Nutrition 148 (2026) 113038

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Review

Effectiveness of Mediterranean diet for the primary prevention of cardiovascular diseases: A systematic review and meta-analysis featured in the Italian National Guidelines "La Dieta Mediterranea"

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https://doi.org/10.1016/j.nut.2025.113038
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ARTICLE INFO

Article History:
Received 12 August 2025
Received in revised form 16 November 2025
Accepted 22 November 2025

Keywords:
Mediterranean diet
Cardiovascular diseases
Prevention
Systematic review
Meta-analysis

ABSTRACT

Background: Cardiovascular diseases (CVDs) are among the leading causes of premature mortality in Europe, with unhealthy diets a major contributing factor. The Mediterranean diet (MD), characterized by high intake of plant-based foods and healthy fats, has been associated with reduced cardiovascular risk. This systematic review and meta-analysis aimed to assess the effectiveness of MD in the primary prevention of CVDs.
Methods: This review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 and Meta-analysis of Observational Studies in Epidemiology guidelines. A comprehensive search of PubMed/MEDLINE, Scopus, Embase, and Cochrane Library was performed up to February 28, 2024. Study quality was assessed using the Newcastle–Ottawa Scale, and the certainty of evidence was evaluated with the NUTRIGRADE approach. Pooled effect sizes were computed using a random-effects model and expressed as risk ratios, hazard ratios (HR), or odds ratios, as appropriate.
Results: A total of 87 studies, encompassing over 1.4 million participants, were included. Higher adherence to the MD was consistently associated with a reduced risk of peripheral artery disease (HR—from 0.34 to 0.54), coronary heart disease (HR: 0.95), atrial fibrillation (HR: 0.65), cerebrovascular disease (HR: 0.97), hypertension (HR: 0.97), and CVDs mortality (HR: 0.97). Even a one-point increase in MD adherence score conferred a statistically significant benefit. The strongest evidence emerged from high-quality RCTs, notably the PREDIMED study.
Conclusions: The MD is an effective strategy for the primary prevention of CVDs. These findings suggest the importance of adherence to MD and support incorporating MD-based recommendations in national dietary guidelines and public health initiatives.
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Introduction

An unhealthy diet worsens the main conditions associated with cardiovascular risk (diabetes, hyperlipidemia, hypertension, obesity) and thus contributes to the development of cardiovascular events (myocardial infarction and stroke) that account for about 20% of the premature causes of death in Europeans who die before the age of 65 [1]. Overweight and obesity are increasing worldwide, primarily as a consequence of sustained exposure to poor-quality diets, deleterious nutritional behaviors, and the persistent lack of effective and adequate preventive strategies [2] The obesity epidemic seems an unstoppable trend that threatens the health, life expectancy, and quality of life starting from childhood and adolescence. This scenario, however, is largely preventable through a healthy diet. The Mediterranean diet (MD) represents a pragmatic and widely investigated approach for improving the nutritional profile [3]. MD continues to represent a point of reference from a nutritional point of view, given the multiple demonstrations of effectiveness in the prevention and management of risk factors and cardiovascular diseases (CVDs), starting from the historical Seven Countries Study to the PREDIMED intervention study [4–6]. This is because the MD is characterized by many foods that we can define as "functional," since they have a beneficial influence, based on scientific evidence, on our body and on the risk of developing chronic-degenerative diseases [7] Moreover, in recent years, the MD has consolidated its leading position thanks to scientific validation not only through research studies, but also through cooking and technological innovations. Its reputation as an excellent nutritional model, for its qualities of low environmental impact and for its socio-cultural and economic value, was also recognized by UNESCO [8]

However, even in the Mediterranean countries globalization is increasing the adoption of "Westernized" dietary models rich in ultra-processed foods, while adherence to the MD is declining [9–11]. The progressive move away from the food model attributable to the MD has negative repercussions that go beyond nutrition and health. Therefore, recovery and promotion of traditional dietary habits of Mediterranean countries is necessary. Greater awareness, as well as policies that make the principles of this nutritional model more accessible, must be promoted. These would ensure that everyone benefits from the healthy and sustainable MD. Relying on the most recent evidence, a broad multidisciplinary team of experts of 20 Italian Scientific Societies, of the National Institute of Health (ISS), and of the National Research Council (CNR) of Italy, have worked on the first "Guidelines on MD" to represent a crucial point of reference for nutritional clinical practice. In this article, we report the data of our search based on a broad systematic review and meta-analysis with a specific focus on the impact of MD on the primary prevention of CVDs.

Materials and methods

This systematic review and meta-analysis was conducted in accordance with the methodological framework outlined by the Cochrane Collaboration [12] and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA 2020) and the Meta-analysis of Observational Studies in Epidemiology guidelines [13]. The study protocol was defined a priori and agreed upon by all members of the research team. It was subsequently published in the website of the Italian National System of Guidelines (Sistema Nazionale Linee Guida—SNLG) [14].

Literature search strategy

A comprehensive literature search was performed concurrently in Cochrane Library, PubMed/Medline, Scopus, and Embase on February 28, 2024, without any temporal filtering. The search was guided by the question: "Is greater adherence to the MD associated with a reduced risk of any CVD among the general population?" The strategy incorporated two conceptual domains: MD adherence (exposure) and CVDs (outcome). Both Medical Subject Headings (MeSH) and free-text terms were utilized and combined using Boolean operators (AND/OR). The initial query was developed for PubMed/MEDLINE and then adapted for the other databases. The complete search strategies are provided in Supplementary Table 1. Two independent reviewers conducted the search in a blinded fashion, retrieving the same number of records. To identify additional relevant studies, reference lists of included articles were manually screened, and domain experts were consulted.

Eligibility criteria

Studies were selected based on the PECOS framework (Population, Exposure, Comparison, Outcome, Study design). Studies were considered eligible for inclusion if the researchers investigated whether adherence to the MD is associated with a reduction in CVDs risk. The population of interest encompassed individuals of all age groups, without CVDs at the baseline. The exposure was defined as adherence to the MD, assessed using any method or dietary index, whether validated or not. In interventional studies, the comparator was represented by any other type of dietary pattern, whereas in observational studies, comparisons were made between individuals

with high versus low adherence to the MD. The primary outcome of interest was the risk of CVDs. Eligible study designs included randomized controlled trials, pre-post intervention studies, prospective and retrospective cohort studies, case-control studies, and cross-sectional studies. Only articles published in English and Italian, in peer-reviewed scientific journals, were included. Exclusion criteria encompassed non-original studies, studies assessing other dietary patterns or outcomes unrelated to cardiovascular risk, people with CVDs, non-English or non-Italian publications, and non-peer-reviewed sources. A detailed list of inclusion and exclusion criteria is available in Supplementary Table 2.

Study selection and data extraction

Study selection followed a two-step process. Initially, pairs of independent reviewers screened titles and abstracts based on the predefined criteria. Study selection was conducted using Covidence (Veritas Health Innovation, Melbourne, Australia), a web-based platform designed to streamline the systematic review process. Full-text articles were retrieved for all potentially relevant records. Eligibility was reassessed through full-text review, and disagreements were resolved through discussion or, if needed, adjudicated by a third senior researcher. Covidence automatically recorded decisions and facilitated the removal of duplicates and documentation of reasons for exclusion at the full-text stage.

Data extraction was performed independently by pairs of reviewers using a standardized and pilot-tested Excel spreadsheet (Microsoft Excel for Microsoft 365 MSO, 2019). The spreadsheet was pretested on a random sample of five studies to ensure consistency. Extracted information included: first author, publication year, study design, country of study, participants' demographics, sample size, age, percentage of women, follow-up duration, MD adherence scoring system, control/comparison diet, number of adjustment variables, and outcomes. Discrepancies were resolved through consensus.

Data synthesis

Following PRISMA 2020 recommendations, the study selection process was visualized using a flow diagram for recording the number of studies excluded at each stage and reasons for exclusion at the full-text review level. Extracted data were synthesized both narratively and in tabular form. Moreover, the contents of this systematic review were reported in accordance with established methodological standards. Given the potential biases inherent in nutritional epidemiology—such as recall bias in dietary assessment [15]—the quality of evidence was assessed using the NUTRIGRADE approach, which is specifically designed for evaluation of the certainty of evidence in nutrition research. Statistical results are presented using both tables and graphical formats.

Quality assessment

The methodological quality of the included studies was assessed using tools appropriate to their study design. For observational studies (cohort, case-control, and cross-sectional), the Newcastle–Ottawa Scale (NOS) was applied to evaluate the risk of bias across three domains: selection of study groups, comparability of groups, and outcome or exposure assessment [16]. For randomized controlled trials and other interventional studies, the Cochrane risk of bias tool (RoB 2.0) was employed to assess potential sources of bias across domains such as randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result [12]. Quality assessment was conducted independently by two reviewers, and any discrepancies were resolved through discussion or consultation with a third reviewer.

Statistical analysis

A meta-analysis on 87 randomized, controlled studies, both observational and interventional, and aimed at evaluating the effectiveness of MD in reducing cardiovascular outcomes in people without previous history of CVD at baseline (primary prevention), has been selected. To reduce heterogeneity about the adherence to MD, pooled risks of the endpoint were computed for an increase in one point in the scale originally reported in the works included. If these estimates were not reported in the original studies, they were calculated as the inverse variance-weighted mean of the logarithm of risk ratio (RR) [17]. Pooled effect size was reported as RR if reported in a different context (e.g., RRs, hazard ratios [HRs], odds ratios [Ors]). Random-effect models were employed. Heterogeneity was assessed using the I^2 statistic, with thresholds defined as follows: ≥75% (high), 50% to 74% (moderate), 25% to 49% (low), and <25% (none). Potential publication bias was evaluated through funnel plot inspection and Egger's regression test (significance level: $P < 0.10$). All analyses were performed using STATA 16.0.

Sensitivity analysis

Sensitivity analysis was conducted stratifying by study design (trials, cohort, case-control, cross-sectional) and CVD type.

Assessment of the level of evidence

For observational studies, we reported associations between higher adherence to the MD and the outcome of interest based on multivariate analyses, whilst for RCTs, original data were extracted. To evaluate the quality of the body of evidence, the NUTRIGRADE system was employed as an alternative to the traditional GRADE approach. NUTRIGRADE was specifically developed to address the methodological challenges inherent in nutritional and diet-related research, such as the limited feasibility of long-term randomized controlled trials, the heterogeneity of dietary exposures, and the complex interplay between diet, lifestyle, and health outcomes [18].

This approach was chosen to provide a more context-appropriate and rigorous appraisal of evidence in the field of nutrition science. NUTRIGRADE allows for the incorporation of nutrition-specific variables, such as exposure assessment quality, residual confounding, and adherence to dietary interventions, which are often not adequately addressed using standard evidence grading tools, such as GRADE [19].

The NUTRIGRADE scoring system assigns a score from 0 to 10 for each body of evidence, which corresponds to four levels of quality: high (8–10), moderate (6–7), low (4–5), and very low (0–3). Higher scores indicate greater confidence in the effect estimates and their applicability to real-world settings. A total of eight domains were evaluated as part of the NUTRIGRADE framework. Six domains can lead to a downgrading of evidence quality:

- Risk of bias, assessed using tools appropriate for study design (e.g., the NOS for observational studies and the Cochrane risk of bias tool for interventional studies);
- Study design, with prospective cohort studies considered more robust than cross-sectional or retrospective designs;
- Consistency of results, evaluating heterogeneity across studies in terms of populations, interventions, and outcomes;
- Imprecision, particularly in studies with small sample sizes or wide confidence intervals;
- Outcome relevance, assessing the clinical or public health importance of the measured outcomes;
- Publication bias, identified through visual and statistical methods.

Three additional factors were considered for upgrading the quality of evidence:

- Effect size, particularly when large and clinically meaningful;
- Dose-response relationship, including linear and non-linear trends in adherence scores, often operationalized through one-point increases in MD scores (MDSs) to enhance comparability across studies (as previously adopted by Sofi et al., 2008 [20]);
- Control of residual confounding, which is especially relevant in nutritional epidemiology, where dietary habits may correlate with multiple socio-demographic and lifestyle variables.

Taken together, the NUTRIGRADE system provided a structured and tailored approach to assessing the certainty of evidence in support of conclusions drawn regarding the association between MD adherence and CVD.

Results

Study selection

A total of 17 350 records were initially identified through database and register searches. After the removal of 8452 duplicates, 8898 records remained for title and abstract screening. Of these, 8543 studies were excluded for not meeting the inclusion criteria. The full texts of 355 studies were assessed for eligibility: two full texts were not available. Among the 355 studies assessed, 266 were excluded for the following reasons: conference abstracts (n = 90), wrong outcomes (n = 76), wrong population (n = 27), followed by other reasons as depicted in Figure 1. No additional studies were identified through citation searching or grey literature sources. Ultimately, 87 studies met the eligibility criteria and were included in the review [21–107]. No studies were excluded due to unavailability of full text, and no ongoing or awaiting-classification studies were identified. Details are depicted in the flow diagram (Fig. 1).

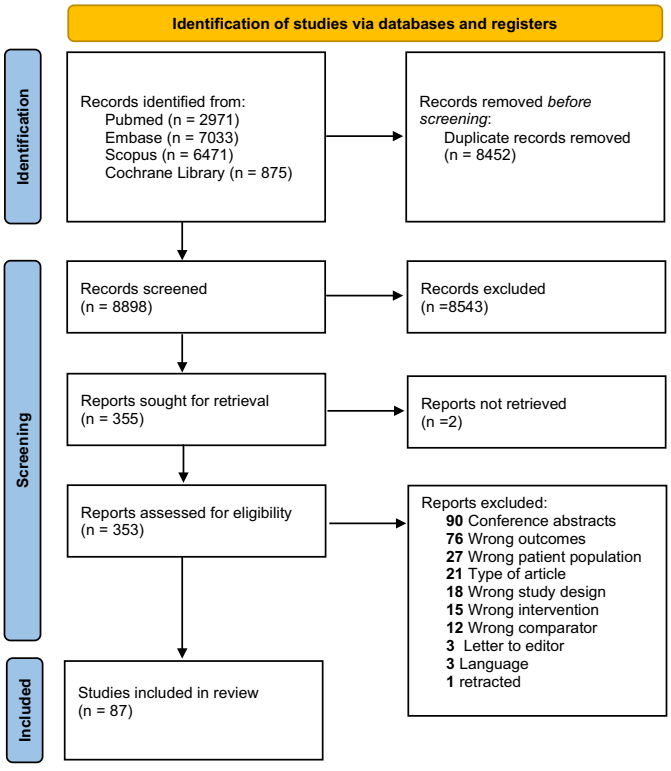


Fig. 1. PRISMA flow diagram.

Main characteristics of included studies

In all studies adherence to the MD was assessed using a variety of validated scoring systems: MDS (0–9 scale), alternate MDS (0–9), alternative MDS (0–18), and MEDI-LITE, or similar. The number of dietary and lifestyle variables included in the statistical adjustments was, in mean, nine. The mean age of participants ranged broadly from 18 to 70+ y, with middle-aged patients making up the largest group. Descriptive characteristics of included studies are reported in Supplementary Table 3. The certainty of the evidence (low, moderate, and high, respectively), assessed using the NUTRIGRADE approach, is reported in Table 1.

Main results

Overall, adherence to the MD was consistently associated with reduced CVD risk across different studies, though the magnitude was not uniform (Table 2).

Incidence of peripheral artery disease

The PREDIMED study [88], involving nearly 5000 adults at high cardiovascular risk, analyzed the incidence of peripheral artery disease in people at high cardiovascular risk (HCVR) by comparing MD enriched with extra virgin olive oil or nuts versus the low-fat diet (LFD). The analysis showed an HR of 0.34 (95% CI 0.20–0.58) for MD with extra virgin olive oil and 0.54 (95% CI 0.30–0.58) for MD with dried fruit, indicating a protective effect of MD versus the LFD. The degree of certainty of the evidence was rated as high for both analyses according to the NUTRIGRADE.

A cohort study, which included 34 708 participants [56], investigated the incidence of peripheral artery disease as an outcome. Overall, 285 events were recorded during 11.8 y of follow-up. The estimated HR was 0.95 (95% CI: 0.88–1.03, comparison of highest category of adherence versus low category of adherence to MD), suggesting a lack of association between MD and the outcome of interest, with a low degree of certainty according to the NUTRI-GRADE.

Atrial fibrillation

A case-control study with 52 cases and 52 controls [75] examined the prevalence of atrial fibrillation as an outcome. The estimated OR was 0.6552 (95% CI: 0.47–0.91, comparison of highest category of adherence versus lowest category of adherence to MD), suggesting an association between MD and the outcome of interest, although supported by a low degree of certainty according to the NUTRIGRADE.

The PREDIMED study [68], involving almost 5000 adults at HCVR, analyzed the incidence of atrial fibrillation in people at HCVR by comparing MD enriched with extra virgin olive oil or nuts versus the LFD. The analysis showed an HR of 0.62 (95% CI 0.45–0.86) for MD with extra-virgin olive oil and 0.86 (95% CI 0.63–1.16) for MD with dried fruit, indicating a protective effect of MD versus the LFD only when supplemented with extra-virgin olive oil. The degree of certainty of the evidence was rated as high for both analyses according to the NUTRIGRADE.

Heart failure

Five cohort studies [64,96–98,105] examined the incidence of heart failure as an outcome, including 228 798 participants. During a follow-up between 8.2 and 13 y, 8423 events were recorded. The estimated relative risk was 0.953 (95% CI: 0.937–0.969, one-point increase in MD adherence), suggesting an association between MD and the outcome of interest, supported by a moderate degree of certainty according to the NUTRIGRADE.

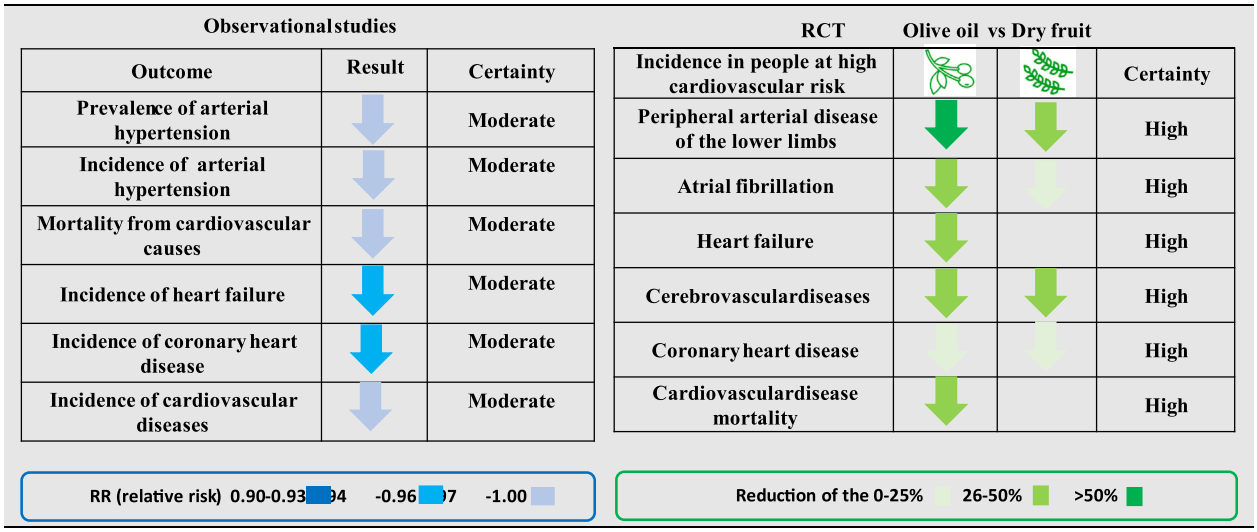
The PREDIMED study [84], involving nearly 5000 adults at HCVR, analyzed the incidence of heart failure in people at HCVR by comparing MD enriched with extra virgin olive oil or dried fruit versus the LFD. The analysis showed a relative risk of 0.74 (95% CI

Table 1
Evaluation of outcomes of interest with the NUTRIGRADE

Number of studies	Study design	Total sample size	Number of events	Estimate	Effect	95% lower	95% higher	Risk of distortion	Accuracy	Lack of reproducibility of results	Lack of generalizability	Publication bias	Funding bias	Effect size	Dose/ response gradient	NUTRIGRADE score	Certainty	Importance
Incidence of lower limb obliterative arteriopathy in persons at high CVD risk (olive oil-enriched vs. hypolipid-enriched Mediterranean diet) (follow-up: 4.8 y)																		
1	RCT	4983	63	HR	0.34	0.20	0.58	3	1	0.2	1	0	1	0	0	8.2	⊕⊕⊕⊕ HIGH	CRITICAL
Incidence of lower limb obliterative arteriopathy in persons at high CVD risk (Mediterranean diet enriched with nuts vs. low-fat) (follow-up: 4.8 y)																		
1	RCT	4896	71	HR	0.54	0.30	0.58	3	1	0.2	1	0	1	0	0	8.2	⊕⊕⊕⊕ HIGH	CRITICAL
Incidence of lower limb obliterative arteriopathy (follow-up: 11.8 y)																		
1	Cohort	34 708	285	HR	0.95	0.88	1.03	2	0	0.2	1	0	1	0	0	4.2	⊕⊕◯◯ LOW	CRITICAL
Prevalence of atrial fibrillation																		
1	Case-control	104	52	OR	0.652	0.47	0.91	2	1	0.2	1	0	1	0	0	5.2	⊕⊕◯◯ LOW	CRITICAL
Incidence of atrial fibrillation in persons at high CVD risk (Mediterranean diet enriched with olive oil vs. low-fat) (follow-up: 4.8 y)																		
1	RCT	4983	161	RR	0.62	0.45	0.86	3	1	0.5	1	0	1	0	0	8.5	⊕⊕⊕⊕ HIGH	CRITICAL
Incidence of atrial fibrillation in persons at high CVD risk (Mediterranean diet enriched with nuts vs. low-fat) (follow-up: 4.8 y)																		
1	RCT	4896	181	RR	0.86	0.63	1.16	3	1	0.5	1	0	1	0	0	8.5	⊕⊕⊕⊕ HIGH	CRITICAL
Incidence of heart failure (follow-up: 8.2–13 y)																		
5	Cohort	228 798	8423	RR	0.953	0.937	0.969	2	1	0.2	1	0	1	0	1	6.2	⊕⊕⊕◯ MODERATE	CRITICAL
Incidence of heart failure in people at high CVD risk (Mediterranean diet enriched with olive oil vs. low-fat) (follow-up: 4.8 y)																		
1	RCT	4893	61	RR	0.74	0.44	1.24	3	1	0.5	1	0	1	0	0	8.5	⊕⊕⊕⊕ HIGH	CRITICAL
Incidence of heart failure in people at high CVD risk (Mediterranean diet enriched with nuts vs. low-fat) (follow-up: 4.8 y)																		
1	RCT	4896	65	RR	1.01	0.61	1.66	3	1	0.5	1	0	1	0	0	8.5	⊕⊕⊕⊕ HIGH	CRITICAL
Incidence of hypertension (mean follow-up: 10.4 y)																		
4	Cohort	22 788	4071	RR	0.97	0.94	0.99	2	1	0.2	1	0	1	0	1	6.2	⊕⊕⊕◯ MODERATE	CRITICAL
Prevalence of high blood pressure																		
6	Cross-sectional	95 889	18 935	OR	0.98	0.97	0.995	2	1	0.2	1	0	1	0	1	6.2	⊕⊕⊕◯ MODERATE	CRITICAL
Incidence of high blood pressure (Mediterranean diet vs. Standard diet. Health restriction or dietary approach to hypertension (DASH)) (follow-up: 3 mo)																		
1	RCT	240	NA	OR	0.11	0.02	0.77	3	0	0.2	1	0	1	0	0	7.2	⊕⊕⊕◯ MODERATE	CRITICAL
Incidence of cardiovascular disease (average follow-up: 11 y)																		
24	Cohort	650 960	51 278	RR	0.967	0.956	0.978	2	1	0.2	1	0	1	0	1	6.2	⊕⊕⊕◯ MODERATE	CRITICAL
Incidence of cerebrovascular disease (TIA stroke) (average follow-up: 13 y)																		
19	Cohort and case-control	562 024	17 632	RR	0.973	0.963	0.984	2	1	0.2	1	0	1	0	1	6.2	⊕⊕⊕◯ MODERATE	CRITICAL
Incidence of cerebrovascular disease in persons at high CVD risk (Mediterranean diet enriched with olive oil vs. low-fat) (follow-up: 4.8 y)																		
1	RCT	4983	107	RR	0.65	0.44	0.95	3	1	0.2	1	0	1	0	0	8.2	⊕⊕⊕⊕ HIGH	CRITICAL
Incidence of cerebrovascular disease in persons at high CVD risk (Mediterranean diet enriched with nuts vs. low-fat) (follow-up: 4.8 y)																		
1	RCT	4896	90	RR	0.54	0.35	0.82	3	1	0.2	1	0	1	0	0	8.2	⊕⊕⊕⊕ HIGH	CRITICAL
Incidence of coronary heart disease (average follow-up: 11 y)																		
30	Cohort and case-control	602 156	33 949	RR	0.95	0.94	0.96	2	1	0.2	1	0	1	0	1	6.2	⊕⊕⊕◯ MODERATE	CRITICAL
Incidence of coronary heart disease in persons at high CVD risk (Mediterranean diet enriched with olive oil vs. low-fat) (follow-up: 4.8 y)																		
1	RCT	4983	75	RR	0.82	0.52	1.13	3	1	0.5	1	0	1	0	0	8.5	⊕⊕⊕⊕ HIGH	CRITICAL
Incidence of coronary heart disease in persons at high CVD risk (Mediterranean diet enriched with nuts vs. low-fat) (follow-up: 4.8 y)																		
1	RCT	4896	69	RR	0.76	0.47	1.25	3	1	0.5	1	0	1	0	0	8.5	⊕⊕⊕⊕ HIGH	CRITICAL
Mortality from cardiovascular causes (average follow-up: 14.9 y)																		
31	Cohort and case-control	1408 613	63 604	RR	0.97	0.96	0.98	2	1	0.2	1	0	1	0	1	6.2	⊕⊕⊕◯ MODERATE	CRITICAL
Cardiovascular disease mortality in persons at high CVD risk (Mediterranean diet enriched with olive oil vs. low-fat) (follow-up: 4.8 y)																		
1	RCT	4983	56	RR	0.62	0.36	1.06	3	1	0.5	1	0	1	0	0	8.5	⊕⊕⊕⊕ HIGH	CRITICAL
Cardiovascular disease mortality in persons at high CVD risk (Mediterranean diet enriched with nuts vs. low-fat) (follow-up: 4.8 y)																		
1	RCT	4896	61	RR	1.02	0.63	1.67	3	1	0.5	1	0	1	0	0	8.5	⊕⊕⊕⊕ HIGH	CRITICAL
Sudden death (follow-up: 9.8 y)																		
1	Cohort	21 609	401	HR	0.96	0.91	1.01	2	0	0.2	1	0	1	0	0	4.2	⊕⊕◯◯ LOW	CRITICAL

Risk of bias, study quality and study limitations (0–2 points): 2 points if the mean Newcastle–Ottawa score for a comparison is ≥7 or if other criteria are met. **Accuracy** (0–1 point): 1 point if ≥500 events and the 95% CI excludes the null value or if ≥500 events and the 95% CI overlaps the null value but excludes a major benefit or harm (relative risk [RR] <0.8 or >1.2). **Heterogeneity (lack of reproducibility of results)** (0–1 point): 1 point if ≥10 studies, adequately reported measures of heterogeneity, no major heterogeneity found or otherwise subgroup/sensitivity analyses conducted. **Lack of generalizability** (0–1 point): 1 point if no significant differences in population or intervention; relevant clinical outcome. **Publication** bias (0–1 point): 1 point if there is no evidence of publication bias through tests or graphs (10 or more studies). **Funding bias** (0–1 point): 1 point if funded by an academic or research institution; 0 points if funded by private sponsors such as pharmaceutical companies. **Effect size** (0–2 points): 2 points if RR < 0.5 or >2.0 and the corresponding test is statistically significant (highest vs. lowest category). **Dose-response** (0–1 point): 1 point if there is a significant linear/non-linear dose-response relationship in prospective cohort studies.

Table 2
Effectiveness of the Mediterranean diet for the primary prevention of cardiovascular diseases



0.44–1.24) for MD with extra virgin olive oil and 1.01 (95% CI 0.61–1.66) for MD with dried fruit, indicating no protective effect of MD versus the LFD. The degree of certainty of the evidence was rated as high for both analyses according to the NUTRIGRADE.

Arterial hypertension

Six cross-sectional studies [26,48,66,74,89,106] examined the prevalence of hypertension as an outcome by including 95 889 participants. A total of 18 935 events were recorded. The estimated OR was 0.98 (95% CI: 0.97–0.995, one-point increase in MD adherence), suggesting an association between MD and the outcome of interest, supported by a moderate degree of certainty according to the NUTRIGRADE.

Four cohort studies [52,58,76,87] examined the incidence of hypertension as an outcome, including 22 788 participants. During a follow-up between 8.2 and 13 y, 4071 events were recorded. The estimated relative risk was 0.97 (95% CI: 0.94–0.99, one-point increase in MD adherence), suggesting an association between MD and the outcome of interest, supported by a moderate degree of certainty according to the NUTRIGRADE.

An intervention study [39] involving 240 people without hypertension or with high blood pressure who were not on treatment, analyzed the incidence of hypertension by comparing MD versus a salt-restricted diet and the DASH diet (dietary approach to hypertension) during 3 mo of follow-up. The analysis showed a relative risk of 0.11 (95% CI 0.02–0.77) for MD, indicating a protective effect of MD compared to the other diets examined. The degree of certainty of the evidence was rated as moderate for both analyses according to the NUTRIGRADE.

Cardiovascular diseases

Twenty-four cohort studies [22,25,32–35,38,40,44,45,55,56,58,61,63,68,79–81,91,92,95,99,100,103] examined the incidence of each CVD as an outcome, including 650 960 participants. A total of 51 278 events were recorded. The estimated relative risk was 0.967 (95% CI: 0.956–0.978, one-point increase in MD adherence), suggesting an association between MD and the outcome of interest, supported by a moderate degree of certainty according to the NUTRIGRADE.

Cerebrovascular diseases

Nineteen case-control and cohort studies [21,29,36,41–43,46,47,55,59,60,65,71,85,92,99–101] examined the incidence of cerebrovascular disease as an outcome, including 562 024 participants. During an average follow-up of 13 y, 17 632 events were recorded. The estimated relative risk was 0.973 (95% CI: 0.963–0.984, one-point increase in MD adherence), suggesting an association between MD and the outcome of interest, supported by a moderate degree of certainty according to the NUTRIGRADE.

The PREDIMED study [37], involving nearly 5000 adults at HCVR, analyzed the incidence of cerebrovascular disease by comparing MD, enriched with extra virgin olive oil or dried fruit, versus the LFD. The analysis showed a relative risk of 0.65 (95% CI 0.44–0.95) for MD with extra virgin olive oil and 0.54 (95% CI 0.35–0.82) for MD with dried fruit, indicating a protective effect of MD versus the LFD. The degree of certainty of the evidence was rated as high for both analyses according to the NUTRIGRADE.

Coronary heart diseases

Thirty case-control and cohort studies [27,29,31,41–43,45,49,52,55,57,59,62,65,67,77,83,86,90,92,98–100,102,107] examined the incidence of coronary artery disease as an outcome, including 602 156 participants. During an average follow-up of 13 y, 33 949 events were recorded. The estimated relative risk was 0.95 (95% CI: 0.94–0.96, one-point increase in MD adherence), suggesting an association between MD and the outcome of interest, supported by a moderate degree of certainty according to the NUTRIGRADE.

The PREDIMED study [37], involving almost 5000 adults at HCVR, analyzed the incidence of coronary heart disease by comparing MD, enriched with extra virgin olive oil or dried fruit, versus the LFD. The analysis showed a relative risk of 0.82 (95% CI 0.52–1.13) for MD with extra virgin olive oil and 0.76 (95% CI 0.47–1.25) for MD with dried fruit, indicating an absence of a protective effect of MD versus the LFD. The degree of certainty of the evidence was rated as high for both analyses according to the NUTRIGRADE.

Mortality from CVDs and sudden death

Thirty-one case-control and cohort studies [22,24,28,30,43,50,51,53–56,65,69–74,94,95,98–100,104,107] examined the

incidence of CVD mortality, as an outcome, including 1408 613 participants. During an average follow-up of 14.9 y, 63 604 events were recorded. The estimated relative risk was 0.97 (95% CI: 0.96−0.98, one-point increase in MD adherence), suggesting an association between MD and the outcome of interest, supported by a moderate degree of certainty according to the NUTRIGRADE.

The PREDIMED study [37], involving almost 5000 adults at HCVR, analyzed the incidence of mortality from cardiovascular causes by comparing MD, enriched with extra virgin olive oil or dried fruit, versus the LFD. The analysis showed a relative risk of 0.62 (95% CI 0.36−1.06) for MD with extra virgin olive oil and 1.02 (95% CI 0.63−1.67) for MD with dried fruit, indicating no protective effect of MD versus the LFD. The degree of certainty of the evidence was rated as high for both analyses according to the NUTRIGRADE.

Finally, a cohort study [79] that included 21 609 participants investigated sudden death as an outcome. A total of 401 events were recorded during 9.8 y of follow-up. The analysis showed a relative risk of 0.96 (95% CI 0.91−1.01, high versus low adherence to MD). The degree of certainty of the evidence was assessed as low according to the NUTRIGRADE.

Quality assessment

All included studies were rated as high quality based on the NOS, with scores ranging from 7 to 9 out of 9, as fully reported in Supplementary Table 4. These results support the methodological robustness of the included literature and provide a strong basis for further synthesis of the associations between adherence to the MD and the risk or prevalence of oncological conditions. All six intervention studies included, derived from the PREDIMED study, were ranked as low risk of bias, as fully detailed in Supplementary Table 5.

Discussion

Interpretation of the main results

This systematic review and meta-analysis provides consistent evidence supporting the role of MD in preventing the incidence of several CVD, such as peripheral artery disease, coronary heart disease, cerebrovascular events, atrial fibrillation, and heart failure. The analysis of over 87 studies, including more than 1.4 million participants, revealed that even a modest one-point increase in MD adherence is associated with a statistically significant reduction in CVD incidence and the related mortality. Particularly, data from the PREDIMED trial, a high-quality RCT, demonstrated particularly strong protective effects, especially when the MD was enriched with extra virgin olive oil. However, the results were not universally consistent; in fact, in some studies considering specific outcomes (e.g., peripheral artery disease, atrial fibrillation, and sudden cardiac death), the associations were weak or non-significant, thus reflecting the complexity and heterogeneity of nutritional epidemiology.

Potential biological mechanisms

The MD diet involves a high consumption of plant-based foods such as vegetables, fresh fruit, nuts, legumes, and preferably whole grains; olive oil serves as the primary source of fat, primarily monounsaturated fatty acids; moderate consumption of fish, seafood, eggs, white meat, milk, and dairy products, limited consumption of red meat and red wine (the less, the better, with one alcoholic drink per day for women and two for men), and occasional consumption of processed meats, sweets, and ultra-processed foods; preference for local, seasonal, and minimally processed products, in line with the principles of biodiversity and sustainability; furthermore, moderate and regular physical activity, adequate rest, and social and intergenerational connection are recommended [97]. Its cardioprotective properties may be attributed to several interrelated biological mechanisms. One of the MD most important features is its high content of monounsaturated fatty acids (primarily coming from olive oil), which have properties in reducing low-density lipoprotein and increasing high-density lipoprotein cholesterol [98]. Additionally, this diet is rich in antioxidants, polyphenols, and anti-inflammatory nutrients such as omega-3 fatty acids from fish and nuts. These components have been demonstrated to improve endothelial function and reduce oxidative stress [99]. Furthermore, high intake of fiber and polyphenol-rich fruits and vegetables may improve insulin sensitivity, promote satiety, and promote a healthy gut microbiome, which has emerging links to cardiovascular health [100,101]. In agreement with Sofi's meta-analysis on the adherence to the MD and health status [108], the synergistic combination of these dietary factors determines the beneficial impact on multiple CVDs outcomes.

Public health implications and future directions

The evidence reinforces the MD, universally and scientifically considered as an example of correct nutrition as well as a key component of dietary-based prevention. Considering the global burden of CVDs, promoting MD through public health campaigns and education programs could reduce the incidence of CVDs, implement healthy physical and mental longevity, and reduce healthcare costs [109,110].

Implementation strategies should be promoted, especially in non-Mediterranean populations, and should also focus on sustainable and equitable access to MD components.

Future research is needed to investigate dose-response relationships and the potential interactions of MD with genetic, pharmacological, and behavioral factors. Furthermore, subgroup analyses (e.g., age, sex, socioeconomic status) could be useful to identify populations that may benefit the most from MD adherence. Additionally, studies conducted in non-Mediterranean populations could also be valuable to assess the cost-effectiveness of MD-based interventions in different settings.

Strengths and limitations

The strengths of the present work include a wide search strategy, rigorous methodological approach following PRISMA and Meta-analysis of Observational Studies in Epidemiology guidelines, an accurate evaluation of evidence quality using the NUTRIGRADE tool, and a good quality of the studies based on the NOS for observational studies (group selection, dietary exposure, and outcomes). Moreover, the inclusion of many participants improves the generalizability and clinical relevance of the findings. However, some limitations must be acknowledged. Some heterogeneity exists regarding the definition of the MD, the duration of follow-up (in observational studies), the heterogeneity of control diets (e.g., standard, low-fat), and the definition of cardiovascular events. Many of the studies included were observational and are therefore subject to confounding and potential measurement bias, particularly regarding diet assessment. Variations in MD adherence scoring systems and population characteristics may contribute to heterogeneity in some results.

Conclusions

This systematic review and meta-analysis supports the MD as an effective dietary strategy for the primary prevention of CVDs. The evidence, particularly from high-quality RCTs such as PREDIMED, indicates that greater adherence to the MD significatively lowers the cardiovascular risk. These results should influence dietary recommendations and public health strategies with the aim of reducing the global burden of CVDs.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.nut.2025.113038.

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