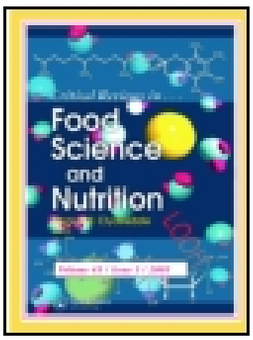

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REVIEW

Mediterranean diet, cardiovascular disease and mortality in diabetes: A systematic review and meta-analysis of prospective cohort studies and randomized clinical trials

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ABSTRACT

To update the clinical practice guidelines for nutrition therapy of the European Association for the Study of Diabetes, we conducted a systematic review and meta-analysis of prospective cohort studies and randomized clinical trials (RCTs) to evaluate the effect of the Mediterranean diet (MedDiet) on the prevention of cardiovascular disease (CVD) incidence and mortality. We searched Medline, EMBASE (through April 20, 2018) and Cochrane (through May 7, 2018) databases. Pooled relative risks (RRs) and 95% confidence interval (CI) were calculated by the generic inverse variance method. A total of 41 reports (3 RCTs and 38 cohorts) were included. Meta-analyses of RCTs revealed a beneficial effect of the MedDiet on total CVD incidence (RR: 0.62; 95% CI: 0.50, 0.78) and total myocardial infarction (MI) incidence (RR: 0.65; 95% CI: 0.49, 0.88). Meta-analyses of prospective cohort studies, which compared the highest versus lowest categories of MedDiet adherence, revealed an inverse association with total CVD mortality (RR: 0.79; 95% CI: 0.77, 0.82), coronary heart disease (CHD) incidence (RR: 0.73; 95% CI: 0.62, 0.86), CHD mortality (RR: 0.83; 95% CI: 0.75, 0.92), stroke incidence (RR: 0.80; 95% CI: 0.71, 0.90), stroke mortality (RR: 0.87; 95% CI: 0.80, 0.96) and MI incidence (RR: 0.73; 95% CI: 0.61, 0.88). The present study suggests that MedDiet has a beneficial role on CVD prevention in populations inclusive of individuals with diabetes.

KEYWORDS

Mediterranean diet; cardiovascular disease; cardiovascular mortality; diabetes; meta-analysis

Background

Cardiovascular diseases (CVDs) are considered to be the leading cause of mortality worldwide, accounting for 31% of all global deaths in 2015 (World Health Organization 2017). Data from epidemiological studies suggest that diabetes is an important predisposing factor for CVD risk. In fact, a collaborative meta-analysis of 97 prospective studies revealed that individuals with diabetes had approximately a two-fold higher risk of coronary heart disease (CHD), stroke and vascular death, than their counterparts without the disease (The Emerging Risk Factors Collaboration et al. 2010).

CVDs are largely preventable by managing modifiable adverse behaviors, such as an unhealthy diet, unhealthy body weight tobacco use or physical inactivity (Institute of Medicine (US) Committee on Preventing the Global Epidemic of Cardiovascular Disease: Meeting the Challenges in Developing countries 2010). Therefore, promoting healthy lifestyles should be an important strategy to reduce CVD burden not only in people with type 2 diabetes (T2D) but also in the general population. In this regard, the traditional Mediterranean diet (MedDiet), which is rich in vegetables, fruits, extra-virgin olive oil, nuts, legumes and whole grains, and low to moderate in animal products, has been identified as one of the healthiest dietary patterns for CVD prevention (Salas-Salvadó et al. 2018).

To date, several meta-analyses of observational studies (Sofi et al. 2014; Martinez-Gonzalez and Bes-Rastrollo 2014; Grosso et al. 2017; Rosato et al. 2017; Psaltopoulou et al. 2013) and clinical trials (Martinez-Gonzalez and Bes-Rastrollo 2014; Liyanage et al. 2016; Grosso et al. 2017) analyzing MedDiet and the risk of incidence of or mortality from total or different types of CVDs support these beneficial effects. It is noteworthy that only one meta-analysis

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evaluated prospective cohort studies and randomized clinical trials (RCT) (Grosso et al. 2017) of the association of MedDiet with CVD, however, it did not report on individual causes of CVD mortality, such as stroke, CHD and myocardial infarction (MI). Moreover, despite the fact that diabetes confers a higher risk of CVDs, no previous meta-analyses took this into consideration when defining their study population. Therefore, there is a gap in knowledge for the value of the MedDiet in preventing CVD in individuals with diabetes. The clinical practice guidelines for nutrition therapy of the European Association for the Study of Diabetes (EASD) have made no specific recommendations regarding the MedDiet. Therefore, in order to develop evidence-based recommendations, the Diabetes and Nutrition Study group (DNSG) of the EASD commissioned a systematic review and meta-analysis (SRMA) of prospective cohort studies and RCTs using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system to summarize the evidence available on the relationship of MedDiet with total CVD, CHD, stroke and MI incidence and mortality in populations inclusive of individuals with diabetes.

Methods

The present SRMA was conducted in accordance with the Cochrane handbook for systematic reviews of interventions (Higgins and Green 2011), and results were reported in accordance with Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al. 2000). The study protocol is available at https://www.crd.york.ac.uk/PROSPERO/ (number of registration: CRD42017057885).

Search strategy and data sources

A comprehensive search, which was limited to human studies without language restrictions, was performed through January 16, 2017 in MEDLINE and EMBASE databases and through February 9, 2017 in the Cochrane Library database. We updated searches in April 20, 2018 and in May 7, 2018, respectively. The complete search strategy is presented in Supplementary Table 1. A manual review of articles' reference lists supplemented the electronic search. We also contacted subject experts for a list of articles on the subject.

Study selection

All titles and abstracts were initially screened to assess the eligibility criteria. We only included prospective cohort studies and RCTs with a study population that included adults with type 1 diabetes or T2D; $\geq$1 year of follow-up; MedDiet as exposure (assessed by indexes or scores in the case of prospective cohort studies); and incidence of or mortality from CVD, CHD, MI and stroke as outcome. When more than one article from the same study was identified, we included both articles if the reported outcomes were different (i.e. CHD in one and total CVD in the other one). When multiple articles conducted in the same study population reported the same outcome, the one with the longest follow-up was selected. We did not include published abstracts.

For the PREDIMED trial, the original article (Estruch et al. 2013) was withdrawn and republished in June 2018 (Estruch et al. 2018) because some deviations from the protocol randomization procedure were detected. Therefore, although our search strategy did not identify this new publication, we felt that it was appropriate to include in the meta-analysis the results of the new report, which were similar to the findings originally reported.

Data extraction

Two independent researchers (NB-T and EV) reviewed the full text of the articles that passed the first screening. A standardized *proforma* was used to extract relevant information including: year of publication, country, characteristics of the participants, study setting, sample size, follow-up duration, outcome assessment, MedDiet assessment method (only in cohort studies), sources of funding, number of incident cases, covariates used for adjustments of the statistical analyses, and effect estimators (risk ratios, odds ratios, hazard ratios) and 95% CIs of CVD, CHD, MI, stroke incidence and mortality per quantiles of MedDiet adherence (in the case of prospective cohort studies) and for intervention arms (in RCTs). If necessary, authors were contacted by email if any additional information was required. All disagreements were resolved by consensus or by a third author (J.L.S.) when necessary.

Study quality

The study quality of prospective cohort studies was assessed using the Newcastle-Ottawa scale (NOS) (Wells et al. 2014). It consists of a rating scale which gives points to studies in three domains: population selection (maximum of 4 points), outcome assessment (maximum 3 points) and comparability of the groups (maximum 2 points). For the present analysis, those studies that received $\geq$7 points were considered to be of high quality. The quality of RCTs was assessed with the Cochrane Collaboration Tool (Higgins and Green 2011), which includes five different domains: sequence generation, allocation concealment, blinding, outcome data and outcome reporting. Each domain was judged to have a high, low or unclear risk of bias. Any disagreements were resolved by consensus.

Outcomes

For the present systematic review and meta-analysis, eight sets of outcomes were considered: incidence (including non-fatal outcomes or a composite of fatal and non-fatal outcomes) of total CVD; CHD; stroke; MI; and mortality (only including fatal outcomes) from total CVD; CHD; stroke and MI. Studies reporting separate risk estimates for hemorrhagic and ischemic stroke (Tsivgoulis et al. 2015; Tektonidis et al. 2015) were combined within each study using a fixed-effects model to generate an overall estimate for stroke incidence. Similarly, we combined non-fatal and fatal MI (Singh et al. 2002) within studies to obtain an overall estimate for MI incidence.

Statistical analyses

In order to obtain summary estimates, the RRs, HRs and ORs were natural log-transformed and pooled using the inverse variance method with random-effects model. Fixed–effects model was used if number of comparisons was less than five. Due to the low incidence of CVD and modest effect sizes, ORs and HRs were treated as RRs (Zhang and Yu 1998; Symons and Moore 2002). Only two studies reported the risk estimates as ORs, which were considered equivalent to RRs (Chrysohoou et al. 2010; Kouvari et al. 2017). We conducted separate meta-analyses for RCTs and prospective cohort studies.

For the meta-analysis of RCTs, we considered the outcome of total CVD incidence to be the composite end-point including MI, CVD death, episodes of unstable angina, heart failure, stroke and pulmonary or peripheral embolism reported by de Lorgeril et al. (1999) in the Lyon Diet Heart Study. In the PREDIMED study including MI, stroke and death from CVD, we used the HRs reported by both MedDiet intervention groups merged versus the control group (Estruch et al. 2018).

For the primary meta-analysis of prospective cohort studies, we used RRs comparing extreme categories of MedDiet adherence. In those studies in which the highest category was considered to be the reference, the RR and 95% CI was recalculated to make the lowest category as the reference (Aigner et al. 2018).

As a secondary analysis, we took the studies that used different scores and cutoff points to assess MedDiet adherence and estimated the RRs for every 2-point increment in the MedDiet score. When studies did not use the traditional MedDiet score proposed by Trichopoulou et al. (2003), ranging from 0 to 9, we re-scaled them to a 9-point scale because it is the most-used score in epidemiological settings. When studies reported the risk for every 2-point increment, we directly used the natural log-transformed risk estimates. For those studies reporting a different point increment, it was transformed as appropriate. For example, if a study reported RRs for 1-point increments, the RRs were calculated by multiplying the natural log-transformed risk estimates by 2. If studies did not report the RRs in a continuous form, we estimated them only when MedDiet adherence was categorized at least in three categories, following the log-linear dose-response model for a single study (Orsini, Bellocco, and Greenland 2006).

Furthermore, the linear dose-response gradient was also assessed by using generalized least squares trend (GLST) following the method described by Greenland and Longnecker (Greenland and Longnecker 1992) and Orsini (Orsini et al. 2012) when at least three study comparisons were available. Non-linear dose-response association was assessed by using a two-stage multivariate random-effects method using restricted cubic splines with three knots. For this analysis, we included only those studies that reported at least three categories of MedDiet as exposure. We converted to the 9-point scale all those studies that used a different point scale from the traditional one (ranging from 0 to 9). We used the mean or median of each category when it was reported or we calculated the midpoint between the upper and lower bound when ranges were described. For those studies that reported open-ended extreme categories, we assumed the width of the adjacent interval. If a study did not report cases or the total number of participants in each category, we imputed them following the method described by Bekkering and coworkers (Bekkering et al. 2008).

For all meta-analyses, inter-study heterogeneity was assessed using the Cochran Q statistic and quantified using the I^2 statistic, where $I^2 > 50\%$ at $P_Q < 0.10$ was considered evidence of substantial heterogeneity (Higgins and Green 2011). Sensitivity analysis was performed by removing one study at a time from the meta-analysis and recalculating the summary risk estimates. We considered a study as influential if removing it changed the magnitude (by >20%), the direction or the significance of the pooled risk estimates, or the evidence of heterogeneity.

A priori and post hoc subgroup analyses were performed using meta-regression when 10 or more comparisons were available a priori subgroup analyses included sex (males vs. females vs. mixed), follow-up (< vs. ≥ median), NOS (<7 vs. ≥7) and individual domains of risk of bias (NOS or The Cochrane Collaboration Tool). A post hoc analyses included MedDiet score assessment (Trichopolou original 9 points vs. adapted from Trichopolou original vs. others) and type of population (Mediterranean vs. non-Mediterranean). If ≥10 comparisons were available, the risk of publication bias was investigated by visually inspecting funnel plots for asymmetry and quantified by Begg's and Egger's tests ($p < 0.05$ was considered significant for small study effects). If there was evidence of publication bias, then we used the Duval and Tweedie trim and fill method to adjust for funnel plot asymmetry by imputing missing study data (Duval and Tweedie 2000).

All data analysis was performed using the Review Manager (RevMan) version 5.3 and Stata version 15 (StataCorp).

Grading the evidence

The GRADE system was used to rate the certainty and strength of the evidence. According to this system, observational studies start at low-certainty of evidence, whereas RCTs start at high-certainty (Guyatt et al. 2011a). The certainty of evidence can be downgraded or upgraded on the basis of some prespecified determinants. Criteria to downgrade include limitations of the study design and execution (weight of studies showed risk of bias by NOS (Guyatt et al. 2011b) or by the Cochrane Collaboration Tool) (Higgins et al. 2011), inconsistency (inter-study heterogeneity that remains unexplained, $I^2 \geq 50\%$ and $p < 0.10$) (Guyatt et al. 2011c), indirectness (existence of factors that limit the generalizability of the results) (Guyatt et al. 2011d), imprecision (wide confidence intervals or overlapping with the minimally important difference of 5% (RR 0.95 to 1.05)) (Guyatt et al. 2011e) and publication bias (evidence of small-study effect) (Guyatt et al. 2011g). Criteria to upgrade include large magnitude of effect (RR ≤2 or <0.5 in the absence of plausible confounders), dose-response gradient, and

attenuation by plausible confounding effects (Guyatt et al. 2011f). Any disagreements were resolved by consensus.

Results

Figure 1 shows the flow of literature and study selection. The literature search yielded 2,592 potential studies for inclusion and one additional study was obtained by making a manual search of the references of the retrieved articles. After duplicate studies had been removed (n = 1,144), 1,448 were screened by title and abstract, and 1,323 were excluded. Of the 125 studies reviewed in full, 41 (Estruch et al. 2018; de Lorgeril et al. 1999; Singh et al. 2002; Buckland et al. 2009; Chrysohoou et al. 2010; Buckland et al. 2011; Chiuve et al. 2011; Gardener et al. 2011; Martínez-González et al. 2010; Dilis et al. 2012; Misirli et al. 2012; Tognon et al. 2012; Atkins et al. 2014; Bertoia et al. 2014; Booth et al. 2014; Cuenca-García et al. 2014; George et al. 2014; Lopez-Garcia et al. 2014; Reedy et al. 2014; Schröder et al. 2014; Tognon et al. 2014; Vormund et al. 2015; Bonaccio et al. 2016; Eguaras et al. 2015; Lau et al. 2015; Panagiotakos et al. 2015; Pignatelli et al. 2015; Tektonidis et al. 2015; Tsivgoulis et al. 2015; Bo et al. 2016; Park et al. 2016; Shvetsov et al. 2016; Stewart et al. 2016; Tong et al. 2016; Kouvari et al. 2017; Hodge et al. 2018; Shah et al. 2018; Whalen et al. 2017; Warensjö Lemming et al. 2018; Al Rifai et al. 2018; Aigner et al. 2018) were finally included in the quantitative synthesis.

Randomized clinical trials

Table 1 shows the characteristics of the RCTs included. A total of 3 RCTs were included (Estruch et al. 2018; de Lorgeril et al. 1999; Singh et al. 2002). The studies were conducted in India, France and Spain and the publication year ranged from 1999 to 2018. The total sample size ranged from 605 to 7,447 with a follow-up ranging from 2 years to 4.8 years. Supplemental Figure 1 shows the assessment of risk of bias according to the Cochrane Risk of Bias tool. Two of the three studies were at unclear risk of bias for random sequence generation and allocation concealment. Risk of bias was high for one study in terms of allocation concealment. For the other three domains, all studies were considered to be at low risk of bias. Furthermore, the study published by Singh et al., appears to have unreliable data, as stated by the editor of the Lancet journal in a letter of expression of concern (Horton 2005).

Total CVD incidence

Two studies (Estruch et al. 2018; de Lorgeril et al. 1999) with 8,052 participants, including 332 cases, analyzed the effect of the MedDiet on total CVD incidence (Figure 2 and Supplemental Figure 2). Pooled analysis showed that MedDiet reduced the risk of total CVD incidence by 38% (RR: 0.62; 95% CI: 0.50, 0.78) with evidence of substantial heterogeneity ($I^2 = 86\%$, $p < 0.01$).

Total CVD mortality

Two studies (Estruch et al. 2018; de Lorgeril et al. 1999) with 8,052 participants, including 106 cases, analyzed the effect of the MedDiet on total CVD mortality (Figure 2 and Supplemental Figure 3). Pooled analysis showed that the MedDiet did not decrease the risk of total CVD mortality (RR: 0.67; 95% CI: 0.45, 1.00) and there was evidence of substantial heterogeneity between studies ($I^2 = 64\%$, $p = 0.09$).

CHD incidence

Only one study (Singh et al. 2002) conducted in 1,000 participants with a previous heart attack or at least one major risk factor for coronary artery disease has analyzed the effect of the MedDiet, specifically an Indo-Mediterranean diet, on risk of CHD incidence (115 cases) (Figure 2 and Supplemental Figure 4). As a consequence, a meta-analysis could not be undertaken for this outcome. The results of this trial showed that compared to a diet similar to a step I diet of the American Heart Association, the MedDiet significantly reduced the risk of CHD incidence by 52% (RR: 0.48; 95% CI: 0.33, 0.71) (Singh et al. 2002).

CHD mortality

The study conducted by Singh et al. (2002) (1,000 participants, 22 cases) is the only randomized clinical trial that has evaluated the effect of an Indo-Mediterranean diet on the risk of CHD mortality. Therefore, we could not undertake a meta-analysis for this outcome (Figure 2 and Supplemental Figure 5). The results of the clinical trial showed that the individuals in the intervention group had a 67% lower risk of sudden cardiac death than those in the control group (RR: 0.33, 95% CI: 0.13, 0.86) after 2 years of follow-up.

Stroke incidence

To date only one RCT (Estruch et al. 2018) has evaluated the effect of the MedDiet on stroke prevention. The study was a multicenter parallel group clinical trial conducted in 7,447 elderly Spanish individuals at high risk of CVD (139 cases). The results showed that the two MedDiet intervention groups (one enriched with extra virgin olive oil and the other with a mix of nuts) had a 42% lower risk of stroke incidence than the control group on a low-fat diet, (RR: 0.58; 95% CI: 0.42, 0.81). Because only one trial comparison was available, we did not conduct a meta-analysis for this outcome (Figure 2 and Supplemental Figure 6).

Stroke mortality

We did not identify any RCTs analyzing the effect of the MedDiet on stroke mortality risk (Figure 2).

MI incidence

Two studies (Singh et al. 2002; Estruch et al. 2018) with 8,447 participants, including 199 cases, analyzed the effect of

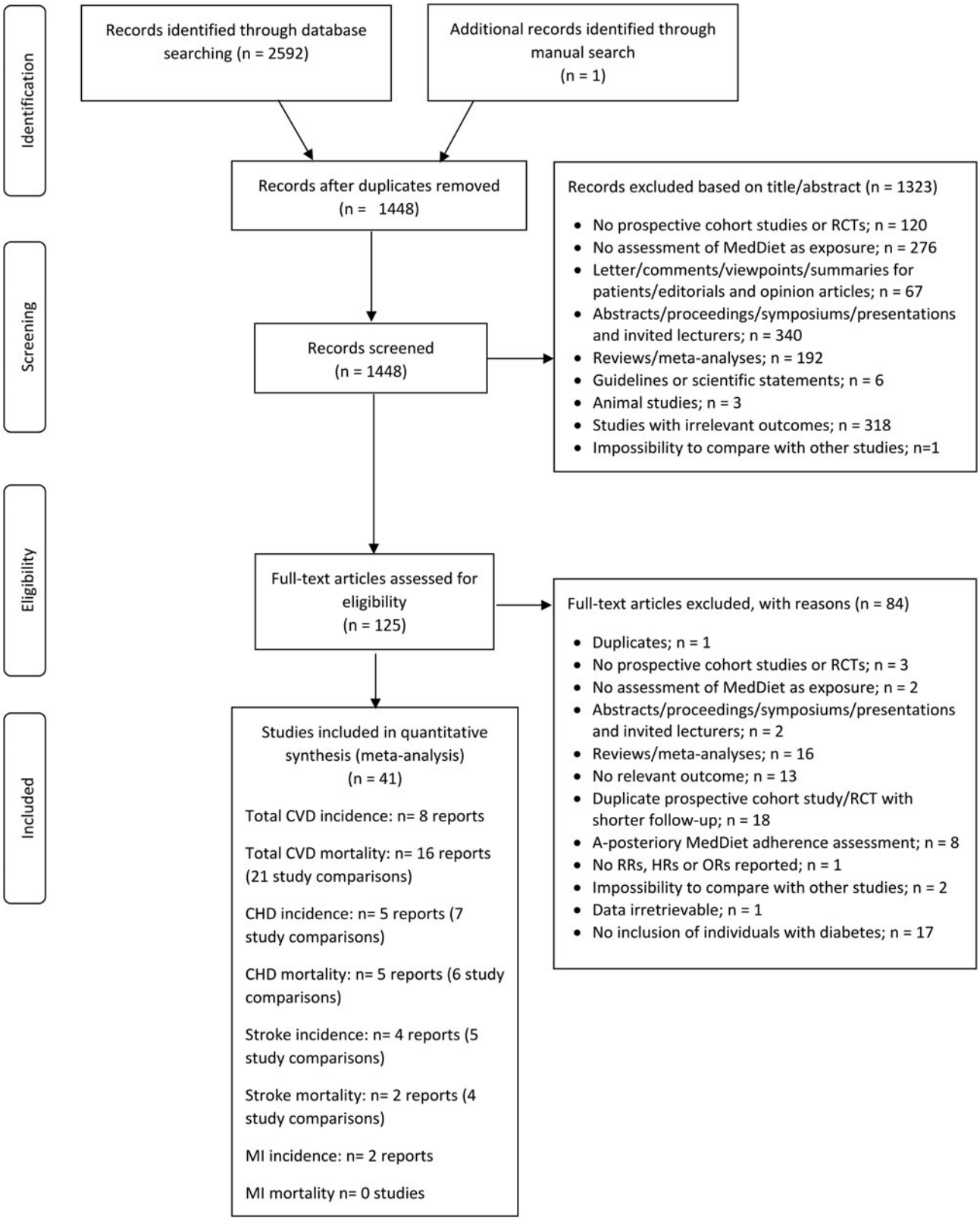

Figure 1. PRISMA flow diagram.

the MedDiet on MI incidence (Figure 2 and Supplemental Figure 7). Pooled analysis showed that the MedDiet significantly decreased the risk of MI by 35% (RR: 0.65; 95% CI: 0.49, 0.88) with no evidence of substantial heterogeneity ($I^2 = 50\%$, $p = 0.16$).

MI mortality

Only one study (Singh et al. 2002) conducted in 1,000 participants with myocardial infarction, angina pectoris or risk factors for coronary artery disease sought to evaluate the effect of the MedDiet on MI mortality. After 2 years of

Table 1. Characteristics of randomized clinical trials evaluating the effect of Mediterranean diet adherence and cardiovascular disease and mortality outcomes.

Study	Design	Participants	Mean age (SD or range), y	Treatment group	Control group	Follow-up	Outcome	Country	Funding sources
de Lorgeril et al. (1999)	Randomized single-blind, multi-clinic secondary prevention trial	605	53.5 (10)	Mediterranean diet	Close to step I diet of the American Heart Association	27 months	Total CVD incidence Total CVD mortality	France	NR
Control group		303							
Experimental group		302							
Singh et al. (2002)	Randomized single-blind, parallel, clinical trial	1,000	48 (9)	Indo-Mediterranean diet	Prudent diet (NCE) in step I	2 years	MI incidence MI mortality CHD incidence CHD mortality	India	Agency
Control group		501	49 (10)						
Experimental group		499							
Estruch et al. (2018)	Randomized parallel, multicenter clinical trial	7,447	Men 50–80 Women 60–80	MedDiet + EVOO MedDiet + nuts	Low-fat diet	4.8 years	Total CVD incidence Total CVD death Stroke MI incidence	Spain	Agency-Industry
Control group		2,543							
Experimental group		2,454							
Experimental group		2,450							

CHD, coronary heart disease; CVD, cardiovascular disease; EVOO, extra virgin olive oil; MedDiet, Mediterranean Diet; MI, myocardial infarction; NR, non-reported.

follow-up, 29 new cases occurred. Compared to those on the control diet, the individuals in the Indo-Mediterranean diet intervention group had a non-significant trend toward lower risk of MI mortality (RR: 0.67; 95% CI: 0.31, 1.43). A meta-analysis was not undertaken for MI mortality because only one trial comparison was identified (Figure 2 and Supplemental Figure 8).

Prospective cohort studies

Table 2 shows the characteristics of the prospective cohort studies. Studies were conducted in USA (n = 15), Europe (n = 20), Australia (n = 1), Asia (n = 1) and internationally level (n = 1) and publication year ranged from 2009 to 2018. The total sample size ranged from 274 to 193,527 participants and the length of follow-up ranged from 2 years to 26 years. According to the NOS scale, 70% of studies were of high quality (Supplemental Table 2).

Total CVD incidence

Eight cohort comparisons (Chrysohoou et al. 2010; Gardener et al. 2011; Eguaras et al. 2015; Atkins et al. 2014; Pignatelli et al. 2015; Bo et al. 2016; Tong et al. 2016; Al Rifai et al. 2018) with 53,508 participants, including 9,758 events, analyzed the association between MedDiet adherence and the risk of total CVD incidence (Figure 2 and Supplemental Figure 9). Comparing highest versus lowest categories of adherence, the summary pooled risk estimate showed a non-significant inverse association (RR: 0.88; 95% CI: 0.74, 1.04), with evidence of substantial heterogeneity (I^2 = 53%; p = 0.04). The continuous analysis shows that a 2-point increment in the MedDiet score was associated with a 10% lower risk of total CVD incidence (RR: 0.90; 95% CI: 0.85, 0.96), and there was also substantial evidence of inter-study heterogeneity (I^2 = 70%; p < 0.01) (Supplemental Figure 10).

Total CVD mortality

Twenty-one cohort comparisons (Lopez-Garcia et al. 2014; Martínez-González et al. 2010; Panagiotakos et al. 2015; Pignatelli et al. 2015; Psaltopoulou et al. 2013; Reedy et al. 2014; Al Rifai et al. 2018; Schröder et al. 2014; Shah et al. 2018; Stroup et al. 2000; Symons and Moore 2002; Tektonidis et al. 2015; Tognon et al. 2012; Tong et al. 2016; Trichopoulou et al. 2003; Tsivgoulis et al. 2015), with 883,878 participants, including 54,728 cases, analyzed the association between MedDiet adherence and the risk of total CVD mortality. There was a significant inverse association (RR: 0.79; 0.77, 0.82) with no evidence of heterogeneity between studies (I^2 = 0%; p = 0.64) when the highest categories were compared with the lowest (Figure 2 and Supplemental Figure 11). Along the same lines, continuous analysis showed that a 2-point increment in the MedDiet score was associated with a 9% lower risk of total CVD mortality (RR: 0.91; 95% CI: 0.87, 0.96) and there was evidence of substantial heterogeneity (I^2 = 95%; p < 0.01) (supplemental Figure 12).

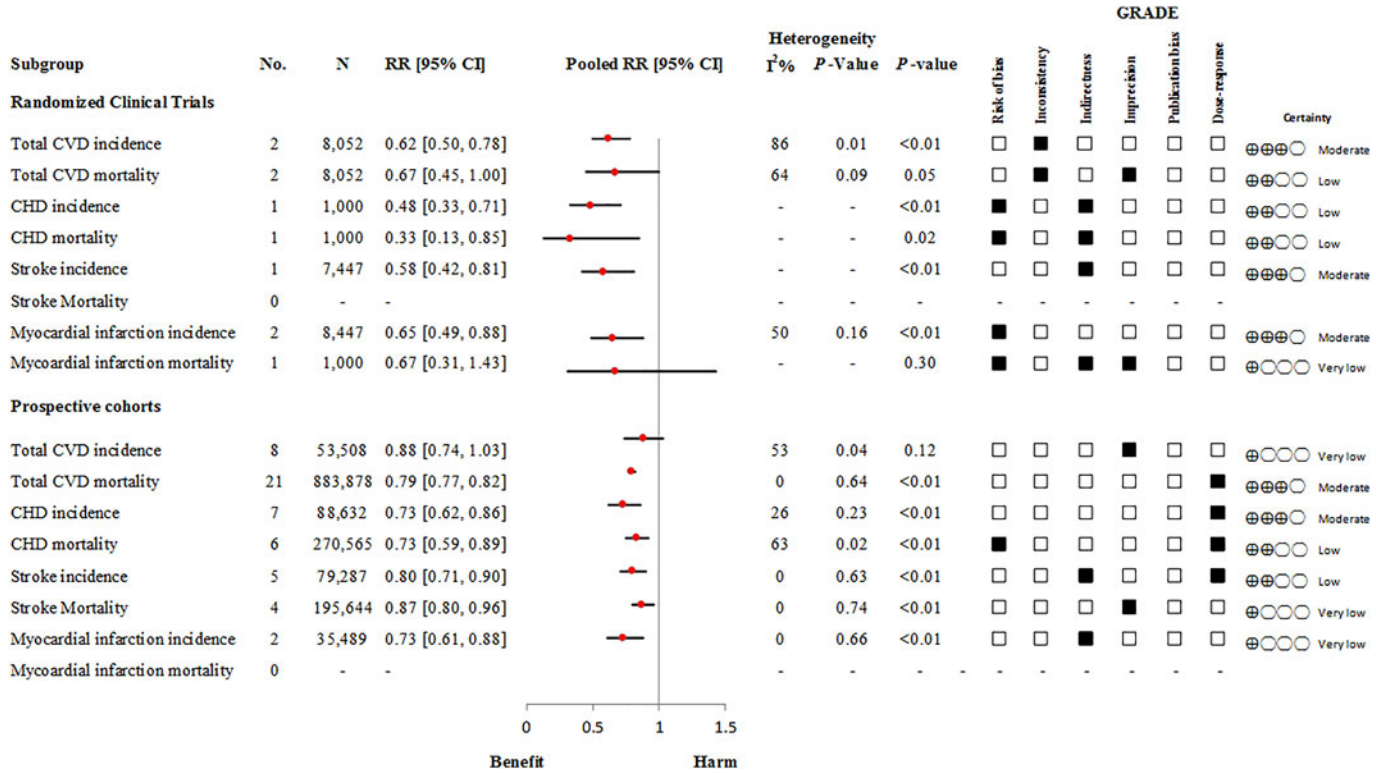

Figure 2. Summary of the pooled-effect estimates of randomized clinical trials and prospective cohort studies assessing the effect/association between Mediterranean diet and cardiovascular disease outcomes. Analyses were conducted using generic inverse variance random-effects models (≥5 trials available) or fixed effects models (<5 trials available). The pooled risk estimates are presented by the circle. $I^2 \geq 50\%$ indicates substantial heterogeneity. CI, confidence interval; CVD, cardiovascular disease; CHD, coronary heart disease.

CHD incidence

Seven cohort comparisons (Buckland et al. 2009; Martínez-González et al. 2010; Dilis et al. 2012; Atkins et al. 2014; Booth et al. 2014) with 88,632 participants, including 2,045 cases have analyzed the association between MedDiet adherence and the risk of CHD incidence. There was a 27% lower risk of total CHD between the highest and lowest categories of adherence (RR: 0.73; 95% CI: 0.62, 0.86), and there was no evidence of inter-study heterogeneity (I^2 =26%, p = 0.23) (Figure 2 and Supplemental Figure 13). Along the same lines, in the continuous analysis (Supplemental Figure 14), each 2-point increment in the MedDiet score was associated with a 20% lower risk of CHD incidence (RR: 0.80; 95% CI: 0.76, 0.85) and there was a high degree of inter-study heterogeneity (I^2 = 90%, p < 0.001).

CHD mortality

Six cohort comparisons (Chiuve et al. 2011; Dilis et al. 2012; Bertoia et al. 2014; Hodge et al. 2018; Warensjö Lemming et al. 2018) with 270,565 participants, including 2,019 cases, have analyzed the association between MedDiet adherence and the risk of CHD mortality. There was a significant inverse association (RR: 0.73; 95% CI: 0.59, 0.89) and evidence of substantial inter-study heterogeneity (I^2 = 63%; p = 0.02) when the highest categories were compared with the lowest (Figure 2 and Supplemental Figure 15). The continuous analysis showed a significant inverse association for each 2-point increment in the MedDiet score and the risk of CHD mortality (RR: 0.94; 95% CI: 0.91, 0.97), as well as evidence of substantial heterogeneity (I^2 = 76%; p < 0.01) (Supplemental Figure 16).

Stroke incidence

Five cohort comparisons (Gardener et al. 2011; Misirli et al. 2012; Tektonidis et al. 2015; Tsivgoulis et al. 2015) with 73,287 participants, including 2,663 cases, have analyzed the association between MedDiet adherence and the risk of stroke incidence. There was a significant inverse association (RR: 0.80; 95% CI: 0.71, 0.90) and no evidence of heterogeneity between studies (I^2 = 0%; p = 0.63) when the highest catergories were compared with the lowest (Figure 2 and Supplemental Figure 17). The continuous analysis showed that a 2-point increment in the MedDiet score was associated with a 10% lower risk of stroke incidence (RR: 0.90; 95% CI: 0.85, 0.96) and there was no evidence of inter-study heterogeneity (I^2 = 35%; p = 0.13) (Supplemental Figure 18).

Stroke mortality

Four cohort comparisons (Misirli et al. 2012; Aigner et al. 2018) with 195,644 participants, including 3,744 cases, have analyzed the association between MedDiet adherence and the risk of stroke mortality. There was a 13% lower risk of stroke mortality (RR: 0.87; 95% CI: 0.80, 0.96) and no evidence of heterogeneity (I^2 =0%, p = 0.74) when highest categories of adherence to MedDiet were compared with the lowest (Figure 2 and Supplemental Figure 19). The continuous analysis showed that a 2-point increment in MedDiet

Table 2. Characteristics of prospective cohort studies evaluating the association between Mediterranean diet adherence and cardiovascular disease and mortality.

Reference	Country	Study name	Participants	Age	Follow-up	Type of score	Divisions	Outcome	Total incidence	Adjustments	Founding source	NOS
Buckland et al. (2009)	Spain	EPIC-Heart	40,757 (15,335 M/25,422 F)	29–69	Mean of 10.4 years	Variation of Trichopolou method: relative MedDiet (score ranging 0–18)	3 categories: Low adherence, medium adherence and high adherence As continuous: 2-point increase	CHD incidence	609	Stratified by age, sex, center. Adjusted for education, physical activity, BMI, smoking status, diabetes, hypertension and hyperlipidemia status and total calorie intake	Agency	9
Chrysohoou et al. (2010)	Greece	—	750	63 (13) males 69 (12) females	2 years	Panagiotakos MedDiet score ranging from 0 to 55	3 categories: Low: <16 Moderate: 17–20 High: >21	Total CVD incidence	464	Age, sex, physical activity, smoking, BMI, hypertension, hypercholesterolemia, diabetes, history of CVD, family history of CVD, revascularization, ejection fraction, creatinine clearance at entry, c-reactive protein and discharge diagnosis	—	5
Buckland et al. (2011)	Spain	EPIC-Spain	40,622 (15,324 M/25,298 F)	29–69	Mean of 13.4 years	Trichopolou method adaptation (score ranging 0–18)	3 categories: Low adherence, medium adherence and high adherence As continuous: 2-point increase	Total CVD mortality	399	Stratified by center, age and sex. Adjusted for BMI, waist circumference, education level, physical activity, smoking status and intensity and total energy intake.	Agency	8
Chiuve et al. (2011)	United States	NHS	81,722 F	30–55	26 years	Alternate MedDiet score (ranging 0–9)	Five categories (cumulative score): <2.5 2.5–3.4 3.5–4.2 4.3–5.4 >5.4	CHD mortality	321	age (months), family history of myocardial infarction (no history, family member 60 years, family member 60 years), menopausal status (yes or no), current hormone therapy use (yes or no), and presence of diabetes, hypertension, high cholesterol, cancer, coronary heart disease, or stroke at baseline (all yes or no).	Agency	6
Gardener et al. (2011)	United States	NOMAS	2,568 (931 M/ 1,637 F)	68.6 (10.3)	Mean of 9 years	Trichopolou method (ranging 0–9)	Quintiles As continuous: 1-point increase	Total CVD incidence Ischemic stroke MI incidence Total CVD mortality	518 171 133 314	Age, sex, race-ethnicity, completion of high school education, moderate-to-heavy physical activity, kilocalories, cigarette	Agency	8

(*continued*)

Table 2. Continued.

Reference	Country	Study name	Participants	Age	Follow-up	Type of score	Divisions	Outcome	Total incidence	Adjustments	Founding source	NOS
										smoking, hypertension, diabetes, hypercholesterolemia and history of self-reported cardiac disease		
Martínez-González et al. (2010)	Spain	SUN	13,609 (5,444 M/8,165 F)	38	Median of 4.9 years	Trichopolou method (ranging 0–9)	4 categories: Low, low-moderate, moderate-high and high As continuous per each 2-point increase	Total CVD incidence CHD incidence	100 68	Age, sex, family history of coronary heart disease, total energy intake, physical activity, smoking, BMI, diabetes at baseline, use of aspirin, history of hypertension and history of hypercholesterolemia.	Agency	8
Dilis et al. (2012)	Greece	Greek EPIC-cohort	23,929 (9,740 M/ 14,189 F)	20–86	Median of 10 years	Trichopolou method (ranging 0–9)	3 categories: 0–3 4–5 6–9 As continuous: 2-point increase	CHD incidence CHD mortality	636 240	Age, sex, BMI, height, physical activity, years of schooling, energy intake, smoking status, arterial blood pressure.	Agency	8
Misirli et al. (2012)	Greece	EPIC-Greece	23,601 (9,617 M/ 13,984 F)	20–86	Median of 10.6 years	Trichopolou method (ranging from 0–9)	3 categories: 0–3 4–5 6–9 As continuous: 2-point increase	Stroke incidence Stroke mortality Ischemic stroke incidence Hemorrhagic stroke incidence	395 196 95 59	sex, age, education, smoking status, body mass index, level of physical activity, hypertension, diabetes and total energy intake	Agency	8
Tognon et al. (2012)	Sweden	The Västerbotten Intervention Programme	73,984 (35,950 M/ 38,034 F)	30–60	Median of 9 years	Trichopolou method (ranging 0–8)	As continuous: 1-point increase	Total CVD mortality MI mortality Stroke mortality	680 305 144	Age, obesity, smoking status, education, and physical activity	Agency-Industry	6
Atkins et al. (2014)	Great Britain	British Regional Heart Study	3,163 M	60–79	Mean of 11.3 years	Trichopolou method (ranging 0–8)	Quartiles	Total CVD mortality Total CVD incidence CHD incidence	302 545 288	Age, energy intake, smoking status, alcohol intake, physical activity, social class, BMI, HDL cholesterol, SBP, diabetes, CRP and vWF	Agency	7
Bertoia et al. (2014)	United States	WHI	93,122 F	50–79	Mean of 10.5 years	Trichopolou method (ranging 0–40)	Quintiles of updated score (baseline and 3 years)	CHD mortality	237	CAD, congestive heart failure, diabetes, hypertension, age, total energy, race, income, smoking, physical activity, waist to hip ratio, BMI, pulse.	Agency	6
Booth et al. (2014)	United States	REGARDS-study	4,174 (2,675 M/1,499 F)	≥45	Median of 4.3 years	Method similar to Trichopolou with 14 components	Quartiles	CHD incidence	447	age, race, sex, and region of residence, education and income, LDL	Agency	6

(*continued*)

Table 2. Continued.

Reference	Country	Study name	Participants	Age	Follow-up	Type of score	Divisions	Outcome	Total incidence	Adjustments	Founding source	NOS
										cholesterol, systolic and diastolic blood pressure, self-rated health, diabetes, albuminuria, estimated glomerular filtration rate, C-reactive protein, aspirin use, clopidogrel use, beta blocker use, angiotensin converting enzyme inhibitor use, angiotensin receptor blocker use, and statin use		
Cuenca-García et al. (2014)	Dallas, Texas	ACLS	12,193 (9,353 M/2,840 F)	20–82	Mean of 11.6 years	Based on Trichopolou method (ranging 0–9)	Quartiles	Total CVD mortality	102	age, sex, energy intake, examination year, physical activity, smoking, abnormal electrocardiogram, parental history of premature CVD and cardiorespiratory fitness	Agency-Industry	7
George et al. (2014)	United States	WHI Extension study	63,805 F	50–79	Median of 12.9 years	Alternate Mediterranean Diet (ranging 0–9)	Quintiles	Total CVD mortality	1,483	Age, energy intake, ethnicity, educational level, marital status, smoking, physical activity, postmenopausal hormone replacement therapy, body mass index and diabetes status	Agency	6
Lopez-Garcia et al. (2014)	United States	HPFS NHS	6,137 M 11,278 F	40–75 30–55	Median of 7.7 y Median of 5.8 y	Alternate Mediterranean Diet score (ranging 0–9)	Quintiles of cumulative MedDiet score As continuous per each 2-point increase	Total CVD mortality	1,142 666	age , smoking status, BMI , leisure-time physical activity, parental history of myocardial infarction before age 65 y, multivitamin use, menopausal status and use of HT in women and medication use (aspirin, diuretics, b-blockers, calcium channel blockers, other blood pressure medication, or statins and other cholesterol-lowering drugs)	Agency	7

(*continued*)

Table 2. Continued.

Reference	Country	Study name	Participants	Age	Follow-up	Type of score	Divisions	Outcome	Total incidence	Adjustments	Founding source	NOS
Reedy et al. (2014)	United States	NIH-AARP Diet and Health Study	424,663 (242,321 M/ 182,342 F)	50–71	15 years	Alternate Mediterranean diet score 0–9	Quintiles	Total CVD mortality	23,502	age, race/ethnicity, education, marital status, physical activity, smoking, energy intake, BMI and diabetes	—	7
Schröder et al. (2014)	Spain	PREDIMED study	7,447 (3,165 M/4,282 F)	Males 55–80 Females 60–80	Median of 4.8 years	MedDiet adherence questionnaire	As continuous per each 2-point increase	Total CVD incidence Total CVD mortality Stroke incidence MI incidence	288 87 139 106	age, gender, smoking, diabetes mellitus, hypertension, dyslipidemia, body mass index, family history of premature coronary heart disease, recruiting center, intervention group, leisure-time physical activity and educational level	Agency-Industry	9
Tognon et al. (2014)	Denmark	Danish MONICA project	1,849 (901 M/ 948 F)	25–74	Average of 14 years	Modified MedDiet score 0–8: adapted from Trichopolou	As continuous per each 1-point increase	Total CVD incidence Total CVD mortality MI incidence MI mortality Stroke incidence Stroke mortality	755 223 161 64 167 40	sex, BMI, education, physical activity and cigarette smoking, blood pressure, TAG and total cholesterol:HDL-cholesterol ratio		7
Vormund et al. (2015)	Switzerland	The National Research Program 1A (NRP 1A) The Swiss MONICA study	17,861 (8,665 M/ 9,196 F)	16–92 25–74		Modified MedDiet score 0–9: adapted from Trichopolou	3 categories	Total CVD mortality	1,385	age, sex and survey wave; marital status, smoking, BMI, region and nationality	Agency	7
Bonaccio et al. (2016)	Italy	MOLI-SANI study	1,995 (1,319 M/676 F)	62.6 (10.2)	Median of 4 years	Trichopolou method (ranging 0–9)	3 categories: Poor, average and high As continuous: 2-point increase	Total CVD mortality	51	Age, sex, smoking, physical activity, energy, education, years of diabetes diagnosis, blood glucose levels, hypercholesterolemia.	Agency-industry	7
Eguaras et al. (2015)	Spain	SUN	19,065 (7,531 M/ 11,534 F)	21–85	Mean of 10.9 years	Trichopolou method (ranging 0–9)	4 categories: Low, low-to-moderate, moderate-to-high and high As continuous: 2-point increase	Total CVD incidence	152	Age (underline time variable plus stratification), sex, smoking, baseline hypercholesterolemia, hypertension, leisure-time physical activity, diabetes and previous history of cardiovascular disease.	Agency	6

(*continued*)

Table 2. Continued.

Reference	Country	Study name	Participants	Age	Follow-up	Type of score	Divisions	Outcome	Total incidence	Adjustments	Founding source	NOS
Lau et al. (2015)	Hong Kong	—	274 (212 M/ 62 F)	68 (10)	Mean of 77 (12) months	Trichopolou 0–8	As continuous per each 1 point increase	Stroke incidence	13	Age, sex, BMI, smoking, diabetes, hypercholesterolemia, mean systolic BP, family history of CVD, CVD medication and hypertension	Agency	6
Panagiotakos et al. (2015)	Greece	ATTICA study	2,009	18–89	Median of 8.4 years	Panagiotakos method (ranging 0–55)	As continuous per each 1 point increase	Total CVD incidence	299	age, sex, smoking, physical activity, diabetes, hypercholesterolemia, hypertension, waist-hip ratio, years of school, family history of cvd, CRP and IL-6	Industry	8
Pignatelli et al. (2015)	Italy	—	801	73.6 (8.9)	Mean of 39.9 months	Mediterranean diet questionnaire ranging 0–9	3 categories: Low: 0–3 Intermediate: 4–6 High: 7–9	Total CVD incidence	72	sNOX2-dp, F2-IsoP, arterial hypertension, diabetes, HF, prior stroke/TIA, prior MI/ CHD, age, gender, antiplatelets, ACE inhibitors/ARBs, b-blockers, and statins	—	5
Tektonidis et al. (2015)	Sweden	SMC	32,921 F	48–83	Mean of 10.4 years	Modified MedDiet score (ranging 0–8) adapted from Trichopolou	Quartiles As continuous per each 1-point increase	MI incidence Ischemic stroke Hemorrhagic stroke	1,109 1,270 262	education level , family history of myocardial infarction, cigarette smoking , physical acitivity, BMI, history of hypertension, history of hypercholesterolemia, history 12 of diabetes, aspirin use and total energy intake	Agency	8
Tsivgoulis et al. (2015)	United States	REGARDS-study	20,197 (8,853 M/ 11,344 F)	≥45	Mean of 6.5 years	Trichopolou method (ranging 0–9)	3 categories	Stroke incidence Ischemic stroke Hemorrhagic stroke	565 497 68	age, race, age-race interaction, region, sex, income, education, total energy, smoking status, sedentary behavior, history of heart disease, atrial fibrillation, body mass index, waist circumference, diabetes mellitus, hypertension, hypertension medication use, systolic and diastolic blood pressure levels	Agency	7

(*continued*)

Table 2. Continued.

Reference	Country	Study name	Participants	Age	Follow-up	Type of score	Divisions	Outcome	Total incidence	Adjustments	Founding source	NOS
Bo et al. (2016)	Italy	—	1,658	45–64	Mean of 12 years	Trichopolou method (ranging 0–9)	3 categories: Low, medium and high. As continuous per 1-unit increase	Total CVD incidence Total CVD mortality	125 84	Age, sex, BMI, smoking, Physical activity, Total cholesterol, HDL-c, SBP, DBP, fasting glucose, education, rural area, CVD score	Agency	7
Park et al. (2016)	United States	NHANES	598 MHO 1,141 MUO	20–88	Median of 18.5 years	Panagiotakos method (ranging 0–50)	Tertiles As continuous per each 5-point increase	Total CVD mortality	16 86	age, gender, race/ethnicity, educational attainment, income, living with spouse, smoking status, level of physical activity, family history of coronary heart disease, body mass index and total calorie intakes.	—	8
Shvetsov et al. (2016)	United States	MEC	193,527 (87,338 M/ 106,189 F)	45–75	13–18 years	Alternate Mediterranean diet score 0–9	Quintiles	Total CVD mortality	10,433 males 8,567 females	age, ethnicity, BMI, physical activity, smoking, education, marital status, hormone replacement therapy (women only) and history of diabetes, heart disease and cancer	Agency	7
Stewart et al. (2016)	International	STABILITY	15,482	67 (9)	Median of 3.7 years	Method described by Sofi et al.	As continuous per each 1-point increase	Total CVD incidence Total CVD mortality MI incidence Stroke incidence	1,588 623 698 267	treatment group, age, sex, smoking, markers of disease severity, history of hypertension, diabetes mellitus, HDL and LDL cholesterol, body mass index, and total physical activity, geographic region, World Bank Country income level, education and Western Dietary Score	Industry	6
Tong et al. (2016)	United Kingdom	EPI-Norfolk cohort	23,902	40–79	Average of 12.2 years	Trichopolou 0–9	3 categories (cumulative score): Low, medium and high As continuous per SD difference	Total CVD incidence Total CVD mortality CHD incidence CHD mortality Stroke incidence Stroke mortality	7,606 1,714 2,967 817 1,023 509	Age, sex, BMI, smoking, physical activity, diabetes, education, social class, marital status, season of FFQ assessment, waist circumference, medication use, family history of diabetes, MI and stroke	Agency	8

(*continued*)

Table 2. Continued.

Reference	Country	Study name	Participants	Age	Follow-up	Type of score	Divisions	Outcome	Total incidence	Adjustments	Founding source	NOS
Kouvari et al. (2017)	Greece	Hellenic Heart Failure Study	690 (483 M/ 207 F)	62 (12)	10 years	Panagiotakos ranging 0–55	continuous per each 1-point increment	CHD incidence	345	Age, gender, BMI, physical activity, hypertension, hypercholesterolemia, diabetes mellitus, family history of CVD, left ventricular ejection fraction	—	7
Whalen et al. (2017)	USA	REGARDS-study	21,423	≥45	Median of 6.25 years	Modified MedDiet score (ranging 11–55)	Quintiles	Total CVD mortality	863	sex, race, total energy intake, BMI, physical activity, smoking, annual income, hormone replacement therapy use (in women) at baseline in an age (in months)-as-time-scale model	Agency	7
Hodge et al. (2018)	Australia	MCCS	39,532 (16,051 M/ 23,481 F)	40–69	Average of 9 years	Trichopolou method (ranging 0–9)	Tertiles As continuous: 1-point increment	Total CVD mortality CHD mortality	2,081 140	birth, SEIFA quintile, alcohol intake, personal history of diabetes, stratified by sex and personal and family history of CVD; CVD model includes DII x attained age interaction.	Agency	7
Shah et al. (2018)	USA	The Cooper Center Longitudinal Study	11,376 (8,577 M/2,799 F)	≥20	Mean of 18 years	Trichopoulou method (Rangin 0–9)	Quintiles	Total CVD mortality	249	Adjusted for sex, age, smoking, calorie intake, physical activity, BMI, family history cardiovascular disease, and baseline glucose, LDL, and SBP	—	8
Warensjö Lemming et al. (2018)	Sweden	SMC	30,338 F 32,260 F	49 – 83	Median of 17 years	Trichopoulou method (ranging 0–8)	Tertiles	Total CVD mortality CHD mortality	3,003 1,081	Educational level, living alone, physical activity, energy intake, smoking habits, Charlson's comorbidity index and healthy diet score	Agency	6
Al Rifai et al. (2018)	USA	MESA	1,601	45–84	Median of 12.1 years	Trichopolou method (ranging 0–11)	Quartiles	Total CVD incidence	276	Age, sex, race/ethnicity, education, MESA site, income, occupational status, marital status, family history of CHD, presence of diabetes, presence of hypertension, baseline statin use, baseline aspirin use,	—	6

(*continued*)

Table 2. Continued.

Reference	Country	Study name	Participants	Age	Follow-up	Type of score	Divisions	Outcome	Total incidence	Adjustments	Founding source	NOS
										baseline anti-hypertensive medication use, baseline glucose-lowering medication use		
Aigner et al. (2018)	USA	MEC	172,043 (80,380 M/ 91,663 F)	45–75	17.6 years	Trichopoulou method (ranging 0–9)	Three categories: High Medium Low	Stroke mortality	3,548	sex, ethnicity, age, BMI, physical activity, hormone therapy, education, USA born, >25 years in USA	Agency	7

ACLS, Aerobics Center Longitudinal Study; CHD, coronary heart disease; COSM, Cohort of Swedish Men; CVD, cardiovascular disease; HPFS, health professionals follow-up study; MEC, multiethnic cohort study; NOMAS, Northern Manhattan Study; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction; NHS, Nurses' Health Study; REGARDS-study, REasons for Geographic and Racial Differences in Stroke; SMC, Swedish Mammography Cohort; SUN, Seguimiento Universidad de Navarra; WHI Extension study, Women's Health Initiative.

adherence was non-significantly inversely associated with the risk of stroke mortality (RR: 0.96; 95% CI: 0.89, 1.04) and there was no evidence of inter-study heterogeneity (I^2 =0%, p = 0.86) (Supplemental Figure 20).

MI incidence

Two cohort comparisons (Gardener et al. 2011; Tektonidis et al. 2015) have analyzed the association between MedDiet adherence and the risk of MI incidence, including 35,489 participants and 1,242 cases. A comparison of the highest and the lowest categories of adherence to the MedDiet showed a 27% lower risk of total MI (RR: 0.73, 95% CI: 0.61, 0.88) and no evidence of heterogeneity (I^2 = 0%, p = 0.66) (Figure 2 and Supplemental Figure 21). The continuous analysis, showed that a 2-point increment in the MedDiet score was associated with a 13% lower risk of MI incidence (RR: 0.79; 95% CI: 0.67, 0.94) and there was evidence of inter-study heterogeneity (I^2 = 74%, p < 0.01) (Supplemental Figure 22).

MI mortality

We did not identify any prospective cohort studies analyzing the association between MedDiet adherence, categorized in quantiles, and the risk of MI mortality (Figure 2). However, four cohort comparisons reported the risk estimate on continuous scale instead of categories of MedDiet adherence. Pooled results showed a 13% lower risk of MI mortality (RR: 0.87; 95% CI: 0.82, 0.92) for every 2-point increment in the MedDiet score and no evidence of inter-study heterogeneity (I^2 = 0%, p = 0.51) (Supplementary Figure 23).

Sensitivity, subgroup and dose-response analyses

In the meta-analyses of RCTs, no study modified the pooled effect estimate or the evidence of heterogeneity for any of the outcomes.

Supplemental Table 3 shows the sensitivity analyses that systematically excluded one study at a time and changed the evidence of heterogeneity or the significance, direction or magnitude of the pooled relative risk from the prospective cohort studies. Removing the study by Eguaras et al. (2015) modified the heterogeneity for total CVD incidence from substantial to non-substantial. Removing the study by Warensjö Lemming et al. (2018) explained the heterogeneity for CHD mortality. No study modified the pooled effect estimate or the evidence of heterogeneity for total CVD mortality, CHD incidence, stroke incidence, MI incidence, stroke mortality or MI mortality.

Supplemental Figures 24 and 25 show the a priori and post hoc subgroup analyses among cohort studies for CVD mortality, the only end-point with more than 10 cohort comparisons. No evidence of effect modification was observed for the association between MedDiet adherence and total CVD mortality.

Supplemental Figures 26–30 show the dose-response analyses from prospective cohort studies. Five of the outcomes (total CV incidence, total CVD mortality, CHD

incidence, CHD mortality and stroke incidence) had sufficient data for the dose-response analysis. No evidence of nonlinear dose-response association was detected between MedDiet adherence and these outcomes ($P_{departure\ from\ linearity} > 0.05$). A statistically significant linear association was observed between MedDiet adherence and the risk of CVD mortality, CHD incidence, CHD mortality and stroke incidence. The RR and 95% confidence interval for every 2-point increment in the MedDiet score was 0.93 (0.92, 0.94) for CVD mortality, 0.89 (0.84, 0.94) for CHD incidence, 0.89 (0.82, 0.96) for CHD mortality and 0.92 (0.88, 0.96) for stroke incidence. For all the other outcomes we could not performed the dose-response analyses because less than 3 study comparisons were present.

Publication bias

Supplemental Figure 31 shows publication bias for total CVD mortality. No evidence of publication bias was detected by visual inspection of funnel plots or by Begg ($p = 0.608$) and Egger ($p = 0.960$) tests. Due to the limited number of studies (<10 for each outcome), we could not assess publication bias for the other outcomes.

Overall quality assessment (GRADE)

Supplemental Table 3 shows the GRADE assessments for the effect of MedDiet on CVD outcomes in RCTs. The evidence for benefit was rated as moderate for total CVD incidence because of downgrade for inconsistency; low for total CVD mortality because of downgrades for inconsistency and imprecision; low for CHD incidence and CHD mortality because of downgrades for inconsistency and indirectness; moderate for stroke incidence because of downgrade for indirectness; moderate for MI incidence because of downgrade for risk of bias; and very low for MI mortality because of downgrades for risk of bias, indirectness and imprecision.

Supplemental Table 4 shows the GRADE assessments for the association between MedDiet adherence and CVD outcomes in prospective cohort studies. The evidence was rated as very low for total CVD incidence and stroke mortality because of downgrade for imprecision; very low for MI incidence because of downgrade for indirectness; low for CHD mortality because of downgrade for risk of bias and upgrade for a dose-response gradient; low for stroke incidence because of downgrade for indirectness and upgrade for a dose-response gradient; and moderate for total CVD mortality and CHD incidence because of upgrade for a dose-response gradient.

Discussion

We conducted a meta-analysis of RCTs and prospective cohort studies to evaluate the MedDiet and the risk of incidence of or mortality from total CVD, CHD, stroke, and MI in populations inclusive of individuals with diabetes. Pooled analyses from RCTs suggest that the MedDiet reduces the risk of total CVD and MI incidence. No significant effect on total CVD mortality was reported. A meta-analysis could not be undertaken for CHD incidence and mortality, stroke incidence or MI mortality.

The results of cohort studies suggest that adherence to the MedDiet is inversely associated with the risk of incidence of or mortality from total CVD causes, except total CVD incidence and stroke mortality, when comparing the highest quantile of adherence to MedDiet to lowest quantile.

Findings in relation to other studies

Our findings from RCT meta-analyses are in line with a previous meta-analysis of RCTs that evaluated the effect of the MedDiet on various CVD outcomes (Salas-Salvadó et al. 2018). However, our results for total CVD mortality are inconsistent with the latest meta-analysis of RCTs, which showed a 41% lower risk of CVD death (Liyanage et al. 2016). This inconsistency might be explained by the fact that the authors included in the analysis two more RCTs than the present study. One of these has only sudden cardiac death as the end-point (Singh et al. 2002) and the other did not evaluate the actual definition of the MedDiet but only some of its components (Burr et al. 2003).

Our results regarding prospective cohort studies are also in line with those of previous systematic reviews and meta-analyses of observational studies evaluating the association between MedDiet and the risk of CVD outcomes (Salas-Salvadó et al. 2018). It is noteworthy that in the present study, no association between MedDiet adherence and the risk of total CVD incidence was observed. However, the previous meta-analysis evaluating this association reported a 27% lower risk of CVD (Grosso et al. 2017). These discrepancies could be attributable to the inclusion criteria (the present study only included studies with populations inclusive of individuals with diabetes). A further explanation may be that the meta-analysis by Grosso et al. (2017) contained a mix of studies on various CVD outcomes not just a cluster of different types of CVD incidence and mortality outcomes as in the present study. In order to make the results comparable across meta-analyses, it would be important to homogenize the definition of total CVD.

The possible mechanisms by which MedDiet could prevent CVDs have been discussed in a narrative review published by our group (Salas-Salvadó et al. 2018). Briefly, the MedDiet is well- characterized by its high lipid (monounsaturated and polyunsaturated fatty acids), fiber, and polyphenols content, which could act synergistically modulating beneficially different CVD risk factors, such as lipid profile, blood pressure, fasting blood glucose and body weight.

Strengths and limitations

Some of the strengths of the present study need to be highlighted. First, we used a comprehensive search strategy of three main databases which identified all the RCTs and prospective cohort studies available. Second, we synthesized and quantified evidence from both RCTs and prospective cohort

studies. Third, we evaluated the overall quality of the evidence by using GRADE.

Nevertheless, its limitations also need to be mentioned. Although we included both RCTs and prospective cohort studies, we cannot discount the presence of residual confounding from the observational studies, which is their main limitation. Furthermore, for the RCTs we only had one study for some analyses and no meta-analysis was performed. Another important limitation is that the certainty of the evidence based on the GRADE approach was low or very low for most of the outcomes. Serious risk of bias were detected in the GRADE assessment for the vast majority of the outcomes from the meta-analysis of RCTs because of the inclusion of only one study (Singh et al. 2002), which appeared to have unreliable data (Horton 2005), and for CHD mortality from the meta-analysis of prospective cohort studies because 50% of the studies were judged to be low quality on the NOS scale. Moreover, serious indirectness was detected for several outcomes in the meta-analysis of RCTs because only one study was included in the analyses and more than 60% of the prospective cohort studies on stroke and MI incidence had been conducted only in females. Finally, it should be pointed out that there was evidence of imprecision in the pooled estimates of total CVD and MI mortality (meta-analysis of RCTs) and in total CVD incidence and stroke mortality (meta-analyses of prospective cohorts).

Balancing the weaknesses and strengths, the overall evidence provided by the meta-analysis of RCTs was graded as very low for MI mortality; low for total CVD mortality, CHD incidence and mortality; and moderate for incidence of total CVD, stroke and MI. The overall evidence provided by the meta-analysis of prospective cohort studies was graded as very low for total CVD incidence, stroke mortality and MI incidence; low for CHD mortality and stroke incidence; and moderate for total CVD mortality and CHD incidence.

Implications

Diet is recognized as a cornerstone in the prevention of CVD in people with and without diabetes. In this regard, the role of the MedDiet in the prevention of CVD outcomes has been extensively studied in several RCTs and prospective cohort studies. Although several meta-analyses of MedDiet and CVD outcomes have been published before, the present study differs in terms of the target population. As far as we know, this is the first meta-analysis that contains only studies with populations that includes individuals with diabetes.

Diabetes is an important predisposing risk factor for the development of CVD, the leading cause of mortality worldwide. The results of the present meta-analysis suggest a beneficial role of the MedDiet in the prevention of the incidence of and mortality from several CVD outcomes. In the light of these findings, there is clearly a need to analyze the effect of the MedDiet on CVD prevention only in individuals with diabetes, who would benefit from adopting this healthy dietary pattern.

Conclusions

In conclusion, the present systematic review and meta-analysis of prospective cohort studies and RCTs demonstrates that the MedDiet has a beneficial role in reducing the risk of the incidence of and mortality from various CVD outcomes in populations inclusive of individuals with diabetes. Our certainty in the pooled estimates ranges from moderate to very low. Future studies are likely to influence our confidence in the pooled estimates. There is an important need for new, large, well-designed RCTs conducted specifically in individuals with diabetes to address uncertainties and to develop evidence-based dietary guidelines for diabetes management.

Conflicts of interest

Jordi Salas-Salvadó reports serving on the board of the International Nut and Dried Fruit Council, and the Eroski Foundation and receiving grant support from these entities through his institution. He also reports serving on the Executive Committee of the Instituto Danone Spain. He has received research funding from the Instituto de Salud Carlos III, Spain; Ministerio de Educación y Ciencia, Spain; Departament de Salut Pública de la Generalitat de Catalunya, Catalonia, Spain, and the European Commission. He has also received research funding from the California Walnut Commission, Sacramento CA, USA; Patrimonio Comunal Olivarero, Spain; La Morella Nuts, Spain; and Borges S.A., Spain. He reports receiving consulting fees or travel expenses from Danone; the California Walnut Commission, the Eroski Foundation, the Instituto Danone - Spain, Nuts for Life, the Australian Nut Industry Council, Nestlé, Abbot Laboratories, and Font Vella Lanjarón. He is on the Clinical Practice Guidelines Expert Committee of the European Association for the study of Diabetes (EASD), and has served on the Scientific Committee of the Spanish Food and Safety Agency, and the Spanish Federation of the Scientific Societies of Food, Nutrition and Dietetics. He is a member of the International Carbohydrate Quality Consortium (ICQC), and Executive Board Member of the Diabetes and Nutrition Study Group (DNSG) of the EASD. John L. Sievenpiper has received research support from the Canadian Institutes of health Research (CIHR), Diabetes Canada, PSI Foundation, Banting and Best Diabetes Centre (BBDC), Canadian Nutrition Society (CNS), 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 the Calorie Control Council). He has received food donations to support randomized controlled trials 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. He has received travel support, speaker

fees and/or honoraria from Diabetes Canada, Canadian Nutrition Society (CNS), Mott's LLP, Dairy Farmers of Canada, Alberta Milk, FoodMinds LLC, Memac Ogilvy & Mather LLC, PepsiCo, The Ginger Network LLC, International Sweeteners Association, Nestlé, Pulse Canada, Canadian Society for Endocrinology and Metabolism (CSEM), GI Foundation, Abbott, Biofortis, California Walnut Commission, American Society of Nutrition (ASN), Loma Linda University, Dietitians of Canada, European Food Safety Authority, and Physicians Committee for Responsible Medicine. He has or has had ad hoc consulting arrangements with Winston & Strawn LLP, Perkins Coie LLP, Tate & Lyle, and Wirtschaftliche Vereinigung Zucker e.V. He is a member of the European Fruit Juice Association Scientific Expert Panel. 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 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 Unilever Canada. Cyril W.C. Kendall has received grants or research support from the Advanced Food Materials Network, Agriculture and Agri-Foods Canada (AAFC), Almond Board of California, American Pistachio Growers, Barilla, Calorie Control Council, 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, Saskatchewan Pulse Growers 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, WhiteWave Foods. He 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. He 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. He is a member of the International Carbohydrate Quality Consortium (ICQC), 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. Dario Rahelić has served as principal investigator or co-investigator in clinical trials of AstraZeneca, Eli Lilly, MSD, Novo Nordisk, Sanofi Aventis, Solvay and Trophos. He has received honoraria for speaking or advisory board engagements and consulting fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Lifescan – Johnson & Johnson, Novartis, Novo Nordisk, MSD, Merck Sharp & Dohme, Pfizer, Pliva, Roche, Salvus, Sanofi Aventis and Takeda. No competing interests were declared by Nerea Becerra-Tomás, Sonia Blanco Mejia, Tauseef Khan, Effie Viguiliouk and by Hana Kahleova.

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