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The role of the Mediterranean diet in secondary cardiovascular disease prevention: a systematic review and meta-analysis of cohort studies

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ABSTRACT

Aims: Although the Mediterranean diet is well established for primary cardiovascular disease (CVD) prevention, its role in secondary prevention is less evidence-based. This systematic review and meta-analysis evaluate its association with CVD incidence and mortality in patients with existing CVD.
Data synthesis: A systematic literature search was conducted in PubMed/MEDLINE, Scopus, Embase, and the Cochrane Library from database inception to February 28, 2026. Thirteen prospective cohort studies including adults with established CVD that assessed adherence to a Mediterranean dietary pattern and reported clinical outcomes were eligible. Pooled risk ratios (RRs) and 95% confidence intervals (CIs) were calculated using fixed- or random-effects models. The protocol was prospectively registered in PROSPERO (CRD420261335357). Thirteen prospective cohort studies comprising 54,034 patients with established CVD, over 13,311 events, and follow-up periods from 2 to 10 years were included. Higher adherence to the Mediterranean diet was associated with lower risk of all-cause mortality (0.74, 95%CI: 0.65–0.84), cardiovascular mortality (0.84, 95%CI: 0.75–0.94), and recurrent cardiovascular events (0.60, 95%CI: 0.39–0.92). Sensitivity analyses confirmed the robustness of the findings. Heterogeneity was moderate to high. No evidence of publication bias was observed for all-cause mortality, whereas publication bias was detected for recurrent CVD events, though the pooled estimate remained unchanged after trim-and-fill adjustment.
Conclusions: These findings support the inclusion of Mediterranean dietary patterns as an important component of secondary CVD prevention strategies, additional to pharmacological therapies and reinforce current guideline recommendations promoting cardioprotective dietary habits.

1. Introduction

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide, accounting for approximately 20 million deaths annually [1]. Unhealthy dietary patterns have been identified as a major modifiable risk factor, contributing to an estimated 11 million deaths globally, and accounting for 153 million disability adjusted life-years lost (DALYs) due to CVDs in 2019 [2]. The Mediterranean diet is one of the most thoroughly researched dietary patterns for preventing cardiovascular disease in the world. It aligns with global guidelines from the FAO and WHO, providing a holistic framework for a healthy and sustainable way of eating that respects cultural traditions while addressing modern nutritional and environmental challenges [3].

Beyond its undoubtable role in primary prevention, the Mediterranean diet has attracted increasing interest in the context of secondary CVD prevention [4]. Evidence from several cohort studies and clinical trials supports a protective role of the Mediterranean diet on long-term survival and cardiovascular outcomes, including recurrent events [5–15]. The latest meta-analysis of prospective cohort studies, published in 2020, reported improved survival and reduced CVD mortality among

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individuals with established CVD who adhered more closely to the Mediterranean diet [11]. Consistently, randomized trials, from the Lyon Diet Heart Study to more recent, large-scale studies such as PREDIMED Study and CARDIOPREV Study, have shown that adherence to a Mediterranean dietary pattern is associated with reduced recurrent myocardial infarction and cardiovascular mortality among post–myocardial infarction patients [12–14]. Moreover, the most recent meta-analysis of randomized trials reported that 15 of 16 trials reviewed supported the Mediterranean diet for the secondary prevention of CVD [15].

Despite accumulating evidence, uncertainty remains regarding the magnitude and consistency of the association between adherence to the Mediterranean diet and outcomes in patients with established CVD. Although dietary interventions, like the Mediterranean diet, are strongly recommended for primary prevention [16,17], they receive less emphasis in secondary prevention, supported by moderate-quality evidence (i.e., Class IIa, Level B) [17]. Importantly, the current evidence regarding the impact of dietary interventions on non-fatal recurrent cardiovascular outcomes remains limited, highlighting the need for further research. This is particularly relevant in light of several studies published after the most recent meta-analyses, which contribute additional evidence and necessitate a methodologically rigorous synthesis to more accurately evaluating the magnitude, consistency, and clinical relevance of these associations.

Thus, this meta-analysis of prospective cohort studies aimed to synthesize the available evidence and evaluate the association between adherence to the Mediterranean diet as compared to any other diet, and all-cause mortality and cardiovascular outcomes, including mortality and major adverse recurrent events, among patients with established CVD. The synthesis of data from prospective cohort studies allows for a more robust evaluation of temporal associations and long-term outcomes in real-world populations.

2. Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement and followed established methodological recommendations for systematic reviews [18].

The study protocol was registered in the PROSPERO database with number CRD420261335357.

2.1. Data sources and search strategy

A systematic literature search was conducted in the databases PubMed/MEDLINE, Scopus, Embase, and the Cochrane Library, from inception to February 28, 2026, in accordance with a predefined protocol and established methodological principles for systematic reviews of cohort observational studies.

The search strategy incorporated both controlled vocabulary (e.g., MeSH and Emtree terms) and free-text keywords related to the Mediterranean diet and cardiovascular outcomes. The strategy incorporated an expanded set of keywords and synonyms, including: *"Mediterranean diet", "Mediterranean dietary pattern", "MedDiet", "cardiovascular disease", "CVD", "coronary artery disease", "heart disease", "myocardial infarction", "stroke", "secondary prevention", "recurrent events", "cohort", "prospective", "longitudinal", "follow-up", "mortality", "all-cause mortality", "cardiovascular mortality", "cardiovascular events", "major adverse cardiovascular events", and "MACE"*. Boolean operators ("AND", "OR") were applied to appropriately combine search terms. No restrictions were applied on publication year. No language restriction was applied. The reference lists of all retrieved articles and relevant reviews were manually screened to identify additional eligible studies.

The completeness of the search strategy was further verified through backward citation tracking. Study selection was performed using a hierarchical approach based on title and abstract screening followed by full-text evaluation. When full-text articles were not accessible, efforts were made to obtain them through institutional access or by contacting the corresponding authors. An updated search was conducted prior to the final analysis to identify any additional eligible studies published up to the search date.

2.2. Study selection

Study eligibility was determined according to the predefined protocol, which specified strict methodological criteria, including study design and population, exposure and comparator, and clinical outcomes. Specifically, only prospective cohort studies were retrieved, the population of interest included adults with established CVD (i.e., secondary prevention setting), the exposure was adherence to a Mediterranean dietary pattern [5] and the comparator was no or low adherence (i.e., highest versus lowest adherence percentile of the relevant diet score), and the outcomes of interest included all-cause mortality, cardiovascular mortality, and recurrent CVD events, including myocardial infarction, stroke, heart failure, coronary revascularization, or hospitalization for cardiovascular outcomes. Observational analyses derived from the Mediterranean diet arm of two randomized trial cohorts (e.g., GISSI-Prevenzione, COMPASS) were considered eligible, provided they fulfilled all pre-specified inclusion criteria; however, potential differences in participant selection, treatment background, and outcome ascertainment relative to conventional cohort studies were acknowledged as a source of heterogeneity.

We excluded sources that: 1) were conducted in primary prevention or general populations without separate data for individuals with established CVD; 2) focused on individual foods or nutrients or overall dietary patterns rather than a strictly defined Mediterranean dietary pattern; and 3) non-original articles (e.g., reviews, editorials, letters).

After removal of duplicates, all records were screened in a two-stage process consisting of title and abstract screening followed by full-text evaluation. The study selection was performed independently by two authors (EG and DP). Disagreements were resolved through discussion of the other authors and consensus. In cases of multiple publications derived from the same cohort, the most comprehensive or most recent report was included in the quantitative synthesis to avoid duplication of data, while additional publications from the same cohort were considered in the qualitative assessment.

2.3. Data extraction and quality assessment

The extracted information included the first author, year of publication, country or region that the study was conducted, sample size, characteristics of the study population, definition of CVD, duration of follow-up, method used to assess adherence to the Mediterranean diet, exposure categories, outcome definitions, number of events, effect estimates (i.e., Hazard Ratios [HR], Relative Risk [RR], or Odds Ratios [OR]) with their corresponding 95% confidence intervals (CIs) or standard errors, and variables included in multivariable models. The methodological quality of the included studies was independently assessed by two reviewers using the Newcastle–Ottawa Scale (NOS) for cohort studies, which evaluates three domains: selection of participants, comparability of study groups, and assessment of outcomes [19]. Studies were classified as low, moderate, or high quality based on their NOS score (Supplementary Table S1). Any disagreements in quality assessment were resolved by consensus. When multiple effect estimates were reported, the most fully adjusted model was selected. Covariates included in the most adjusted model for each study are reported in Supplementary Table S2. Any discrepancies in data extraction were resolved through discussion and consensus between the authors.

2.4. Statistical analysis

Meta-analysis was performed using STATA statistical software v.19.0 (Stata Corp, College Station, TX, USA).

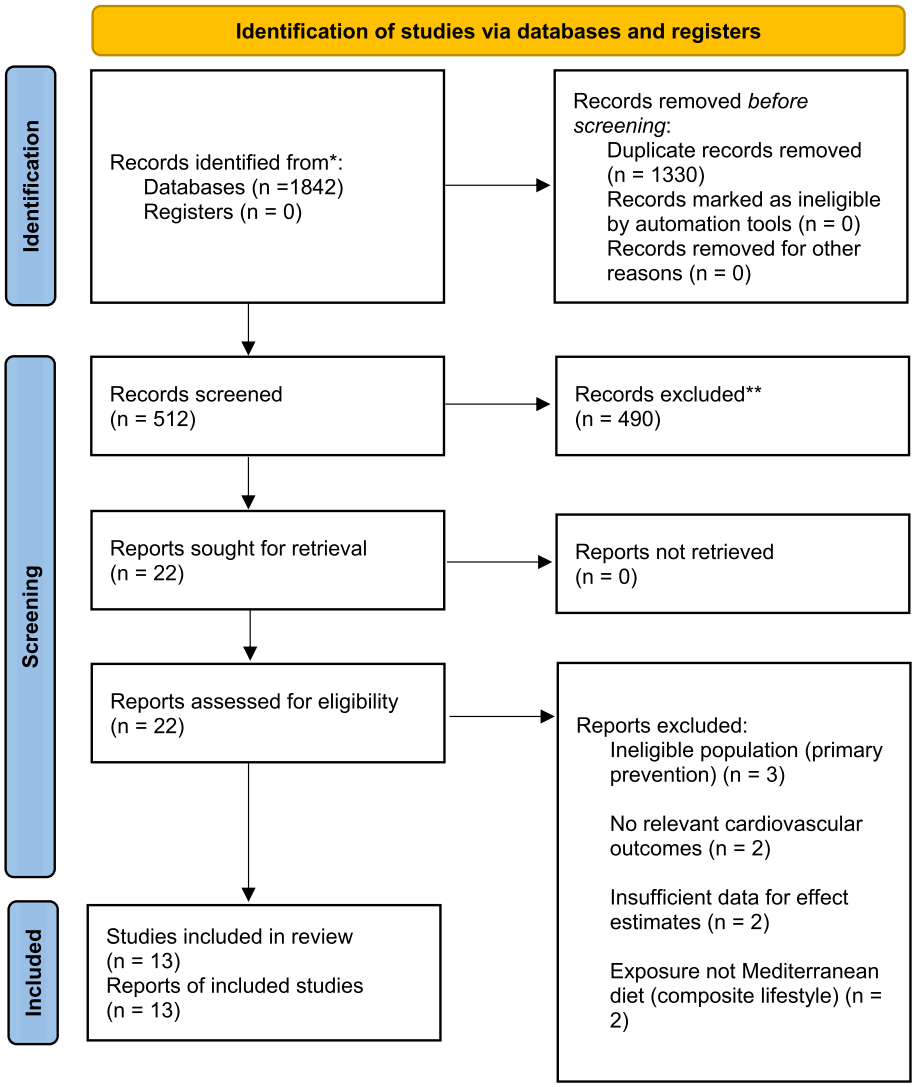

Fig. 1. Flow-diagram of the meta-analysis
Source: Page MJ et al. BMJ 2021; 372:n71. doi:10.1136/bmj.n71. This work is licensed under CC BY 4.0. To view a copy of this license, visit https://creativecommons.org/licenses/by/4.0/.

Pooled estimates from fully adjusted models were calculated to examine the association between the highest versus lowest percentile of adherence and the outcomes of interest. Retrieved effect size measures and their corresponding CIs were transformed to their natural logarithms. When standard errors were provided, the 95%CIs were calculated using standard formula. The choice of a fixed-effects or random-effects model was guided by the magnitude of between-study heterogeneity. Fixed effect meta-analysis was conducted using the inverse variance model and random effect meta-analysis was conducted using the Restricted Maximum Likelihood (REML) estimator. For interpretability, pooled log-effect estimates were exponentiated to obtain pooled RRs and their corresponding 95% CIs. Robustness of the summary estimates was assessed through leave-one-out sensitivity analyses, sequentially excluding each study to evaluate its influence on the pooled RRs and 95% CIs. Between-study heterogeneity was quantified using Q test and the I^2 statistic, with thresholds of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively. Meta-regression was applied to explore potential sources of between-study heterogeneity.

2.5. Risk of bias assessment

Risk of bias was assessed by systematically evaluating both individual studies and the overall synthesis using established methods. At the study level, the use of confounding, selection of participants, handling of missing data, measurement of outcomes, and selective reporting of results, was evaluated and reported for each study. At the synthesis level, publication bias was assessed visually through contour-enhanced funnel plots and statistically using Begg's adjusted rank correlation test and Egger's regression asymmetry test [20,21]. The trim-and-fill method was additionally applied to estimate the potential influence of unpublished studies and to adjust the pooled estimates accordingly [22]. Sensitivity analyses were conducted to determine whether excluding high-risk studies changes the overall results, while heterogeneity was assessed to identify inconsistencies that may reflect bias.

3. Results

3.1. Search results and characteristics of studies

The study selection process was conducted manually and was documented using a PRISMA 2020 flow diagram, including reasons for

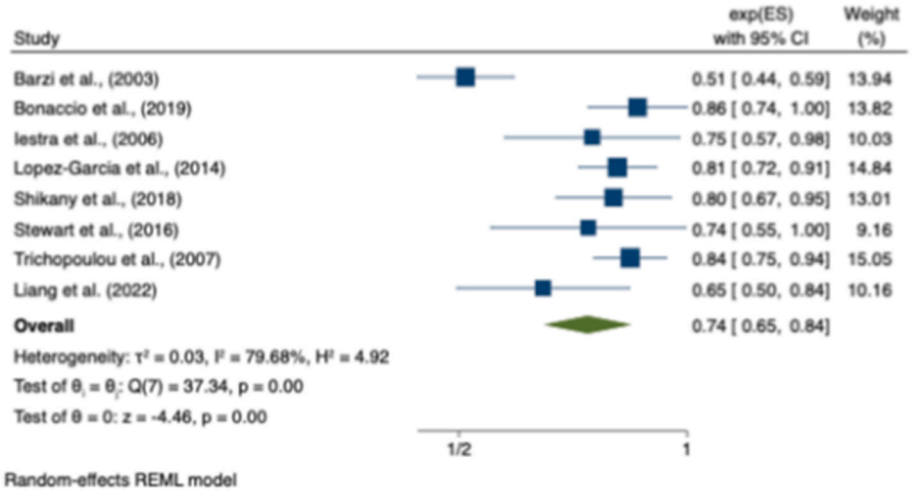

Fig. 2. Forest-plot illustrating the association between adherence to the Mediterranean diet (highest versus lowest available adherence category) and all-cause mortality, among CVD patients. Results are presented as pooled Risk Ratios and their corresponding 95% confidence intervals.

exclusion at the full-text stage (Fig. 1).

Main characteristics of the included studies are presented in Table 1. Overall, 13 prospective cohorts in secondary CVD prevention settings were studied, i.e., 6 studies more than the latest meta-analysis, comprising in total 54,034 patients with established CVD [23–35]. The studies were conducted across diverse geographic regions, including European countries, the United States of America, and multinational cohorts, with sample sizes ranging from small single-center studies to large international cohorts. Included patients had a history of myocardial infarction, acute coronary syndrome, coronary artery disease or stroke [23,25,27–35], while some cohorts also included patients with polyvascular disease or mixed cardiovascular conditions [32–35]. The outcomes included all-cause mortality (8 studies), cardiovascular mortality (3 studies), and recurrent cardiovascular outcomes (7 studies), which were analyzed separately. Follow-up duration ranged from 2 to 10 years, allowing for the assessment of both short- and long-term clinical outcomes. Adherence to the Mediterranean diet was evaluated across studies using predefined dietary scores including the MDS [24, 25] and a modified MDS [29], the MedDietScore [30,31], the alternate Mediterranean Diet score (aMED) [26,34], the 14-item Mediterranean Diet Adherence Screener (MEDAS) [35], and study-specific dietary scores [23,27,28,32,33], derived either directly or indirectly from food frequency questionnaires.

The following paragraphs provide a brief overview of the cohort studies identified through the systematic literature review, by mortality and CVD incidence outcomes.

Greater adherence to the Mediterranean diet was consistently associated with lower all-cause and CVD-specific mortality across studies, although effect sizes varied [23–25,29,34]. For example, the GISSI-Prevenzione study reported a 49% lower risk of all-cause mortality among high adherers to the Mediterranean diet pattern [23], while the Moli-sani study observed 16% and 23% reductions in all-cause and CVD mortality, respectively, with stronger benefits in patients receiving statins [24]. A multicenter European post–myocardial infarction study reported similar reductions of 20%–25% in all-cause mortality [25], whereas US cohorts demonstrated the modest effects, with approximately a 5% reduction [26].

Evidence regarding recurrent, non-fatal cardiovascular outcomes was also consistent across studies, with a considerable variation in effect size, as well [27,28,30–35]. For example, in the REGARDS cohort, higher adherence to the Mediterranean diet was associated with 22% lower risk of recurrent coronary heart disease events [27], whereas in a large multinational cohort of patients with stable coronary artery disease, greater adherence to the Mediterranean diet was associated with

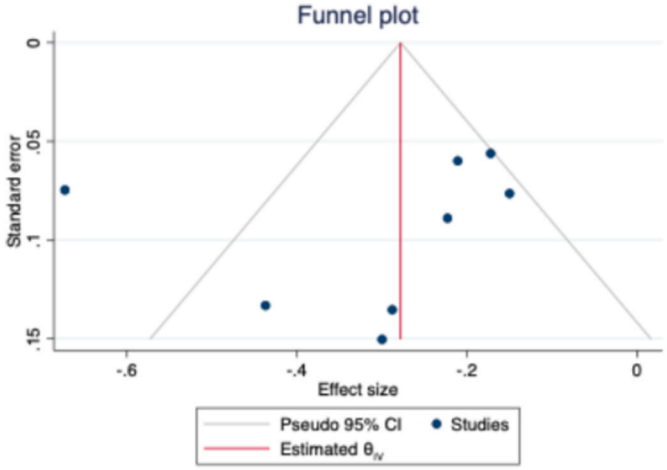

Fig. 3. Funnel-plot for the meta-analysis of the association adherence to the Mediterranean diet (highest versus lowest available adherence category) and all-cause mortality among CVD patients.

5% lower risk of recurrent major adverse cardiovascular events [28].

3.1.1. *Evidence synthesis*

3.1.1.1. Mediterranean diet and all-cause mortality among CVD patients. Eight studies evaluated all-cause mortality and Mediterranean diet adherence among patients with established CVD [23–29,34]. In total, 54,034 CVD patients were followed for a median of 7 years, during which 8891 deaths from any cause were observed. Random effects meta-analysis showed a protective association of greater adherence to the Mediterranean diet on all-cause mortality ($p < 0.001$). Comparing the highest versus lowest categories of adherence, patients had 26% lower risk of death from any cause (pooled RR = 0.740, 95% CI: 0.648, 0.844) (Fig. 2). Fixed-effects meta-analysis yielded similar results. Sensitivity analyses demonstrated that exclusion of any single study did not materially alter the pooled estimates, with RRs ranging from 0.72 to 0.81. No evidence of publication bias was detected (Egger test $z = -0.46$, $p = 0.643$; Begg test $z = -1.16$, $p = 0.173$), consistent with visual inspection of the funnel plot (Fig. 3). The pooled-effect estimate remained unchanged after application of the trim-and-fill method. However, between-study heterogeneity was high ($I^2 = 79.68\%$, Q-test $p < 0.001$), supporting the use of random effects model and indicating

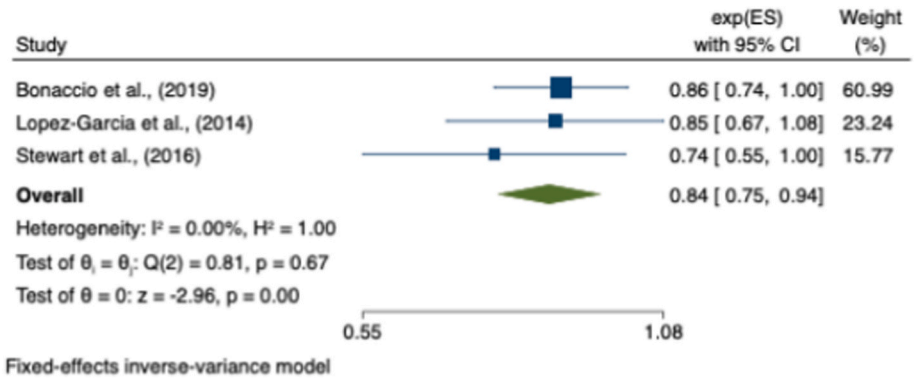

Fig. 4. Forest-plot illustrating the association between adherence to the Mediterranean diet (highest versus lowest available adherence category) and CVD mortality, among CVD patients. Results are presented as pooled Risk Ratios and their corresponding 95% confidence intervals.

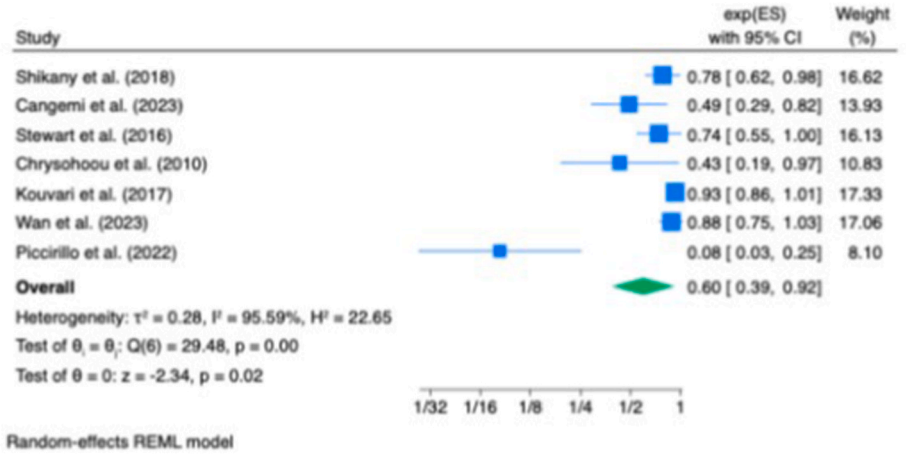

Fig. 5. Forest-plot illustrating the association between adherence to the Mediterranean diet (highest versus lowest available adherence category) and recurrent CVD events, among CVD patients. Results are presented as pooled Risk Ratios and their corresponding 95% confidence intervals.

substantial variability across studies. Meta-regression analyses did not identify significant sources of heterogeneity, including study duration (p = 0.554), year of publication (p = 0.408), and number of patients (p = 0.639) or number of deaths (p = 0.762).

3.1.1.2. Mediterranean diet and CVD mortality among CVD patients. Only three studies evaluated CVD mortality among patients with CVD [24,26,35]. In total, 34,077 CVD patients were included, with 2562 cardiovascular deaths observed. Random effects meta-analysis showed a significant protective association between greater adherence to the Mediterranean diet and CVD mortality (p = 0.0031). Fixed-effects analyses yield similar estimates. Specifically, comparing the highest versus lowest categories, patients had 16% lower risk of CVD death (pooled RR = 0.838, 95% CI: 0.745, 0.942) (Fig. 4). Sensitivity analyses demonstrated that exclusion of any single study did not alter the pooled estimates, with RRs ranging from 0.80 to 0.86. Because the number of included studies was limited ($n = 3$), publication bias was not assessed. Between-study heterogeneity was negligible (I^2 = 0.01%, Q-test p = 0.67), supporting the use of fixed effects model and indicating consistency across studies. Meta-regression analyses did not identify significant sources of heterogeneity, including study duration (p = 0.554), year of publication (p = 0.408), number of patients (p = 0.639) and deaths (p = 0.762).

3.1.1.3. Mediterranean diet and recurrent CVD events. Seven studies evaluated recurrence of CVD events among patients with CVD [27,28,30–33,35], including a total of 47,883 patients and 4420 cardiovascular events. Random effects meta-analysis revealed a significant protective association between greater adherence to the Mediterranean diet and recurrent CVD events (p = 0.0192). Comparing the highest versus the lowest categories of adherence, patients had 40% lower risk of recurrent CVD events (pooled RR = 0.596, 95% CI: 0.387, 0.919) (Fig. 5). Fixed-effects analyses yield similar estimates. Sensitivity analyses showed that exclusion of any single study did not alter the pooled estimates, with RRs ranging from 0.53 to 0.81. Evidence of publication bias was detected (Egger test z = −5.07, p < 0.001; Begg test z = −3.00, p = 0.0069); however, the pooled-effect estimate remained similar after application of the trim-and-fill method. Between-study heterogeneity was very high (I^2 = 95.59%, Q-test $p < 0.001$), supporting the use of random-effects model, and indicating substantial inconsistency among studies. Meta-regression analyses did not identify significant sources of heterogeneity, including study duration (p = 0.434), year of publication (p = 0.911), number of participants (p = 0.954) and recurrent CVD events (p = 0.700).

4. Discussion

The present systematic review and meta-analysis examined the association between adherence to the Mediterranean diet and all-cause and CVD-specific mortality, as well as recurrent cardiovascular outcomes among patients with established CVD, thereby addressing a critical gap in evidence regarding dietary strategies for secondary prevention. By synthesizing data from prospective cohort studies encompassing more than 50,000 patients with established CVD and over

12,000 events, this analysis provides comprehensive evidence on the prognostic relevance of dietary patterns in this high-risk population.

Evidence synthesis suggested that higher adherence to the Mediterranean diet was associated with improved cardiovascular outcomes, including lower all-cause and cardiovascular mortality and a reduced risk of recurrent cardiovascular events compared with low adherence. Despite advances in pharmacological and interventional therapies, these findings support the potential relevance of dietary patterns as an adjunct component of secondary prevention. From a public health perspective, this is particularly important in the context of the rising global CVD burden and increasing consumption of unhealthy diets [36,37].

4.1. Evidence synthesis in the context of secondary CVD prevention

The literature consistently supports the protective role of the Mediterranean diet in primary and secondary cardiovascular prevention, as well. Particularly in secondary prevention settings systematic reviews of randomized controlled trials report meaningful reductions in CVD mortality (approximately 20–30%) and recurrent events (approximately 20–40%) [6,38–41]. However, randomized controlled trials face substantial challenges in sustaining long-term adherence to complex dietary interventions, rendering prospective cohort studies more appropriate for capturing habitual, real-world dietary exposures and their associations with cardiovascular outcomes. In line with randomized trials, a number of observational cohort studies in secondary prevention setting also supports the beneficial hypothesis of Mediterranean diet and CVD. The most recent meta-analysis of prospective cohort studies by Tang et al., which included seven studies, demonstrated a strong inverse association between adherence to the Mediterranean diet and mortality outcomes (i.e., 15% risk reduction for all-cause mortality and 9% risk reduction for cardiovascular mortality per 22% increment in adherence), in individuals with established CVD [11]. However, substantial heterogeneity was observed ($I^2 > 70\%$), reflecting marked variability in study populations, methods for assessing Mediterranean diet adherence, and outcome definitions, thereby limiting the robustness and generalizability of the pooled estimates. Importantly, this analysis did not account for recurrent, non-fatal cardiovascular events, which are highly relevant in modern clinical settings given the increasing survival after acute cardiovascular events and the growing burden of recurrent disease [1].

This meta-analysis builds on prior evidence by incorporating six additional cohort studies, resulting in a total of 13 studies. The findings indicate a greater effect than previous meta-analyses, i.e., a 26% reduction in all-cause mortality risk, and 16% lower CVD mortality risk, while exhibiting like the previous meta-analysis heterogeneity, reflecting the observed differences across cohorts in population characteristics and exposure assessment.

The present meta-analysis also revealed a protective association between adherence to the Mediterranean diet and recurrent CVD events, corresponding to an approximately 40% lower risk of recurrent cardiovascular events, though this estimate should be interpreted cautiously given the extreme between-study heterogeneity and evidence of publication bias. These findings are particularly relevant in the context of secondary prevention, where patients with established CVD remain at substantial risk of subsequent events despite advances in pharmacological and interventional therapies. Recurrent cardiovascular events contribute significantly to morbidity, mortality, and healthcare burden, highlighting the need for effective, scalable, and sustainable preventive strategies. In this regard, dietary interventions such as the Mediterranean diet represent a promising complementary approach to standard medical therapy. Therefore, promoting adherence to the Mediterranean diet among patients with CVD may represent an important lifestyle-based strategy to reduce residual cardiovascular risk and improve long-term outcomes.

4.2. Supporting mechanisms underlying the association between Mediterranean diet and CVD in a secondary prevention setting

The Mediterranean dietary pattern is among the most extensively studied dietary models in relation to cardiovascular health. Multiple biological mechanisms have been proposed to explain the cardioprotective effects of the Mediterranean diet, including improvements in lipid profiles, reductions in systemic inflammation, enhancement of endothelial function, better blood pressure regulation, modulation of glucose metabolism, antioxidant activity, and favorable effects on platelet aggregation and vascular remodeling [42,43]. Particularly, in the context of secondary CVD prevention, where myocardial damage has already occurred, the Mediterranean diet benefits patients through several interrelated mechanisms. Specifically, Mediterranean diet exerts potent anti-inflammatory and antioxidant effects, reducing pro-inflammatory cytokines, while limiting oxidative stress of the heart and LDL oxidation through compounds such as hydroxytyrosol and resveratrol [43–45]. Also improves the already vulnerable endothelial function by enhancing nitric oxide bioavailability, promoting vasodilation, and improving flow-mediated dilation, while also facilitating vascular repair via endothelial progenitor cells [46,47]. Moreover, favorably modulates metabolic and lipid profiles by replacing saturated fats with monounsaturated and polyunsaturated fatty acids, lowering triglyceride levels, improving HDL functionality, enhancing insulin sensitivity, and contributing to better blood pressure control through its high content of potassium- and magnesium-rich foods [44]. Emerging evidence also highlights Mediterranean diet role in modulating the gut–heart axis, including reductions in trimethylamine N-oxide production and increased generation of short-chain fatty acids, which exert systemic anti-inflammatory effects [47–49].

However, not all analyses have demonstrated consistent improvements in traditional cardiovascular risk factors. A network meta-analysis including 17 randomized trials reported modest improvements in body weight and systolic blood pressure across dietary interventions but no consistent advantage in lipid outcomes, suggesting that the benefits of Mediterranean dietary patterns may extend beyond conventional cardiovascular risk factor modification [50].

5. Strengths and limitations

A major strength of the present study is the inclusion of a large number of patients with established CVD across 13 prospective cohort studies, throughout the world, allowing evaluation of clinically relevant outcomes such as all-cause and CVD mortality and, recurrent cardiovascular events. Sensitivity analyses suggest that the pooled estimates remained stable when individual studies were excluded, or fixed-effects analysis was applied, supporting the robustness of the observed associations.

Several limitations should be acknowledged. Adherence to the Mediterranean diet was assessed using different scoring systems across studies, which may introduce measurement variability, and the dietary composition may vary across populations. Differences in follow-up duration and study characteristics may also have contributed to the heterogeneity observed in some analyses. As this meta-analysis included only observational studies, causal inference cannot be established, and residual confounding cannot be excluded. Although randomized controlled trials remain the gold standard for causality, prospective cohort studies provide valuable insights under real-world conditions and complement trial evidence. Because only a small number of studies were available for cardiovascular mortality outcome ($n = 3$), publication bias was not assessed and meta-regression findings should be interpreted as exploratory. Furthermore, the analysis of recurrent cardiovascular events is limited by substantial clinical and methodological heterogeneity across studies, including varying definitions of cardiovascular outcomes (i.e., myocardial infarction, stroke, heart failure, revascularization, and composite endpoints), which may affect comparability. In

Table 1
Characteristics of included prospective cohort studies.

Study (Author, year)	Ref	Region	Sample size	Events	Follow-up duration	Outcome	Effect size (95% CI)
Barzi et al., 2003	23	Italy	11,246	1660	6.5 years	All-cause mortality	0.51 (0.44–0.59)
Iestra et al., 2006	25	Europe	426	226	10 years	All-cause mortality	0.75 (0.57–0.97)
Trichopoulou et al., 2007	29	Europe	2671	467	6.7 years	All-cause mortality	0.82 (0.73–0.94)
Chrysohoou et al., 2010	30	Greece	1000	464	2 years	Recurrent CVD events	0.43 (0.19–0.96)
Lopez-Garcia et al., 2014	26	USA	17,415	3450	20 years	All-cause mortality	0.81 (0.72–0.91)
				1808		Cardiovascular mortality	0.85 (0.67–1.09)
Stewart et al., 2016	28	International	15,482	1159	3.7 years	All-cause mortality	0.96 (0.92–1.00)
				623		Cardiovascular mortality	0.97 (0.92–1.03)
				1588		Recurrent CVD events	0.95 (0.91–0.98)
Kouvari et al., 2017	31	Greece	690	331	10 years	Recurrent CVD events	0.93 (0.85–1.00)
Shikany et al., 2018	27	USA	3562	1098	7.1 years	All-cause mortality	0.80 (0.67–0.95)
				581		Recurrent CVD events	0.78 (0.62–0.98)
Bonaccio et al., 2019	24	Italy	1180	235	7.3 years	All-cause mortality	0.84 (0.70–1.00)
				131		Cardiovascular mortality	0.77 (0.61–0.97)
Liang et al., 2022	34	USA	2052	596	5.6 years	All-cause mortality	0.65 (0.50–0.84)
Piccirillo et al., 2022	33	Italy	107	17	34 months	Recurrent CVD events	0.08 (0.03–0.25)
Cangemi et al., 2023	32	Italy	503	48	22 months	Recurrent CVD events	0.49 (0.29–0.82)
Wan et al., 2023	35	International	26,539	1391	3 years	Recurrent CVD events	0.88 (0.75–1.02)

addition, high between-study heterogeneity and evidence of publication bias, together with differences in study populations, exposure definitions, and follow-up durations, limit the robustness of the pooled estimates. Therefore, these findings should be interpreted cautiously and considered exploratory in nature. Additionally, as the included studies span different time periods, Mediterranean diet adherence may interact with concomitant pharmacological treatments, particularly statins, potentially introducing residual confounding that could not be accounted for in the present analysis. The inclusion of trial-derived observational analyses may differ from traditional cohort studies in terms of participant selection, treatment background, follow-up procedures, and outcome ascertainment, and we have explicitly note this as a potential source of heterogeneity.

6. Conclusion

In conclusion, while clinical guidelines consistently endorse the Mediterranean diet as a cornerstone of primary CVD prevention, its role in secondary prevention remains less clearly defined despite growing evidence suggesting potential benefit. The present findings indicate a possible association between higher adherence to Mediterranean dietary patterns and improved cardiovascular outcomes in secondary prevention; however, these results should be interpreted cautiously given the observational nature and heterogeneity of the available evidence.

Trial/protocol registration

This systematic review and meta-analysis was prospectively registered in the PROSPERO database (registration number: CRD420261335357).

Authors' contributions

D.*P. and* E.G. conceived and designed the study, conducted the literature search and data extraction, performed the statistical analyses, and interpreted the results. E.G. drafted the manuscript. All authors critically revised it for important intellectual content. C.A., M.Y., R.E., P. M-V., and D.P. provided supervision and oversight of the study. All authors have read and approved the final version of the manuscript.

Data availability statement

Data extracted from included studies are presented in Table 1. Statistical code is available upon reasonable request from the corresponding author.

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None.

Declaration of competing interest

None to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2026.104854.

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