordant	Not concordant	Not concordant	Not concordant
Jenkins et al. 2018 (18) + Hunnicutt et al. 2014 (60)	Iron	Myocardial infarction	RR	Decreasing	Not sign	Decreasing	Not sign	Increasing	Sign	Not concordant	Not concordant	Not concordant	Not concordant
Khan et al. 2019 (17) + Chen et al. 2016 (61)	Omega-3	All-cause mortality	RR	Decreasing	Not sign	Decreasing	Sign	Decreasing	Sign	Not concordant	Not concordant	Concordant	Not concordant
Moazzen et al. 2018 (19) + Moazzen et al. 2018 (19)	Folate	Colorectal cancer	RR	Increasing	Not sign	Decreasing	Not sign	Decreasing	Sign	Not concordant	Not concordant	Not concordant	Not concordant
Park et al. 2017 (20) + Wu et al. 2020 (62)	Vitamin A/carotenoids	Bladder cancer	RR	Decreasing	Not sign	Increasing	Not sign	Decreasing	Not sign	Not concordant	Not concordant	Not concordant	Not concordant
Rees et al. 2013 (45) + Jayedi et al. 2018 (63)	Selenium	All-cause mortality	RR	Decreasing	Not sign	Decreasing	Sign	Decreasing	Sign	Not concordant	Not concordant	Concordant	Not concordant
Rutjes et al. 2018 (44) + Doets et al. 2013 (64)	B-vitamins	Dementia/MCI	RR	Increasing	Not sign	Decreasing	Not sign	Same effect	Not sign	Not concordant	Not concordant	Concordant	Not concordant
Schwingshackl et al. 2017 (22) + Aune et al. 2018 (50)	Vitamin C	Cancer	RR	Decreasing	Not sign	Decreasing	Sign	Decreasing	Sign	Not concordant	Not concordant	Concordant	Not concordant

(*Continued*)

TABLE 2 (*Continued*)

Study (reference)	Intervention /exposure category	Outcome category	Summary measure	Direction of effect (RCTs)	Significance (RCTs)	Direction of association: CS dietary intake	Significance (CSs)	Direction of association: CS biomarkers	Significance (CSs)	Qualitative concordance			
										RCTs vs. CSs: dietary intake	RCTs vs. CSs: biomarker	CS biomarker vs. CS dietary intake	Overall
Schwingshackl et al. 2017 (22) + Aune et al. 2018 (50)	Vitamin E	Cancer	RR	Increasing	Not sign	Increasing	Not sign	Decreasing	Sign	Concordant	Not concordant	Not concordant	Not concordant
van Die et al. 2014 (21) + Applegate et al. 2018 (25)	Isoflavones	Prostate cancer	RR	Decreasing	Sign	Decreasing	Sign	Decreasing	Not sign	Concordant	Not concordant	Not concordant	Not concordant
Vinceti 2018 (39) + Vinceti 2018 (39)	Selenium	Cancer mortality	RR	Decreasing	Not sign	Decreasing	Not sign	Decreasing	Not sign	Not concordant	Not concordant	Not concordant	Not concordant
Vinceti et al. 2018 (39) + Vinceti et al. 2018 (39)	Selenium	Lung cancer	RR	Increasing	Not sign	Increasing	Not sign	Decreasing	Not sign	Not concordant	Not concordant	Not concordant	Not concordant
Vinceti et al. 2018 (39) + Vinceti et al. 2018 (39)	Selenium	Prostate cancer	RR	Decreasing	Not sign	Decreasing	Not sign	Decreasing	Sign	Not concordant	Not concordant	Not concordant	Not concordant
Vollset et al. 2013 (23) + Wang et al. 2014 (65)	Folate	Prostate cancer	RR	Increasing	Not sign	Increasing	Not sign	Increasing	Sign	Not concordant	Not concordant	Not concordant	Not concordant
Zhao et al. 2017 (24) + Zhao et al. 2017 (24)	Iron	Gestational diabetes	RR	Decreasing	Not sign	Increasing	Not sign	Increasing	Sign	Not concordant	Not concordant	Not concordant	Not concordant

[1]CS, cohort study; MCI, mild cognitive impairment; RCT, randomized controlled trial; RR, risk ratio; sign, significant.

Comparison with other studies

We could not identify any similar meta-epidemiological study comparing the concordance between BoE from RCTs, CSs on dietary intake, and CSs on biomarkers of dietary intake. However, a review published in 2013 identified 34 diet–disease outcome pairs comparing of SRs of RCTs or a large single RCT (>1000 participants) compared with SRs of case-control or CSs or a large single observational study (>5000 participants). Comparable to our findings, 6 of 34 diet–disease associations (18%) were qualitatively concordant and 12 diet–disease associations (35%) were quantitatively discordant (32). In contrast to our study, the authors of this review included a smaller sample of diet–disease pairs, did not include solely findings from SRs (8 out of 34 associations derived from single studies), did not pool the effect estimate to generate an RRR, and did not differentiate between dietary intake and biomarkers of dietary intake.

Our findings are also in line with a statement by Satija and colleagues (66), which argued that, more often than not, when RCTs are able to successfully examine diet–disease relations, their results are remarkably in line with those of CSs. In the medical field, Anglemyer et al. (67) observed that there is little difference between the results obtained from RCTs and observational studies (cohort and case-control studies). Eleven out of 14 estimates were quantitatively concordant (79%). Moreover, although not significant, the point estimates suggest that BoE from RCTs may have a relative larger estimate than those obtained in observational studies (RRR: 1.08; 95% CI: 0.96, 1.22), which is similar to our findings (RRR: 1.09; 95% CI: 1.06, 1.13; and RRR: 1.18; 95% CI: 1.10, 1.25).

Implications for the broader research field

There has been a long debate regarding what constitutes best evidence in nutrition research, and whether it emerges from RCTs, which are considered the ideal methodology for causal inference and in which the effects of a dietary change on disease or intermediate disease markers are evaluated (68, 69). However, most dietary interventional RCTs are of short duration and often do not target patient-relevant outcomes such as morbidity or mortality. CSs, on the other hand, provide less-robust information regarding causality, but are usually considered more applicable for nutrition research. Biomarkers allow for objective measurement of intake without any bias due to self-reporting. Biomarkers as defined by the Biomarker Definitions Working Group show "characteristics that are objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (70). If the required accuracy is given, they can differentiate between specific diseases as well as their severity, and serve to predict the likely outcome or the effectiveness of a therapy (71). At best, they can be used as surrogate markers replacing patient-relevant clinical endpoints (72). Thus, the indicators termed biomarkers in the present study

TABLE 3 Analysis of quantitative concordance of the 49 included diet–disease outcomes[1]

Study (reference)	Intervention/ exposure category	Outcome category	Summary measure	RCTs vs. CS dietary intake (reference)			RCTs vs. CS biomarkers (reference)			CS biomarkers vs. CS dietary intake (reference)			Overall quantitative concordance
				z	*P*	Quantitative concordance	*z*	*P*	Quantitative concordance	*z*	*P*	Quantitative concordance	
Abdelhamid et al. 2018 (40) + Chowdhury et al. 2014 (47)	Omega-3	Cardiovascular disease	RR	2.1078	0.0350	Concordant	1.1194	0.2630	Concordant	− 0.2267	0.8207	Concordant	Concordant
Abdelhamid et al. 2018 (40) + Chowdhury et al. 2014 (47)	Omega-3	Cardiovascular mortality	RR	0.4107	0.6813	Concordant	2.1138	0.0345	Concordant	− 1.3531	0.1760	Concordant	Concordant
Abdelhamid et al. 2018 (40) + Pan et al. 2012 (48)	α-Linolenic acid	Cardiovascular disease	RR	0.2619	0.7934	Concordant	0.6939	0.4877	Concordant	− 0.5427	0.5873	Concordant	Concordant
Adler et al. 2014 (41) + Aburto et al. 2013 (49)	Low sodium	All-cause mortality	RR	0.0635	0.9493	Concordant	0.2061	0.8367	Concordant	− 0.0641	0.9489	Concordant	Concordant
Adler et al. 2014 (41) + Aburto et al. 2013 (49)	Low sodium	Cardiovascular disease	RR	− 0.6326	0.5270	Concordant	− 0.9437	0.3453	Concordant	0.2262	0.8211	Concordant	Concordant
Adler et al. 2014 (41) + Aburto et al. 2013 (49)	Low sodium	Cardiovascular mortality	RR	− 1.0100	0.3125	Concordant	− 1.4874	0.1369	Concordant	0.5481	0.5836	Concordant	Concordant
Bjelakovic et al. 2012 (42) + Aune et al. 2018 (50)	Vitamin C	All-cause mortality	RR	3.9226	0.0001	Not concordant	5.9248	0.0000	Not concordant	− 3.2194	0.0013	Not concordant	Not concordant
Bjelakovic et al. 2012 (42) + Aune et al. 2018 (50)	Vitamin E	All-cause mortality	RR	1.2837	0.1993	Concordant	1.3085	0.1907	Concordant	− 0.8978	0.3693	Concordant	Concordant
Bjelakovic et al. 2012 (42) + Aune et al. 2018 (50)	β-Carotene	All-cause mortality	RR	6.1042	0.0000	Not concordant	3.7773	0.0002	Not concordant	− 1.7237	0.0848	Concordant	Not concordant
Bjelakovic et al. 2014 (46) + Hossain et al. 2019 (51)	Vitamin D	Breast cancer	RR	0.4315	0.6661	Concordant	− 0.2332	0.8156	Concordant	0.3874	0.6984	Concordant	Concordant
Bjelakovic et al. 2014 (46) + Touvier et al. 2011 (52)	Vitamin D	Colorectal cancer	RR	1.6070	0.1080	Concordant	1.5081	0.1315	Concordant	0.6722	0.5015	Concordant	Concordant
Bjelakovic et al. 2014 (46) + Zhang et al. 2015 (53)	Vitamin D	Lung cancer	RR	− 0.2370	0.8126	Concordant	0.2989	0.7650	Concordant	− 0.6984	0.4850	Concordant	Concordant

(*Continued*)

TABLE 3 (*Continued*)

Study (reference)	Intervention/ exposure category	Outcome category	Summary measure	RCTs vs. CS dietary intake (reference)			RCTs vs. CS biomarkers (reference)			CS biomarkers vs. CS dietary intake (reference)			Overall quantitative concordance
				z	*P*	Quantitative concordance	*z*	*P*	Quantitative concordance	*z*	*P*	Quantitative concordance	
Brown et al. 2019 (14) + Wu et al. 2012 (54)	Omega-3	Type 2 diabetes	RR	−0.4019	0.6877	Concordant	0.5668	0.5708	Concordant	−1.1198	0.2628	Concordant	Concordant
Brown et al. 2019 (14) + Wu et al. 2012 (54)	α-Linolenic acid	Type 2 diabetes	RR	−0.8097	0.4181	Concordant	−0.6565	0.5115	Concordant	−0.5302	0.5960	Concordant	Concordant
Chowdhury et al. 2012 (12) + Chowdhury et al. 2012 (12)	Omega-3	Stroke	RR	1.8137	0.0697	Concordant	−0.1124	0.9105	Concordant	1.5307	0.1258	Concordant	Concordant
Druesne-Pecollo et al. 2010 (15) + Aune et al. 2012 (55)	β-Carotene	Breast cancer	RR	0.4454	0.6560	Concordant	1.1240	0.2610	Concordant	−0.9923	0.3211	Concordant	Concordant
Druesne-Pecollo et al. 2010 (15) + Aune et al. 2018 (50)	β-Carotene	Cancer	RR	2.0646	0.0390	Concordant	3.4857	0.0005	Not concordant	−1.7517	0.0798	Concordant	Not concordant
Hanson et al. 2020 (16) + Alexander et al. 2015 (56)	Omega-3	Prostate cancer	RR	1.2777	0.2014	Concordant	0.3130	0.7543	Concordant	0.9106	0.3625	Concordant	Concordant
Hanson et al. 2020 (16) + Cao et al. 2016 (57)	Omega-6	Breast cancer	RR	−0.0950	0.9243	Concordant	0.1724	0.8631	Concordant	−1.3013	0.1932	Concordant	Concordant
Hanson et al. 2020 (16) + Cao et al. 2016 (57)	PUFA	Breast cancer	RR	0.2402	0.8102	Concordant	1.3714	0.1703	Concordant	−1.4291	0.1530	Concordant	Concordant
Hanson et al. 2020 (16) + Fu et al. 2015 (58)	α-Linolenic acid	Prostate cancer	RR	0.9125	0.3615	Concordant	0.8782	0.3798	Concordant	0.7336	0.4632	Concordant	Concordant
Hanson et al. 2020 (16) + Zheng et al. 2013 (59)	Omega-3	Breast cancer	RR	1.9849	0.0472	Concordant	1.4817	0.1384	Concordant	0.1044	0.9169	Concordant	Concordant
Hooper et al. 2018 (43) + Chowdhury et al. 2014 (47)	Omega-6	Cardiovascular disease	RR	−0.1039	0.9172	Concordant	0.2928	0.7697	Concordant	−0.5744	0.5657	Concordant	Concordant
Hooper et al. 2018 (43) + Li et al. 2020 (26)	Omega-6	All-cause mortality	RR	1.9263	0.0541	Concordant	1.7234	0.0848	Concordant	−0.1586	0.8740	Concordant	Concordant
Hooper et al. 2018 (43) + Li et al. 2020 (26)	Omega-6	Cardiovascular mortality	RR	1.2241	0.2209	Concordant	1.6912	0.0908	Concordant	−1.3087	0.1906	Concordant	Concordant

(*Continued*)

TABLE 3 (*Continued*)

Study (reference)	Intervention/ exposure category	Outcome category	Summary measure	RCTs vs. CS dietary intake (reference)			RCTs vs. CS biomarkers (reference)			CS biomarkers vs. CS dietary intake (reference)			Overall quantitative concordance
				z	*P*	Quantitative concordance	*z*	*P*	Quantitative concordance	*z*	*P*	Quantitative concordance	
Jenkins et al. 2018 (18) + Aune et al. 2018 (50)	Vitamin C	Cardiovascular disease	RR	2.4667	0.0136	Not concordant	2.9465	0.0032	Not concordant	− 1.9764	0.0481	Concordant	Not concordant
Jenkins et al. 2018 (18) + Aune et al. 2018 (50)	Vitamin C	Cardiovascular mortality	RR	2.3164	0.0205	Concordant	3.1514	0.0016	Not concordant	− 1.8327	0.0669	Concordant	Not concordant
Jenkins et al. 2018 (18) + Aune et al. 2018 (50)	Vitamin C	Stroke	RR	0.9535	0.3404	Concordant	3.2193	0.0013	Not concordant	− 3.0516	0.0023	Not concordant	Not concordant
Jenkins et al. 2018 (18) + Aune et al. 2018 (50)	Vitamin E	Cardiovascular disease	RR	0.8055	0.4205	Concordant	1.1061	0.2687	Concordant	− 0.6999	0.4840	Concordant	Concordant
Jenkins et al. 2018 (18) + Aune et al. 2018 (50)	Vitamin E	Cardiovascular mortality	RR	− 1.4151	0.1570	Concordant	− 0.5498	0.5825	Concordant	− 0.4416	0.6588	Concordant	Concordant
Jenkins et al. 2018 (18) + Aune et al. 2018 (50)	Vitamin E	Stroke	RR	1.1189	0.2632	Concordant	2.9136	0.0036	Not concordant	− 1.8969	0.0578	Concordant	Not concordant
Jenkins et al. 2018 (18) + Aune et al. 2018 (50)	β-Carotene	Cardiovascular disease	RR	0.5698	0.5688	Concordant	3.2045	0.0014	Not concordant	− 2.3571	0.0184	Concordant	Not concordant
Jenkins et al. 2018 (18) + Aune et al. 2018 (50)	β-Carotene	Coronary heart disease	RR	3.8766	0.0001	Not concordant	2.5008	0.0124	Not concordant	0.0000	1.0000	Concordant	Not concordant
Jenkins et al. 2018 (18) + Aune et al. 2018 (50)	β-Carotene	Stroke	RR	2.8591	0.0042	Not concordant	2.0692	0.0385	Concordant	0.1108	0.9117	Concordant	Not concordant
Jenkins et al. 2018 (18) + Hunnicutt et al. 2014 (60)	Iron	Cardiovascular mortality	RR	− 0.3417	0.7326	Concordant	− 0.5920	0.5539	Concordant	0.4799	0.6313	Concordant	Concordant
Jenkins et al. 2018 (18) + Hunnicutt et al. 2014 (60)	Iron	Myocardial infarction	RR	− 1.0240	0.3058	Concordant	− 1.9709	0.0487	Concordant	2.7827	0.0054	Not concordant	Not concordant
Khan et al. 2019 (17) + Chen et al. 2016 (61)	Omega-3	All-cause mortality	RR	1.6165	0.1060	Concordant	2.6479	0.0081	Not concordant	− 1.8688	0.0617	Concordant	Not concordant
Moazzen et al. 2018 (19) + Moazzen et al. 2018 (19)	Folate	Colorectal cancer	RR	0.6171	0.5372	Concordant	2.5404	0.0111	Not concordant	− 1.9757	0.0482	Concordant	Not concordant
Park et al. 2017 (20) + Wu et al. 2020 (62)	Vitamin A	Bladder cancer	RR	− 1.4637	0.1433	Concordant	1.0497	0.2939	Concordant	− 2.1549	0.0312	Concordant	Concordant
Rees et al. 2013 (45) + Jayedi et al. 2018 (63)	Selenium	All-cause mortality	RR	3.1535	0.0016	Not concordant	2.9296	0.0034	Not concordant	− 1.6293	0.1033	Concordant	Not concordant

(*Continued*)

TABLE 3 (*Continued*)

Study (reference)	Intervention/ exposure category	Outcome category	Summary measure	RCTs vs. CS dietary intake (reference)			RCTs vs. CS biomarkers (reference)			CS biomarkers vs. CS dietary intake (reference)			Overall quantitative concordance
				z	*P*	Quantitative concordance	*z*	*P*	Quantitative concordance	*z*	*P*	Quantitative concordance	
Rutjes et al. 2018 (44) + Doets et al. 2013 (64)	B-vitamins	Dementia/MCI	RR	0.1027	0.9182	Concordant	0.0510	0.9593	Concordant	0.9551	0.3395	Concordant	Concordant
Schwingshackl et al. 2017 (22) + Aune et al. 2018 (50)	Vitamin C	Cancer	RR	2.0316	0.0422	Concordant	3.9609	0.0001	Not concordant	− 2.4631	0.0138	Not concordant	Not concordant
Schwingshackl et al. 2017 (22) + Aune et al. 2018 (50)	Vitamin E	Cancer	RR	0.2019	0.8400	Concordant	5.4212	0.0000	Not concordant	− 3.7900	0.0002	Not concordant	Not concordant
van Die et al. 2014 (21) + Applegate et al. 2018 (25)	Isoflavones	Prostate cancer	RR	− 1.8202	0.0687	Concordant	− 2.0097	0.0445	Concordant	0.8122	0.4167	Concordant	Concordant
Vinceti et al. 2018 (39) + Vinceti et al. 2018 (39)	Selenium	Cancer mortality	RR	− 0.5342	0.5932	Concordant	0.6774	0.4982	Concordant	− 1.5258	0.1271	Concordant	Concordant
Vinceti et al. 2018 (39) + Vinceti et al. 2018 (39)	Selenium	Lung cancer	RR	− 1.0873	0.2769	Concordant	0.6450	0.5189	Concordant	− 1.7522	0.0797	Concordant	Concordant
Vinceti et al. 2018 (39) + Vinceti et al. 2018 (39)	Selenium	Prostate cancer	RR	− 0.6808	0.4960	Concordant	0.3723	0.7096	Concordant	− 1.3649	0.1723	Concordant	Concordant
Vollset et al. 2013 (23) + Wang et al. 2014 (65)	Folate	Prostate cancer	RR	1.4144	0.1573	Concordant	− 0.4831	0.6290	Concordant	2.1435	0.0321	Concordant	Concordant
Zhao et al. 2017 (24) + Zhao et al. 2017 (24)	Iron	Gestational diabetes	RR	− 1.1649	0.2440	Concordant	− 2.9681	0.0030	Not concordant	− 0.1269	0.8990	Concordant	Not concordant

[1] CS, cohort study; MCI, mild cognitive impairment; RCT, randomized controlled trial; RR, risk ratio.

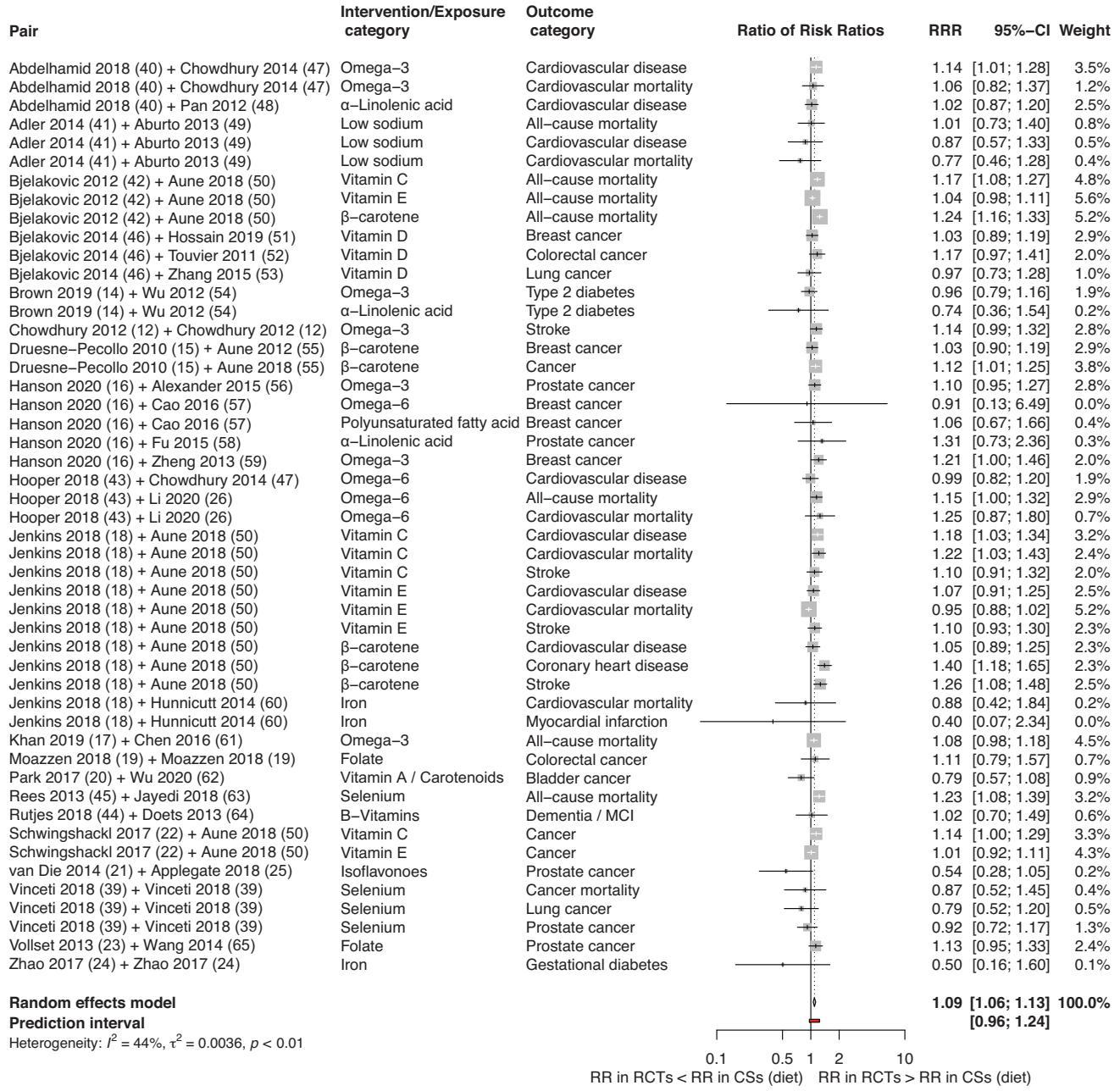

FIGURE 1 Forest plot of comparisons between bodies of evidence from RCTs vs. cohort studies (on dietary intake: reference) as pooled RRRs. CS, cohort study; diet, dietary intake; MCI, mild cognitive impairment; RCT, randomized controlled trial; RR, risk ratio; RRR, ratio of risk ratio.

are rather descriptors of dietary conditions and therefore have limitations.

For example, many dietary patterns, foods groups, or nutrients are not sensitive for or lack specific biomarkers, may not be reliable indicators of individual long-term intake, and are often expensive to measure. Therefore, a food-frequency questionnaire is the most common choice for measuring dietary intake in CSs (73). In our study, the biomarkers included were circulating fatty acids, sodium urinary excretion, status of vitamins (e.g., vitamins E, C, D), ferritin, micronutrients status such as folic acid and selenium, and circulating genistein, all of which are considered relevant biomarkers of dietary intake (74).

Confirmation of research findings or rather lack of confirmatory data is not a problem exclusively reserved for nutritional sciences. In recent years, different projects dedicated to the reproducibility of study data in the medical fields of oncology and cardiovascular disease have shown

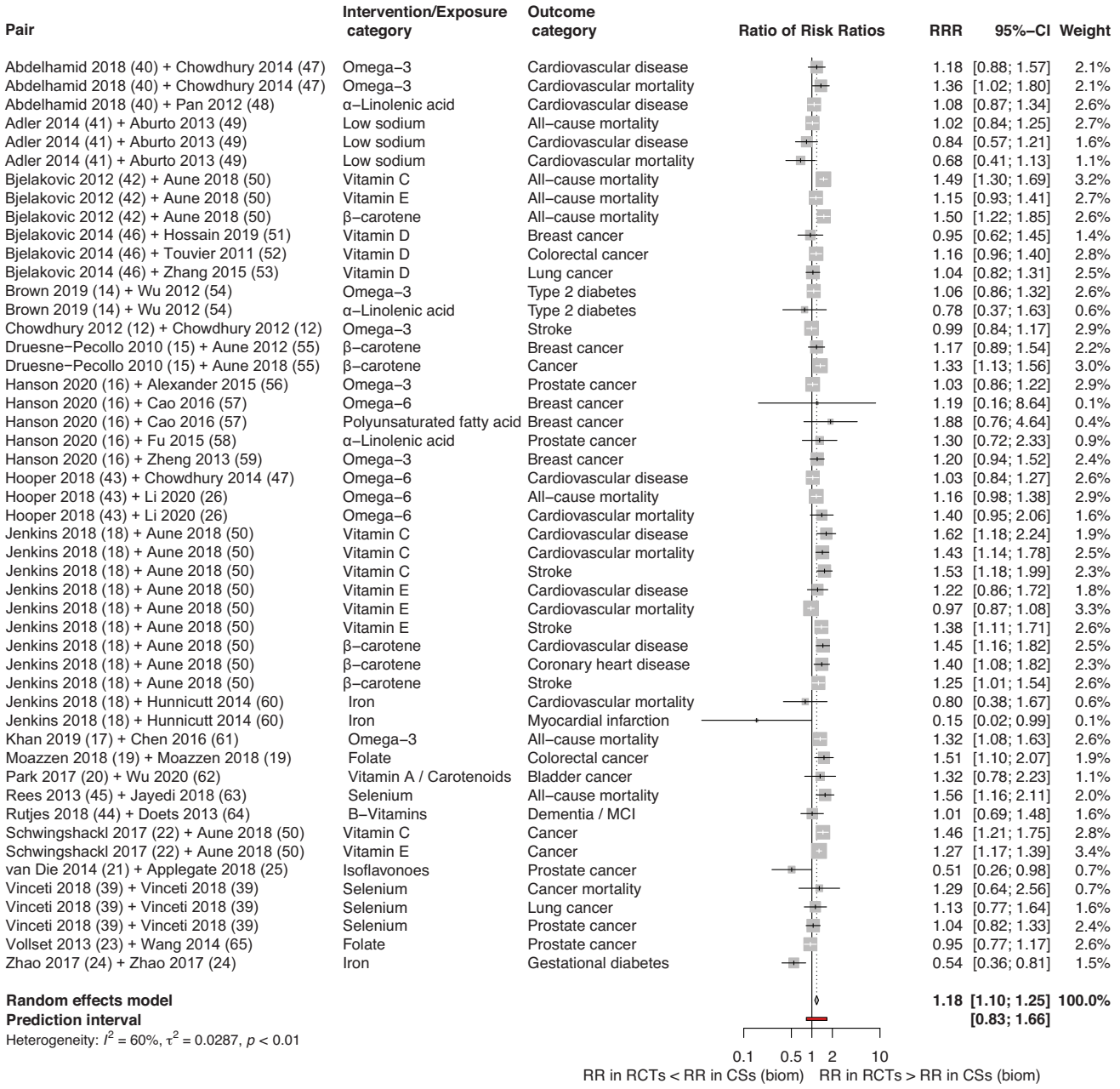

FIGURE 2 Forest plot of comparisons between bodies of evidence from RCTs vs. cohort studies (on biomarkers of dietary intake: reference) as pooled RRRs. Biom, biomarkers; CS, cohort study; MCI, mild cognitive impairment; RCT, randomized controlled trial; RR, risk ratio; RRR, ratio of risk ratio.

that it can be quite hard to verify preclinical observations (75–77). To check for concordance between different study designs as done in the present study might represent a useful tool to increase the reliability of studies in nutritional sciences.

Since BoE from CSs on dietary intake and biomarkers of intake can complement BoE from RCTs, and vice versa, our meta-epidemiological study provides a first insight that integration of all these BoE in nutrition evidence syntheses is recommended.

Strengths and limitations

This meta-epidemiological study has several strengths. First, we included a large sample of diet–disease associations ($n = 49$), which were based on >400 RCTs and >550 CSs, both study designs considered as the most trustworthy in nutrition research (6); second, the various statistical analyses conducted, such as recalculating 10 pooled estimates, converting ORs to RRs, the qualitative and quantitative assessment of concordance, and pooling the estimates across all diet–disease pairs; and finally, the exploration of potential

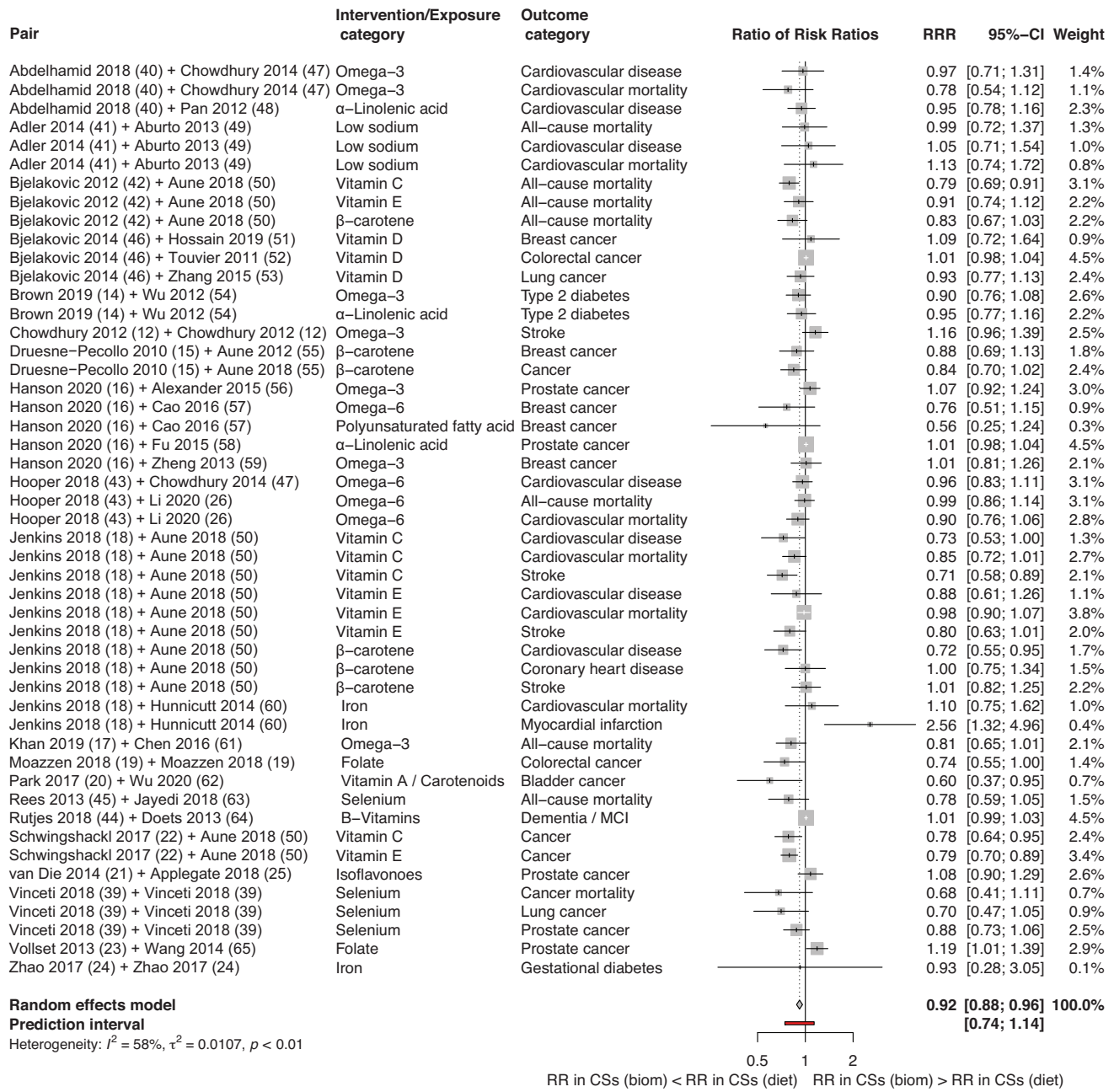

FIGURE 3 Forest plot of comparisons between bodies of evidence from cohort studies (on biomarkers of dietary intake) vs. cohort studies (on dietary intake: reference) as pooled RRRs. Biom, biomarkers; CS, cohort study; diet, dietary intake; MCI, mild cognitive impairment; RCT, randomized controlled trial; RR, risk ratio; RRR, ratio of risk ratio.

sources of concordance due to subgroup analyses for types of intervention/exposure and outcomes was an additional strength of this study.

Limitations of this study are as follows: first, although we included a large sample of diet–disease pairs, including (and pooling) the totality of evidence of available diet–disease associations might provide different results; second, the definitions of qualitative and quantitative concordance used have some limitations as well (definition of qualitative concordance was relatively strict). However, for the qualitative assessment we also included nonsignificant findings based on the imprecision criteria by the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) Working Group (30), previously not used, as well as the results considering a less strict definition. Finally, we did not explore all potential reasons of concordance, such as dietary adherence or validity and reliability of the dietary biomarkers in the underlying RCTs, or risk of bias of primary studies.

Conclusions

Our findings suggest that BoE from RCTs and CSs are often quantitatively concordant. Prospective SRs in nutrition

research should include, whenever possible, BoE from RCTs and CSs on dietary intake and biomarkers of intake to provide the whole picture for an investigated diet–disease association.

Acknowledgments

All authors substantially contributed to the concept, data collection and analysis, or preparation of the manuscript.

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