REVIEW

Association between Adherence to the Mediterranean Diet and Risk of Type 2 Diabetes: An Updated Systematic Review and Dose–Response Meta-Analysis of Prospective Cohort Studies

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ABSTRACT

Despite earlier meta-analyses on the association between adherence to a Mediterranean diet (MD) and risk of diabetes, there is no comprehensive and updated study assessing this issue. Furthermore, no earlier study has examined the nonlinear dose–response relation between consumption of an MD and risk of diabetes. The current systematic review and meta-analysis was conducted to investigate the linear and nonlinear dose–response relation between MD and incidence of diabetes. Using relevant keywords, electronic searches for prospective studies were conducted in ISI Web of Science, PubMed, and Scopus until January 2022. The reported HRs or ORs in the primary studies were regarded as RRs. The overall effect was calculated using a random-effects model that accounts for between-study variability. The potential nonlinear dose–response associations were tested using a 2-stage hierarchical regression model. Based on 16 prospective studies (with 17 effect sizes), we found that the greatest adherence to the MD was significantly associated with a reduced risk of diabetes (pooled RR: 0.83; 95% CI: 0.77, 0.90; $I^2 = 79\%$, $P \leq 0.001$). Based on linear dose–response analysis, each 1-score increase in the Mediterranean diet score was associated with a 3% decreased risk of diabetes (HR = 0.97; 95% CI: 0.96, 0.98; $P < 0.001$). A nonlinear relation (P-nonlinearity = 0.001) was also observed between MD score and risk of type 2 diabetes. Even modest adherence to the MD was linked to a decreased incidence of type 2 diabetes. The protocol is also registered in the International Prospective Register Of Systematic Reviews (PROSPERO) database (https://www.crd.york.ac.uk/PROSPERO/; registration ID: CRD 42021265332). *Adv Nutr* 2022;13:1787–1798.

Statement of Significance: Based on the literature, although previous meta-analyses have reviewed the association between Mediterranean diet and risk of type 2 diabetes, several restrictions may distort these results. Notably, this is the first study to assess whether there is a nonlinear dose–response relation between adherences to Mediterranean diet and the risk of type 2 diabetes.

Keywords: Mediterranean diet, incidence, review, meta-analysis, dose-response analysis, type 2 diabetes

Introduction

Diabetes affected at least 463 million persons aged 20 to 79 y worldwide in 2019, and caused approximately 4 million deaths (1). It is projected that this condition will affect 693 million people in 2045 (2). Individuals with diabetes are more likely to develop cardiovascular disease (3) and cancers (4, 5). The International Diabetes Federation has reported that approximately 10% of the global health expenditure is spent on diabetes (1); therefore, preventive measures to reduce the incidence of diabetes are of high priority.

Physical activity, dietary factors, smoking, and alcohol use are contributing factors to the risk of diabetes (6). In terms of dietary factors, specific dietary patterns have received great attention in recent years. The Mediterranean diet (MD) is a well-known healthy diet, whose beneficial effects on human health have earlier been investigated (7). It must be kept in mind that the prevalence of obesity among residents of Mediterranean areas is high (8). Given the role of obesity in the incidence of noncommunicable diseases, including diabetes, increasing prevalence of these

conditions along with obesity is expected (9). Earlier studies have demonstrated an inverse association between adherence to an MD and incidence of diabetes (10–12); however, some other studies have reached no significant link between the MD and diabetes (13). Although the MD is high in fat, it contains high amounts of olive oil, nuts, and magnesium, which may beneficially affect the risk of diabetes (14–16). In a meta-analysis in 2017, a strong inverse relation was found between adherence to an MD and incidence of diabetes (10). Since the publication of that meta-analysis, several prospective studies have appeared. The latest meta-analysis in this regard had several drawbacks: some original articles were missing, errors in data extraction, and inclusion of relevant papers as well as lack of assessment for a nonlinear dose–response relation (17). We therefore aimed to perform a comprehensive updated systematic review and a dose–response meta-analysis of prospective cohort studies on the relation between adherence to the MD diet and risk of type 2 diabetes.

Methods

We followed the guidelines of Meta-Analysis of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to report the current study (18, 19). The study's protocol was registered in the International Prospective Registry of Systematic Reviews (https://www.crd.york.ac.uk/prospero/, registration code: CRD42021265332).

Literature search

Literature searches were conduct∗ed using electronic databases, including Institute for Scientific Information Web of Science (ISI Web of Science), PubMed, and Scopus until 11 January 2022. Our search strategy included the following keywords: *1*) ("Mediterranean diet" and "Mediterranean"), *2*) ("Diabetes Mellitus," "diabetes," and "insulin resistance"), *3*) ("Cohort Studies," "Cohort," "prospective," "longitudinal," "Case-Control Studies," "nested case control," prospective∗, "risk," and "follow-up"). Keywords in groups 1, 2, and 3 were combined with "AND" as a Boolean operator. No publication date or language restrictions were applied. In addition, the reference lists of the pertinent publications were examined to ensure that no publication was missed. The titles and abstracts of the identified papers were separately examined by 2 reviewers (PS and SE-K), and differences were resolved through consultation with AS-A.

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Supplemental Tables 1–3 and Supplemental Figure 1 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances/.
The current meta-analysis was reported using the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) checklist and Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA). The protocol is also registered in the International Prospective Register Of Systematic Reviews (PROSPERO) database (https://www.crd.york.ac.uk/PROSPERO/; registration ID: CRD 42021265332).
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Eligibility criteria

The following criteria were used to determine whether or not an article was to be included: *1*) prospective cohort design (cohort, case-cohort, or nested case-control), *2*) studies that examined the relation between adherence to the MD and incidence of diabetes as the outcome, *3*) those that reported the risk estimates (HRs or RRs) along with 95% CIs, and *4*) studies in the general population (i.e., those that were conducted in patients only were not included). If more than 1 study published data on the same cohort, we used the record with the largest sample size and/or the longest follow-up duration.

Data extraction

The first author's last name, study location, publication year, sample size, number of individuals with diabetes, follow-up duration, participants' sex and age, assessment of exposure, assessment of outcome, confounders adjusted for in multivariate analyses, and multivariable-adjusted risk estimates were extracted independently by 2 investigators (PS and SE-K). When several regression models had been applied in an article, the risk estimate with the fully adjusted model was considered.

Quality assessment

The Newcastle-Ottawa Scale (NOS) was used to evaluate the study's quality (scores ranged from 0 to 9) (20). This scale considers 3 primary domains for quality evaluation: "selection," "comparability," and "outcome."

1) In the "selection" domain, 4 elements are examined: representatives of the exposed cohort, selection of the nonexposed cohort, exposure determination, and proof that the outcomes did not exist at baseline.
2) In the "comparability" domain, the control of confounders in study design or analysis was taken into account.
3) The "outcome" domain evaluates the ascertainment of outcomes, the follow-up time, and the adequacy of cohort follow-up.
4) Studies that received 1–2 points in the "comparability" domain, 3–4 points in the "selection" domain, and 2–3 points in the "outcome" domain were regarded to have good overall quality. They were rated fair if they received 2, 1–2, and, 2–3 points in the "selection" domain, "comparability" domain, and "outcome" domain, respectively, and low if they received 0–1, 0, and 0–1 points, in the "selection" domain, "comparability" domain, and "outcome" domain, respectively. High-quality studies were considered as those with a score of 7 points or higher.

Statistical analyses

For all analyses in this study, we used the RRs and 95% CIs as effect sizes. In the original papers, the published ORs or HRs were considered as RRs. A random-effects model was used to calculate the overall effect, which takes into account the variability between studies. Cochran's Q

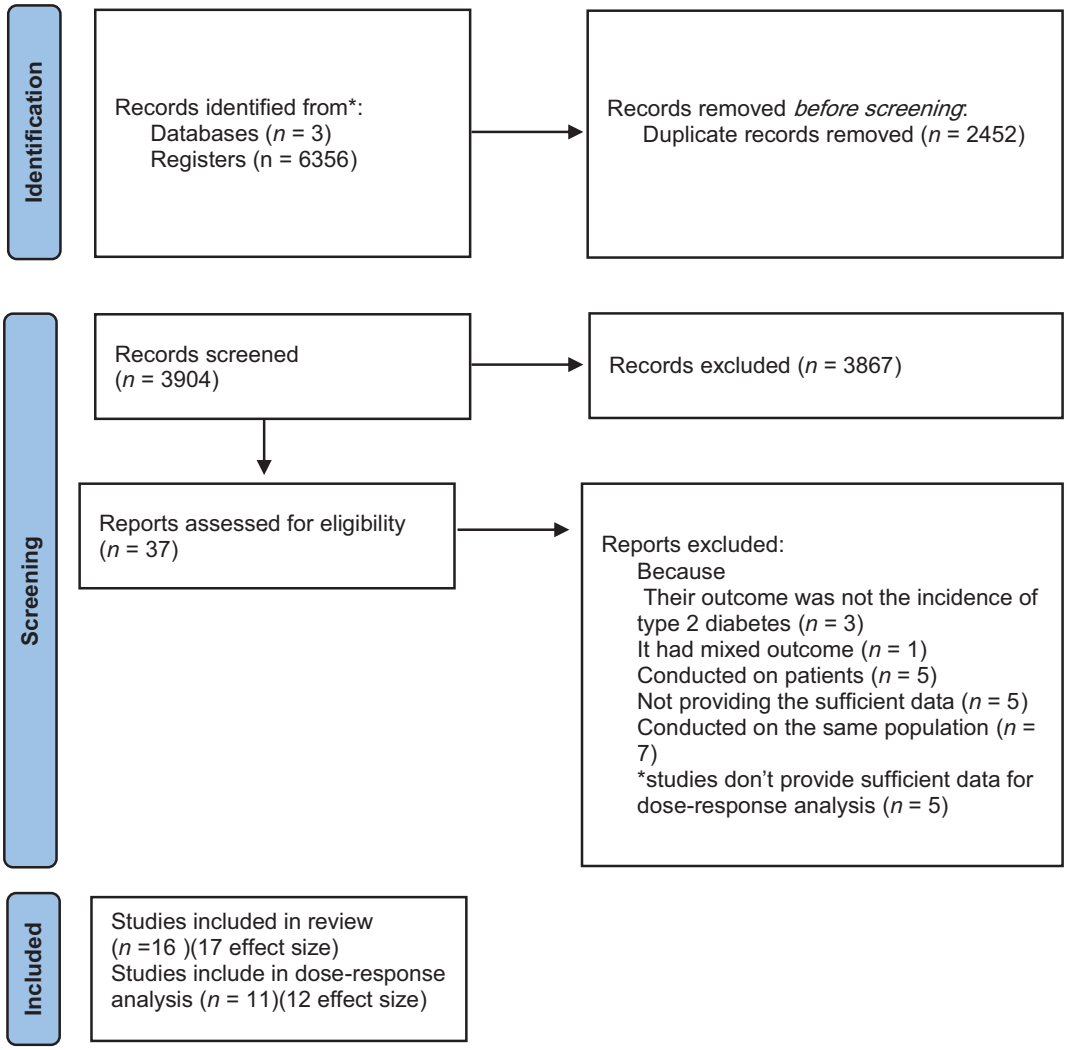

FIGURE 1 Flowchart of study selection process.

test and I^2 were used to assess statistical heterogeneity between studies (21). We used a priori subgroup analysis based on gender and geographical location at first (as mentioned in our PROSPERO registration); however, after reviewing all the included studies, we performed further subgroup analyses based on the number of study participants, follow-up duration, diabetes assessment method, quality of studies, and MD scoring methods to find possible sources of heterogeneity (these factors were not registered in our PROSPERO registration). The sensitivity analysis was carried out by removing effect sizes from the analysis one by one to examine the potential effect of each article on pooled effect sizes. Egger's test was used to assess publication bias (weighted linear regression test) (22). For dose–response meta-analysis, log RRs and their corresponding SEs, as well as number of incident diabetes cases and person-years for n-tiles of Mediterranean diet score were extracted. A method recommended by Aune et al. (23) was applied to calculate the number of incident cases of diabetes if it was not reported. A 2-stage random-effects nonlinear dose–response meta-analysis using restricted cubic splines was conducted to assess the nonlinear dose–response association. This method was performed to find the dose with the optimum effect. Furthermore, we examined changes in disease risk per each point increment in the Mediterranean diet score using a 1-stage random-effects dose–response model assuming a linear trend. The dose–response analyses were conducted using DRMETA package developed for STATA by Orsini et al (24). STATA version 16.0 was used for all analyses (StataCorp 2019; Stata Statistical Software: release 16; StataCorp LLC). $P < 0.05$ was regarded as statistically significant. The certainty of evidence was assessed by the use of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method (25).

TABLE 1 The main characteristics of cohort studies that examined the association of Mediterranean diet and risk of diabetes[1]

Study (year) (ref)	Country	Cohort	Age range/mean age, y	Sex	Sample size	Number of diabetes cases	Study duration	Person-years	Exposure/ assessment	Outcome/ assessment	Comparison	OR or RR or HR (95% CI)	Quality assessment score
Bantle et al. (2016) (50)	USA	CARDIA study	18–30	Male and female	3358	2249	25 y	—	diet history questionnaire/baseline measurement	T2D incidence / FPG ≥126 mg/dL, self-reported medication use, 2-h OGTT ≥200 mg/dL, or HbA1c ≥6.5%	Tertile 3 vs. tertile 1	OR: 0.87; 95% CI: 0.72, 1.04; $P = 0.13$	9
Martínez-González et al. (2008) (41)	Spain	SUN	20–90	Male and female	13,380	33	4.4 y	58,918	FFQ/baseline measurement	T2D incidence/ADA (symptoms of diabetes + random plasma glucose concentration ≥11·1 mmol/L or FPG ≥7.0 mmol/L, OGTT)	Tertile 3 vs. tertile 1	RR: 0.17; 95% CI: 0.04, 0.72; $P = 0.04$	8
Cespedes et al. (2015) (51)	USA	WHI	50–79	Female	88,091	9268	15 y	1,311,138	FFQ/baseline measurement	T2D incidence/self-report	Quintile 5 vs. quintile 1	HR (aMED quintile): 0.85; 95% CI: 0.80, 0.90; $P < 0.001$	5
de Koning et al. (2011) (52)	USA	HPFS	40–75	Male	41,615	2795	20 y	733,291	FFQ/repeated measurements	T2D incidence/self-report medication use or positive glucose test (until 1998: NDDG criteria; after 1998: ADA criteria; 97% of the cases were validated by medical record)	Quintile 5 vs. quintile 1	HR: 0.75; 95% CI: 0.66, 0.86; $P < 0.01$	9
Jacobs et al. (2015) (48)	USA	MEC study	45–75	Male and female	89,185	11,217	6 y	—	FFQ/baseline measurement	T2D incidence/ short follow-up questionnaire (1999–2003): medical conditions (response rate 84%), a medication inventory (2003–2006) including diabetes drugs	Quintile 5 vs. quintile 1 per 1-SD increase	HR (men): 0.89; 95% CI: 0.80, 0.99 HR (women): 0.92; 95% CI: 0.84, 1.02	7
Khalili-Moghadam et al. (2018) (49)	Iran	TLGS	20—70	Male and female	2139	143	6 y	—	FFQ/baseline measurement	T2D incidence/at least 1 of the following criteria exist: medication use, 2-h PG ≥200 mg/dL, or FPG ≥126 mg/dL	Tertile 3 vs. tertile 1	HR: 0.47; 95% CI: 0.28, 0.83	8
Koloverou et al. (2015) (53)	Greece	Attica study	18–89	Male and female	3042 (1514 men and 1528 women)	129	10 y	—	FFQ/baseline measurement	T2D incidence/FPG >125 mg/dL or medication use	Tertile 3 vs. tertile 1	RR: 0.38; 95% CI: 0.16, 0.88; P: 0.045	9
O'Connor et al. (2020) (11)	USA	ARIC study	45–65	Male and female	11,991	3804	22 y	223,764	FFQ/repeated measurements	T2D incidence/ (1) self-reported physician diagnosis, (2) self-reported medication use, (3) FPG ≥126 mg/dL, or (4) measured OGTT ≥200 mg/dL	Quintile 5 vs. quintile 1	HR: 0.94; 95% CI: 0.82, 1.07; *P*: 0.03	9
Ahmad S et al. (2020) (12)	USA	WHS	Mean age: 52.9	Female	25,317	3053	19.8 y	—	FFQ/baseline measurement	T2D incidence/self-report	Tertile 3 vs. tertile 1	HR: 0.70; 95% CI: 0.62, 0.79; $P < 0.01$	5
de Leon et al. (2011) (54)	Spain	"CDC de Canarias" study	18–75	Male and female	5521	146	3.5 y	—	FFQ/baseline measurement	T2D incidence/self-report	Tertile 3 vs. tertile 1	HR: 1.1; 95% CI: 0.70, 1.7; *P*: 0.718	5
Rossi et al. (2013) (45)	Greece	EPIC	20–86	Male and female	22,295	2330	11.34 y	234,935	FFQ/baseline measurement	T2D incidence/self-report, medical record, diabetic medication use	Quartile 4 vs. quartile 1	HR: 0.88; 95% CI: 0.78, 0.99; $P = 0.021$	7
Eguaras et al. (2017) (40)	Spain	SUN	Mean: 38	Male and female	18,225	136	9.5 y	173,591	FFQ/baseline measurement	T2D incidence/self-report	Highest vs. lowest	RR: 1.5; 95%CI: 1.08, 2.12	7
Jacobs et al. (2017) (47)	USA	MEC study	45–75	Male and female	166,550	9200	11 y	—	FFQ/baseline measurement	T2D incidence/self-reported, confirmed by administrative data	Highest vs. lowest	HR (men): 0.85; 95% CI: 0.79, 0.92 HR (women): 0.93; 95% CI: 0.86, 1.00	7

(*Continued*)

TABLE 1 (*Continued*)

Study (year) (ref)	Country	Cohort	Age range/mean age, y	Sex	Sample size	Number of diabetes cases	Study duration	Person-years	Exposure/ assessment	Outcome/ assessment	Comparison	OR or RR or HR (95% CI)	Quality assessment score
André et al. (2017) (55)	UK	UK Biobank	40–75	Male and female	21,585	473	6.1 y	—	24-h dietary / repeated measurements	T2D incidence/self-report	Highest vs. lowest	RR: 0.54; 95% CI: 0.33, 0.86	8
Freisling et al. (2020) (46)	10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the UK)	EPIC study	35–70	Male and female	291,778	10,295	11 y	—	Validated country-specific or center-specific dietary questionnaires/baseline measurement	T2D incidence/combination of self-report, linkage to primary care registers, secondary-care registers, medication use, hospital admissions, and mortality data	Highest vs. lowest	RR: 0.54; 95% CI: 0.47, 0.67	7
Abiemo et al. (2013) (56)	USA	MESA study	45–84	Male and female	5390	412	6 y	17,957	FFQ/baseline measurement	FPG ≥7.0 mmol/L, self-reported diabetes, hypoglycemic drug treatment	Quintile 5 vs. quintile 1	HR: 1.09; 95% CI: 0.80, 1.49; *P*: 0.51	7
Chen et al. (2018) (59)	Singapore	Singapore Chinese Health Study (SCHS)	45–75	Male and female	45,411	5207	11.1 y	475,458	FFQ/baseline measurement	T2D incidence/self-reported, confirmed by administrative data	Quintile 5 vs. quintile 1	HR: 0.84; 95% CI: 0.77, 092; *P* < 0.001	9
Hlaing-Hlaing et al. (2021) (57)	Australia	Australian Longitudinal Study on Women's Health (ALSWH)	50–55	Female	3905	375	15 y	—	FFQ/baseline measurement	T2D incidence/self-reported	Quintile 5 vs. quintile 1	HR: 0.76; 95% CI: 0.48, 1.21	8
Hodge et al. (2021) (58)	Australia	The Melbourne Collaborative Cohort Study (MCCS)	40–69	Male and female	25,888	1989	13 y	—	FFQ/baseline measurement	T2D incidence/self-reported	—	IRR: 0.98; 95% CI: 0.85, 1.13; *P*: 0.37	5

[1] aMED, alternate Mediterranean diet score; ADA, American Diabetes Association; ARIC, Atherosclerosis Risk in Communities; CARDIA, Coronary Artery Risk Development in Young Adults; EPIC, European Investigation into Cancer and Nutrition; FFQ, food-frequency questionnaire; FPG, fasting plasma glucose; HbA1C, glycated hemoglobin; HPFS, Health Professionals Follow-Up Study; IRR, incidence rate ratio; MEC, Multi-Ethnic Cohort; MESA, Multi-Ethnic Study of Atherosclerosis; NDDG, National Diabetes Data Group; OGTT, oral-glucose-tolerance test; PG, plasma glucose; ref, reference; SUN, Seguimiento Universidad de Navarra; T2D, type 2 diabetes; TLGS, Tehran Lipid and Glucose Study; WHI, Women's Health Initiative; WHS, Women's Health Study; .

Results

Literature search and study characteristics

Our initial search yielded 6356 papers, of which 2452 were duplicates. After reviewing the titles and/or abstracts, 3867 articles did not meet the inclusion criteria. Then, after reading the full text of the remaining 37 papers, 3 studies were excluded because their outcome was not the incidence of diabetes (e.g., the outcomes were improvement in metabolic syndrome components and development of impaired fasting glucose) (26–28). One study was excluded because of assessing a mixed outcome (e.g., diabetes with cardiovascular events and death together) (29). Five studies that were conducted on patients [patients with recent myocardial infarction (30), patients with prediabetes (31), patients after renal transplantation (32), patients with nonalcoholic fatty liver disease (33), women who have had gestational diabetes mellitus in the past (34)] were also excluded. Five additional papers did not provide sufficient data (35–39). Out of 23 remaining studies, some were conducted on the same population [3 on the Seguimiento Universidad de Navarra (SUN) cohort (40–42), 4 on the European Prospective Investigation into Cancer and Nutrition (EPIC) study (43–46), 2 on the Multi-Ethnic Cohort (MEC) study (47, 48), 2 on the Tehran Lipid and Glucose Study (TLGS) study (13, 49)]. Therefore, we included the one with the largest sample size and the longest follow-up (40, 46, 47). One article reported the results for men and women separately; therefore, it was considered as 2 separate effect sizes (47). Finally, the current analysis contained 16 articles (11, 12, 40, 46, 47, 49–59).

For the dose–response analysis, 5 publications were excluded because they did not report sufficient data on the number of individuals with diabetes or person-years of follow-up (49, 54, 55, 57, 58). In case of several publications from the same cohort, we included the article with sufficient data (41, 46, 48). **Figure 1** shows the article selection procedure.

Seven studies were from the United States (11, 12, 47, 50–52, 56), 5 from Europe (40, 46, 53–55), 2 from Asia (49, 59), and 2 from Oceania (57, 58). All studies reported data on diabetes incidence, assessed dietary intakes using a validated food-frequency questionnaire, and gave adjusted risk estimates. All studies, except for 4, were of high quality (12, 45, 51, 58) (**Supplemental Table 1**). **Table 1** summarizes the general characteristics of all qualified papers.

Findings from the meta-analysis

Using random-effects meta-analysis of 16 prospective studies (17 effect sizes, $n = 759{,}806$), we observed that individuals who adhered most to the MD were less likely to develop type 2 diabetes than those who adhered least to the MD (pooled RR: 0.83; 95% CI: 0.77, 0.90; $I^2 = 79\%$, $P \leq 0.001$); however, significant between-study heterogeneity was seen. In Egger's test, there was no evidence of publication bias ($P = 0.26$) (**Figure 2**). The pooled RR did not considerably change

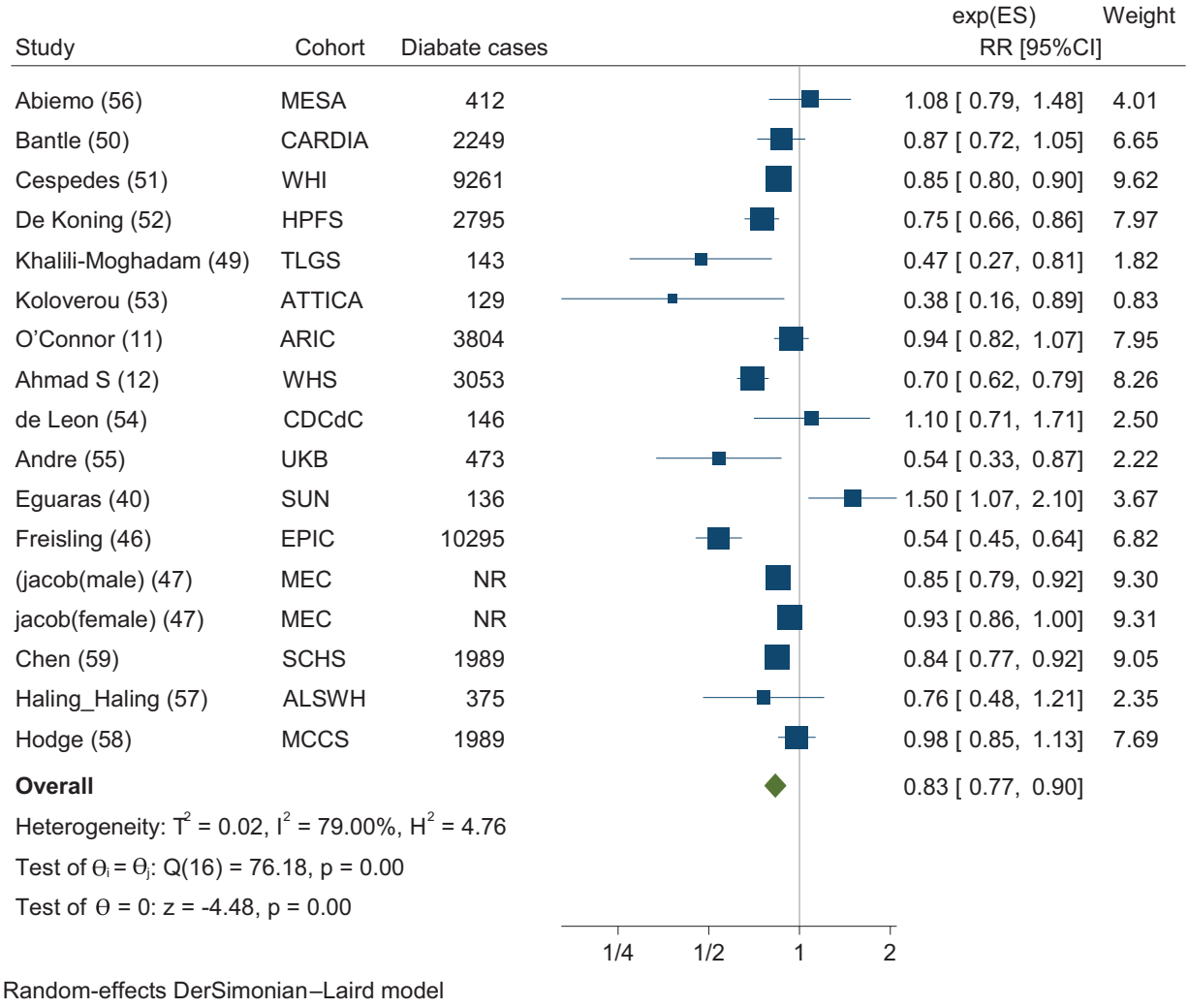

FIGURE 2 Forest plot displaying the RRs and 95% CIs of type 2 diabetes for the highest compared with lowest adherence to the Mediterranean diet based on prospective cohort studies. The black squares represent the RRs, the size of which shows the study's weight in the analysis (weights come from random-effects analysis), and the horizontal lines represent the 95% CIs for each study. The diamond's center is the RR's summary estimate, and its width represents the summary estimate's 95% CIs. ALSWH, Australian Longitudinal Study on Women's Health; ARIC, Atherosclerosis Risk in Communities; CARDIA, Coronary Artery Risk Development in Young Adults; CDCdC, CDC de Canarias; EPIC, European Investigation into Cancer and Nutrition; ES, effect size; HPFS, Health Professionals Follow-Up Study; MCCS, Melbourne Collaborative Cohort Study; MESA, Multi-Ethnic Study of Atherosclerosis; MEC, Multi-Ethnic Cohort; SCHS, Singapore Chinese Health Study; SUN, Seguimiento Universidad de Navarra; TLGS, Tehran Lipid and Glucose Study; UKB, UK Biobank; WHI, Women's Health Initiative; WHS, Women's Health Study.

when a single study was excluded in the sensitivity analysis (**Supplemental Figure 1**).

Subgroup analyses based on gender, geographical location, number of study participants, duration of follow-up, diabetes assessment method, quality of studies, and MD scoring methods were conducted. We found that between-study heterogeneity was explained by the MD scoring methods (*P*-between-study heterogeneity = 0.05) (**Supplemental Table 2**).

Different scoring methods had been used in the included papers, as is shown in **Table 2**. All of the articles that were included in our dose–response analysis used a 9-point scale of MD, except for 1 study, for which we converted the dose in each category to a 9-point scale. To do this, we considered the median points of the Mediterranean score in the 15-point scale (score medians across tertiles in the paper were 3, 6.5, and 10.5, respectively) as 1.8, 3.9, and 7.6 as the median points in the traditional 9-point scale (60). According to the linear dose–response analysis, each 1-point increase in the score of MD was related to a 3% decreased risk of diabetes (RR = 0.97; 95% CI: 0.96, 0.98; $P \leq 0.001$). A nonlinear relation between MD score and risk of

TABLE 2 Methods of scoring used in different cohort studies on Mediterranean diet score and diabetes

First author (reference)	Mediterranean diet name	Mediterranean diet score range	Mediterranean diet component (definition based)	Scoring calculation method
Bantle (50)	Americanized Mediterranean diet score (AmMedDiet score)	0–15	↑ Legumes, ↑ vegetables, ↑ fruit and nuts, ↑ fish and seafood, ↑ eggs, ↑ milk, ↑ whole grains, ↑ beneficial fat ratio, ↓ refined grains, ↓ meat and poultry, ↓ snacks, ↓ potatoes, ↓ sweets, ↓ beverages, ↔ alcohol	Individuals awarded 1 point for above-median intakes of beneficial food groups, moderate intakes of alcohol (men between 10 and 50 g/d and women between 5 and 25 g/d), and below-median intakes of harmful food groups
Martínez-González (41)	Mediterranean diet score (MDS)	0–9	↑ (MUFA/SFA), ↑ legumes, ↑ grains, ↑ fruit and nuts, ↑ vegetables, ↑ fish, ↓ red and processed meat, ↓ dairy products, ↔ alcohol	Participants received 1 point for above-median intakes of beneficial food groups, moderate intakes of alcohol (men between 10 and 50 g/d and women between 5 and 25 g/d)m and below-median intakes of harmful food groups
Cespedes (51)	Alternate Mediterranean diet (aMED)	0–9	↑ Minimally processed plant-based foods, ↑ olive oil, ↓ red meat, ↔ dairy products, ↔ fish, ↔ poultry, ↔ wine	Subjects received 1 point for above-median intakes of beneficial food groups, moderate intakes of alcohol (5–15 g/d)m and below-median intakes of harmful food groups
de Koning (52)	Alternate Mediterranean diet (aMED)	0–9	↑ Vegetables (no potatoes), ↑ legumes, ↑ whole grains, ↑ fruit, ↑ nuts, ↑ fish, ↑ (MUFA/SFA), ↓ red and processed meat, ↔ alcohol	Individuals awarded 1 point for above-median intakes of beneficial food groups, moderate intakes of alcohol (5–15 g/d), and below-median intakes of harmful food groups
Jacobs (47)	Alternate Mediterranean diet (aMED)	0–9	↑ Vegetables, ↑ legumes, ↑ fruit, ↑ nuts, ↑ whole grains, ↑ fish, ↑ (MUFA/SFA), ↓ red and processed meat, ↔ alcohol	Subjects awarded 1 point for above-median intakes of beneficial food groups, moderate intakes of alcohol (5–15 g/d), and below-median intakes of harmful food groups
Khalili-Moghadam (49)	Mediterranean diet score (MDS)	0–8	↑ Vegetables, ↑ nuts, ↑ fruit, ↑ whole grains, ↑ legumes ↑ fish, ↑ (MUFA/SFA), ↓ red and processed meat	Study participants gained 1 point for above-median intakes of beneficial food groups and below-median intakes of harmful food groups
Koloverou (53)	MedDietSCore	0–55	↑ Nonrefined cereals, ↑ fruit, ↑ vegetables, ↑ legumes, ↑ potatoes, ↑fish, ↑ olive oil, ↓ meat and meat products, ↓ poultry, ↓ full-fat dairy products, ↔ alcohol	For each food group, 0–5 points were assigned based on the frequency of food group consumption (no consumption, rare, frequent, very frequent, weekly, and daily), so that more consumption of beneficial food groups scored higher and less consumption scored less (reverse scoring for harmful food groups); for alcohol consumption of <300 mL/d, a score of 5 was assigned and for consumption of >700 mL/d, a score of 0 was assigned; scores of 4 to 1 were assigned to consumption of 300, 400–500, 600, 700, or 0 mL per day, respectively

(*Continued*)

TABLE 2 (*Continued*)

First author (reference)	Mediterranean diet name	Mediterranean diet score range	Mediterranean diet component (definition based)	Scoring calculation method
O'Connor (11)	Alternate Mediterranean diet (aMed)	0–9	↑ Vegetables, ↑ fruit, ↑ nuts, ↑ whole grains, ↑ legumes, ↑ fish, ↑ (MUFA/SFA), ↓ red and processed meat, ↔ alcohol	Individuals awarded 1 point for above-median intakes of beneficial food groups, moderate intakes of alcohol (5–15 g/d), and below-median intakes of harmful food groups
Ahmad S (12)	MED intake score	0–9	↑ Vegetables (no potatoes), ↑ legumes, ↑ whole grains, ↑ fruit, ↑ nuts, ↑ fish, ↑ (MUFA/SFA), ↓ red and processed meat, ↔ alcohol	Participants received 1 point for above-median intakes of beneficial food groups, moderate intakes of alcohol (5–15 g/d), and below-median intakes of harmful food groups
de Leon (54)	Mediterranean diet score (MDS)	0–9	↑ (MUFA/SFA), ↑ legumes, ↑ grains, ↑ fruit and nuts, ↑ vegetables, ↑ fish, ↓ red and processed meat, ↓ dairy products, ↔ alcohol	Study subjects gained 1 point for above-median intakes of beneficial food groups, moderate intakes of alcohol (men between 10 and 50 g/d and women between 5 and 25 g/d), and below-median intakes of harmful food groups
Rossi (45)	Mediterranean diet score (MDS)	0–9	↑ Vegetables, ↑ legumes, ↑ fruit and nuts, ↑ cereals, ↑ fish and seafood, ↑ (MUFA/SFA), ↓ dairy products, ↓ red and meat products, ↔ alcohol	Participants received 1 point for above-median intakes of beneficial food groups, moderate intakes of alcohol (men between 10 and 50 g/d and women between 5 and 25 g/d), and below-median intakes of harmful food groups
Eguaras (40)	Mediterranean diet score (MDS)	0–9	↑ Vegetables, ↑ legumes, ↑ fruit and nuts, ↑ cereals, ↑ fish and seafood, ↑ (MUFA/ SFA), ↓ dairy products, ↓ red and meat products, ↔ alcohol	Participants received 1 point for above-median intakes of beneficial food groups, moderate intakes of alcohol (men between 10 and 50 g/d and women between 5 and 25 g/d), and below-median intakes of harmful food groups
André (55)	Medi diet score	0–18	↑ Vegetables, ↑ fruits, ↑ legumes, ↑ cereals, ↑ fish, ↑ olive oil, ↓ meat and meat products, ↓ dairy products, ↔ alcohol	For each food group, 0–2 points were assigned based on literature-based thresholds, so that more consumption of beneficial food groups scored higher and less consumption scored less (reverse scoring for harmful food groups); for alcohol, moderate consumption was assigned a higher score
Freisling (46)	Modified relative Mediterranean diet score (mrMDS)	0–18	↑ Vegetables, ↑ legumes, ↑ fruit and nuts, ↑ cereals, ↑ fish and seafood, ↑ vegetable oil, ↓ meat and meat products, ↓ dairy products, ↔ alcohol	For each food group, 0–2 points were assigned based on country-specific tertiles, so that more consumption of beneficial food groups scored higher and less consumption scored less; for alcohol, moderate consumption scored high
Abiemo (56)	MeDiet score (MDS)	0–9	↑ Vegetables, ↑ legumes, ↑ fruit, ↑ nuts, ↑ whole grains, ↑ fish, ↑ (MUFA/SFA), ↓ red and processed meat, ↓ dairy, ↔ alcohol	Participants awarded 1 point for above-median intakes of beneficial food groups, moderate intakes of alcohol (men between 10 and 50 g/d and women between 5 and 25 g/d), and below-median intakes of harmful food groups

(*Continued*)

TABLE 2 (*Continued*)

First author (reference)	Mediterranean diet name	Mediterranean diet score range	Mediterranean diet component (definition based)	Scoring calculation method
Chen (59)	Alternate Mediterranean diet score (aMED)	0–9	↑ Vegetables, ↑ legumes, ↑ fruit, ↑ nuts, ↑ whole grains, ↑ fish, ↑ (MUFA/SFA), ↓ red and processed meat, ↔ alcohol	Study subjects received 1 point for above-median intakes of beneficial food groups, moderate intakes of alcohol (5–15 g/d), and below-median intakes of harmful food groups
Hlaing-Hlaing (57)	Mediterranean diet score (MDS)	0–9	↑ Vegetables, ↑ fruits, ↑ legumes, ↑ cereals, ↑ fish, ↑ (MUFA+PUFA/SFA), ↓ red meat and meat products, ↓ dairy products, ↔ alcohol	Participants awarded 1 point for above-median intakes of useful food groups, moderate intakes of alcohol (men between 10 and 50 g/d and women between 5 and 25 g/d), and below-median intakes of harmful food groups
Hodge (58)	Mediterranean diet score (MDS)	0–9	↑ (MUFA/SFA), ↑ legumes, ↑ grains, ↑ fruit and nuts, ↑ vegetables, ↑ fish, ↓ red and processed meat, ↓ dairy products, ↔ alcohol	Subjects awarded 1 point for above-median intakes of beneficial food groups, moderate intakes of alcohol (men between 10 and 50 g/d and women between 5 and 25 g/d), and below-median intakes of harmful food groups

type 2 diabetes was also observed (P-nonlinearity = 0.003), with a steeper inverse relation at greater scores (**Figure 3**). Between-study heterogeneity for dose–response meta-analysis was significant ($P = 0.001$). The certainty of evidence was rated as low due to downgrades for inconsistency and an upgrade for dose–response gradient (**Supplemental Table 3**).

Discussion

In the current meta-analysis, we observed a significant inverse relation between greater adherence to the MD and the risk of diabetes in a total sample of 759,806 subjects from diverse parts of the world. Each 1-point increase in the MD score was linked to a 3% reduction in diabetes risk. To the best of our knowledge, this is the most updated and comprehensive dose–response meta-analysis on adherence to the MD and risk of diabetes.

In the late 1970s, Ancel Keys of the Seven Countries Study established the typical MD (61). The main characteristics of the MD are high consumption of vegetables and fruits, MUFAs, whole grains, fish, plant proteins, and low-fat dairy products; moderate alcohol consumption (red wine); and low consumption of red meat (62). In a longitudinal clinical trial, administration of an MD resulted in a reduced risk of diabetes after a median of 4 y of follow-up (63). Earlier meta-analyses (10, 17, 64–66) on adherence to the MD and incidence of diabetes have shown a significant inverse association between these 2. In the latest meta-analysis in this regard, Zeraattalab-Motlagh et al. (17) reached an inverse association; however, that publication had some drawbacks. For example, they missed some original articles, including the study of Bantle et al. (50) and they had some errors in data extraction and choosing the appropriate articles for inclusion in the meta-analysis. Moreover, they did not investigate the nonlinear dose–response relation. Earlier meta-analyses reported RRs of 0.87 (10), 0.79 (17), 0.83 (64), 0.77 (65), and 0.80 (66) for adherence to the MD and risk of type 2 diabetes. Given that adherence to the MD was associated with a reduced risk of obesity and overweight (67), many cancers (68), cognitive impairment (69), cardiovascular disease, and mortality (70), it is concluded that the MD can be recommended to people in the community.

As a biological explanation for our findings, the antioxidant load of the MD can be considered. The antioxidant content of this dietary pattern can affect the risk of diabetes through inhibiting oxidative stress, which is involved in the development of insulin resistance and dysfunction of beta cells (71). This diet is also high in magnesium, due to its high content of vegetables, legumes, and nuts. Magnesium deficiency has been linked to insulin resistance; therefore, the high magnesium content of this dietary pattern might also play a role in protecting against diabetes (72). Moreover, dietary fiber in several food items in this dietary pattern can help delay gastric emptying, which could, in turn, slow down digestion and glucose absorption and, as a result, it might help lower serum insulin concentrations (73). Moderate

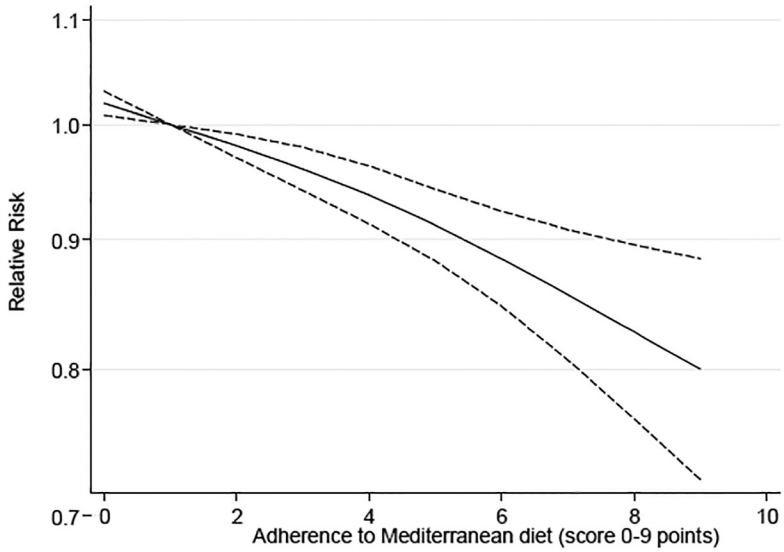

FIGURE 3 Linear dose–response association between adherence to the Mediterranean diet and risk of diabetes. Adjusted RRs and 95% CIs (dashed lines) are reported. The horizontal axis represents the score of adherence to the Mediterranean diet and the vertical axis represents the risk ratio for diabetes. A nonlinear relation between Mediterranean diet score and risk of type 2 diabetes was observed, with a steeper inverse relation with greater scores.

alcohol consumption in the MD can also provide a reason for improving insulin sensitivity (74). Another benefit of the MD is its effect on weight control (75), through which it might affect the risk of diabetes (76).

When interpreting our findings, there are some limitations to consider. Although a higher adherence to the MD was associated with a lower risk of diabetes, statistical heterogeneity between studies was significant. Various subgroup analyses based on the number of study participants, follow-up duration, sex, diabetes assessment method, geographical location, quality of studies, and MD scoring methods were conducted; however, the heterogeneity found between studies was not fully explained by any of the above-mentioned variables. One more point to consider is the single measurement of diet at study baseline in most included studies, while dietary intakes might have changed over years of follow-up. Moreover, most included studies in the meta-analysis had adjusted for the majority of probable confounders; however, residual confounding cannot be ignored due to the observational nature of these investigations. Although prospective cohort studies are less prone to recall bias, a large number of articles assessed dietary intakes using food-frequency questionnaires, in which misclassification is unavoidable. Additionally, only 2 studies were from Asia, and all other studies came from Western countries. To confirm our findings, further investigation is needed in other populations with various environmental conditions, genetic susceptibilities, and dietary preferences.

In conclusion, the current systematic review and meta-analysis of prospective cohort studies found evidence of a dose–response relation between adherence to the MD and incidence of diabetes. Even individuals with moderate to high adherence to the MD were less likely to develop diabetes than those with a poor adherence to this dietary pattern. Prospective studies in different regions of the world, in particular in underdeveloped and developing nations, are needed in the future to confirm the current findings.

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Data Availability

The data that support the findings of this study are available from the corresponding author, [author initials], upon reasonable request.

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