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REVIEW

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The effects of the mediterranean diet supplemented with olive oils on pro-inflammatory biomarkers and soluble adhesion molecules: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background Inflammation plays a pivotal role in Cardiovascular disease (CVD) which are a major global health burden. The oil-supplemented Mediterranean diet (MED) is associated with anti-inflammatory effects. The current study evaluates the impact of an olive oils-supplemented MED on pro-inflammatory biomarkers and soluble adhesion molecules.

Methods Regarding PRISMA guideline, this study was conducted and PubMed, Scopus, Web of Science (ISI), Embase, CINAHL databases as well as Google Scholar and Cochrane Library were systematically searched till June 2024.

Results 15 clinical trials (20 arms) comprising 2477 adults aged 23–80 years were included in the systematic review and 9 of them were entered in the meta-analysis. We revealed that following an enriched MED with olive oils can reduce Interleukin-6 (IL-6) *(SMD: – 1.85; 95% CI: -3.69 to -0.01, I^2: 99.29%)* and c-reactive protein (CRP) or high-sensitivity CRP (hs-CRP) *(SMD: – 0.96; 95% CI: -1.49 to -0.44, I^2: 91.85%)*; however, tumor necrosis factor α (TNFα), monocyte chemoattractant protein-1 (MCP-1) and interferon gamma (IFN-γ) did not improved. Moreover, a positive impact on the levels of soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1) and P-selectin [*(SMD: -2.37; 95% CI: -4.34 to -0.40, I^2: 99.38%), (SMD: -1.10; 95% CI: -2.10 to -0.10, I^2: 94.96%) and (SMD: -0.65; 95% CI: -1.18 to -0.12, I^2: 59.33%)*, respectively] were observed; however, E-selectin was unchanged.

Conclusions The olive oils-supplemented MED demonstrates significant anti-inflammatory benefits and improvements in soluble adhesion molecules, supporting its role in reducing CVD risk. However, further studies are required to address the high heterogeneity and confirm these findings in diverse populations.

Trial registration/protocol registration PROSPERO (CRD42023425225).

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Keywords CRP, IL-6, Inflammation, Mediterranean diet, Olive oil, sICAM-1, sVCAM-1

Introduction

Generally speaking, CVD is the first cause of early mortality in the world, which leads to death and disability in industrialized and developed countries, particularly among the elderly [1]. World Health Organization (WHO) reported that CVD approximately claiming 17.9 million lives in 2019 and it is projected to reach 23.6 million deaths by 2030 [2, 3]. Coronary heart disease (CHD) is the most common type of CVD that led to 17.1 million deaths in 2004 [3–5]. The leading cause of CHD is atherosclerosis and inflammation plays a vital role in the incidence and progression of its final lesions [6]. In the earliest stages of CHD the secretion of primary inflammatory cytokines which lead to producing endothelial adhesion molecules and other chemoattractant is induced by proinflammatory stimuli such as metabolic syndrome, smoking, and saturated fat intake, and vascular inflammation is activated [6, 7].

In Mediterranean countries and Japan, the rate of CVD is lower than United States and Eastern and Northern areas of Europe [1, 8]. According to Epidemiological studies, it seems that the dietary pattern in Southern Europe -the Mediterranean diet (MED)- which is enriched in healthy foods such as legumes, grains, fruit, vegetables, and olive oils and is poor in red meat, dairy, and industrial bakery products, has a great beneficial effect on cardiovascular health [9–11]. The cardioprotective effects of MED and its alternative mechanisms are not very clear [12]; However, it seems that some of the functional compounds in this diet play a key role in its protective effect [13]. For instance, this dietary pattern is rich in plant polyphenols [14–18] and essential fatty acids (EFA) from vegetables and olive oils [19–22]. Moreover, many previous studies revealed that plant-based oils or phytochemicals from plant-based diets such as curcumin have anti-inflammatory properties which can play a crucial role in the management of CVD. For instance, sesame oil and olive oils shown a significant negative trend in for CRP and IL-6 in participants [23–25]. In addition, consuming olive oil has. According to previous studies that have evaluated the effects of MED supplemented with olive oils on inflammation, vascular adhesion factors, and antioxidant status, the outcomes are contradictory. Therefore, we designed this systematic review and meta-analysis of clinical trials to assess the effects of this enriched dietary pattern on Pro-inflammatory biomarkers such as c-reactive protein (CRP) or high-sensitivity CRP (hs-CRP), Interleukin-6 (IL-6), tumor necrosis factor α (TNFα), monocyte chemoattractant protein-1 (MCP-1) and interferon gamma (IFN-γ), as well as soluble adhesion molecules including soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1), P-selectin and E-selectin.

Materials and methods

Search strategy

Regarding Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline (Appendix 5) [26], the current study was performed. We carried out an online systematic search on medical databases including PubMed, Scopus, ISI Web of Science, Embase, CINAHL as well as Google Scholar and Cochrane Library up to 3 June 2024. Search words included ("Mediterranean Diet" OR "Mediterranean Diets" OR "Medi diet" OR "Med diet" OR "Meddiet") AND ("Supplementation" OR "Supplemented" OR "Enrich" OR "Rich") AND ("trial" OR "random*" OR "control" OR "clinical" OR "intervention" OR "randomized" OR "placebo" OR "blind" OR "Intervention Study" OR "Intervention Studies" OR "Controlled trial" OR "Randomized controlled trial" OR "Randomized clinical trial" OR "Non-Randomized Controlled Trials" OR "Clinical Trial" OR "Non-Randomized Controlled Trials" OR "Cross-Over study" OR "Cross-Over trial" OR "Cross Over trial" OR "Cross Over study" OR "Double-Blind Method" OR "Double-Blind" OR "Double-Blind trial" OR "Double-Blind study"). Medical Subject Heading (MESH) terms were applied to identify qualified articles.

This study is registered in PROSPERO, The International Prospective Register of Systematic Reviews (registration number: CRD42023425225).

In total, this search strategy is related to a whole project in which all eligible citations including pro-inflammatory biomarkers (IL-6 OR TNFα OR CRP or hs-CRP OR MCP-1 OR IFN-γ) and soluble adhesion molecules (sICAM-1 OR sVCAM-1 OR P-selectin OR E-selectin) were retrieved from all searched citations. Another part of the findings of this project has been published elsewhere [27]. The complete search strategy is provided in Appendix 1.

Finally, for avoiding missing any relevant interventions, we checked all the reference lists of included articles and related reviews manually. The primary extraction including screening the titles, abstracts, and full texts of selected eligible articles and excluding duplicates was performed by S.D.T and N.S (investigators). We entered all interventional studies that met the eligibility criteria to our study. We limited our sources to peer-reviewed literature to ensure the inclusion of high-quality studies with standardized reporting practices.

Inclusion and exclusion criteria

Overall, by using EndNote software (version X9), and after excluding duplicated records the title, abstract of articles, and the full text if required were screened by two independent investigators (S.D.T and N.S). Studies with criteria including clinical trials administered MED supplemented or enriched with diverse olive oil types [olive oil or virgin olive oil (VOO) or extra virgin olive oil (EVOO)] as the intervention with the active control arm and enrolled adults were collected. The exclusion criteria were as follows: [1] non-interventional studies [2], preclinical studies [3], studies using MED in combination with other agents or supplements, and [3] studies which had not assessed inflammatory biomarkers and cell adhesion molecules. Controversy in this process was discussed between investigators and resolved.

Data extraction

Overall, the full text of remaining articles was reviewed in detail and extracted the following required data: [1] First author's name [2], Year of publication [3], Study location [4], Sample size [5], Target population [6], Study design [7], Participants' characteristics (gender, mean age) [8], Duration of intervention [9], Control arm intervention [10] Main outcomes, and [11] Possibility of adverse effects. If there was any incomplete or unclear information, we emailed it to the relevant author of each article.

The consistency of study selection between two reviewers (S.D.T and N.S) in first screening and full-text eligibility evaluation were assessed using Cohen's kappa. Additionally, any disagreement was settled by the third reviewer (M.K).

Quality assessment

SDT and MK separately evaluated the risk of bias of included studies using the Cochrane Risk of Bias Tool for Randomized Controlled Trials [28]. Conflicts among the authors were addressed and amicably resolved. The identified sources of bias included the following:

1. **Selection Bias**: Issues related to random sequence generation and allocation concealment.
2. **Performance/Detection Bias**: Lack of proper blinding of participants, personnel, and outcome assessors, potentially influencing results.
3. **Attrition Bias**: Challenges arising from incomplete outcome data, which could affect the integrity of the findings.
4. **Reporting Bias**: Selective reporting of outcomes, leading to an unbalanced presentation of results.
5. **Other Bias**: Additional, unspecified factors that may have influenced the study outcomes.

These biases were carefully reviewed and accounted for to ensure the robustness and reliability of the analysis.

Statistical analysis

In general, to perform the fixed method meta-analysis, the effect size, as estimated by the mean difference (MD), was applied. Additionally, if there was a methodologic or statistic heterogeneity between studies, we performed random-effects meta-analysis for each measurement [29]. If there was any difference in the reporting methods that could not be converted to each other, effect sizes were pooled as standardized mean difference (SMD) using Hedge's g method. Heterogeneity was assessed using the I^2 index, and by testing the null hypothesis that all studies reveal a common effect size. Heterogeneity was considered low if $I^2 < 30\%$, moderate if I^2 30–75%, and high if $I^2 > 75\%$ [29]. Moreover, to identify the source of heterogeneity, subgroup, sensitivity and meta-regression analyses were performed and Galbraith and Bubble plots were drawn. Furthermore, in meta-regression analysis we assessed the confounding effects of participants' mean age, duration of treatment and male percent on heterogeneity. In addition, Funnel plots were drawn to determine the presence of publication bias visually, and to observe the further investigation of this kind of bias, Begg's rank correlation and Egger's linear regression tests were handled. In the case of significant publication bias, the trim and fill test were applied to impute studies that may have been excluded. We carried out all of the mentioned analyses by **Stata**, version 12 SE (Stata Crop, College Station, TX, USA) software, and P-values < 0.05 were considered statistically significant.

Results

Search results and study selection

The literature search yielded 3303 references, Scopus ($n = 1668$), ISI ($n = 1316$), PubMed ($n = 44$), Embase ($n = 269$) and CINAHL ($n = 6$). Additionally, the first 100 Google Scholar records and 454 records from Cochran Library records were screened, as shown in Fig. 1. From 3303 records which retrieved from databases, a total of 585 duplicated references were excluded, and from the 2718 remaining records, subsequently, 1397 records were excluded due to an obviously irrelevant title and abstract. In the next step, the full text of the 1321 remaining articles were reviewed and 1279 irrelevant references were excluded. In the last part, we omitted 27 articles due to unrelated outcomes and incomplete data. All the records from Google Scholar and Cochrane Library were before retrieved from other databases and were repetitive. Therefore, 15 clinical trials (20 intervention arms) were entered in the systematic review and only 9 studies were eligible to enter into the current meta-analysis. Seven studies for CRP or hs-CRP [30–36], 5 studies for

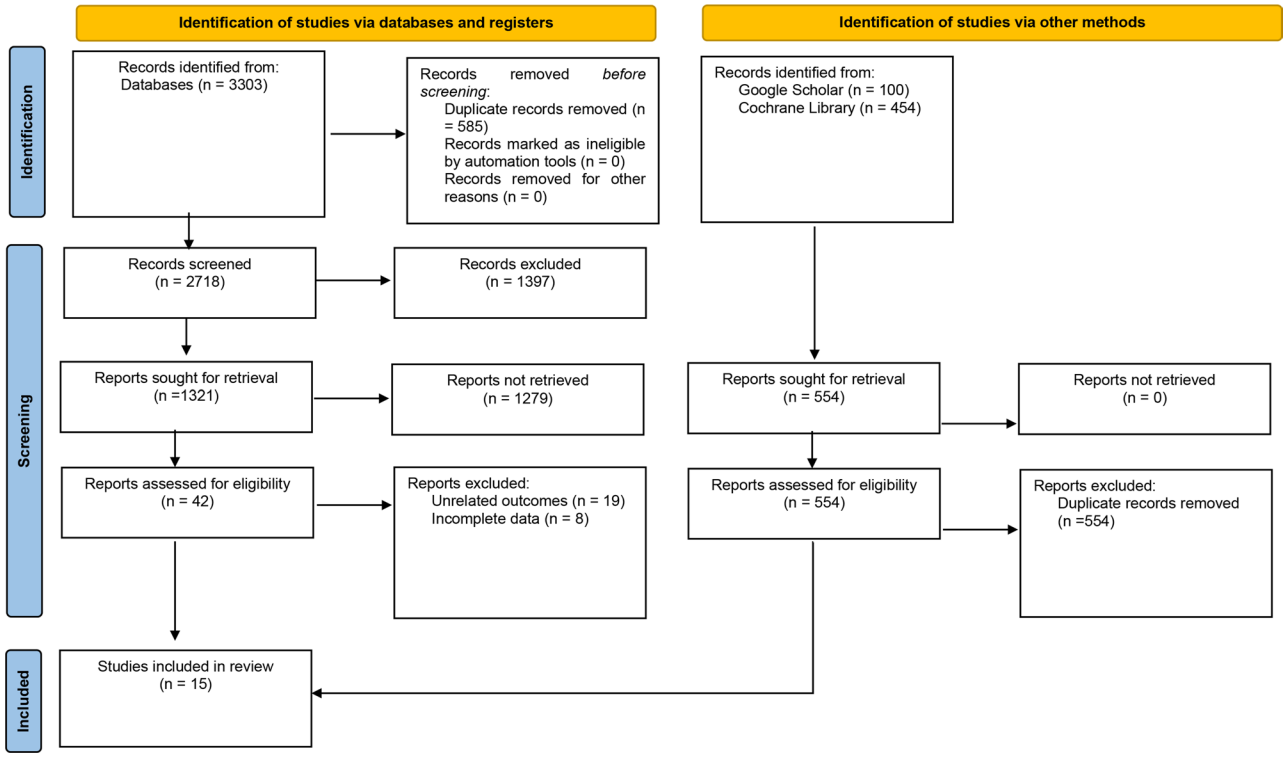

Fig. 1 Flow diagram of the study selection process

sICAM-1 [30–32, 36, 37], 4 studies for sVCAM-1 [30, 32, 36, 38], 6 studies IL-6 [30, 32, 34, 36–38], 3 studies for P-Selectin [30, 35, 38], 2 studies for E-selectin [30, 38], 2 studies for MCP-1 [35, 38], 2 studies for IFN-γ [35, 38] and 3 studies for TNFα [34, 38, 39] provided data on the comparison of mean changes. At the end of the screening process, the kappa statistics was 0.89. Upon completing the selection by full-text reading, the kappa coefficient reached 1.0 and there was a perfect agreement between reviewers.

We extracted two studies by the same author [31, 38] that involved the same population but had different study durations. Since the studies seemed to overlap, we decided to analyze only the study with the longer duration, which was also more comprehensive. However, since some parameters were not reported in the longer study, we had to refer to the shorter one for that information. Additionally, we found that the samples of two other studies conducted by Urpi-*Sarda et al.*, had overlap [13, 36]. In cases where a larger study with an extended follow-up period reported a relevant variable -such as ICAM-6- we prioritized it, as it provided data on a greater sample size and a longer intervention duration. However, if the larger study did not include our variables of interest, we incorporated data from a smaller study when it reported the necessary variables, ensuring comprehensive analysis and inclusion of relevant findings.

Characteristics of the included studies

All of the main characteristics of the eligible studies have been shown in the Table 1. This review included a total of 15 trials (20 arms) comprising 2477 adults with mean age of 23–80 years that were published between 2007 and 2023. Twelve studies were conducted in Spain [13, 31, 32, 35–43], 1 in Australia [33], 1 in Iran [34] and 1 intervention in the USA [30]. Totally, just 2 out of 15 studies applied cross-over design and all of the other interventions were parallel in design. Studies used MED supplemented with diverse types of olive oils as an intervention and the duration of the interventions and follow ups was between 1 months to 5 years. In total, 368 participants were elderly, 95 subjects were healthy, 46 cachectic patients (induced by colorectal cancer) and 1968 patients were with type 2 diabetes mellites (T2DM) or at high risk for CVD or with at least 2 or 3 CVD risk factors. In control groups, participants followed a western, low-fat or their own habitual diets or only received nutritional instruction with dietary recommendations in cancer.

Risk of bias assessment results

Overall and detailed studies' quality assessment are disclosed in Fig. 2. At overall, there was a low risk of bias for random sequence generation (selection bias) and selective reporting (reporting bias). Blinding of participants and personnel, and blinding of outcome assessment, a

Table 1 Main characteristics of the included studies

ID	The first author (publication year), Country	Sample size (Male/Female)	Target Population	Mean Age (or range of age)	Study design	Duration	The intervention of the experimental group	The intervention of the control group	Main Results	Side Effects
1	Bagheri (2023), Iran (34)	46 (32/14)	Cachectic Patients (Induced by Colorectal Cancer)	58.38 ± 9.94	RCT	2 m	MED + EVOO	Receiving nutritional instruction with dietary recommendations in cancer patients	IL-6 ↓ hs-CRP ↓ TNFα ↓	NM
2a	Casas (2017), Spain (38)	46 (27/19)	At a High Risk for CVD	67	Randomized	3y	MED + EVOO	LFD	IL-6 ↓ IFN-γ ↓ TNFα ↓ MCP-1↓ sICAM-1↔ sVCAM-1↔ E-selectin ↔	NM
2b	Casas (2017), Spain (38)	46 (19/27)	At a High Risk for CVD	67	Randomized	5y	MED + EVOO	LFD	IL-6 ↓ IFN-γ ↓ TNFα ↓ MCP-1↓ sICAM-1↔ sVCAM-1↔ E-selectin ↔	NM
3a	Davis (2017), Australia (33)	141	Older adults	≥ 65 y	RCT Parallel	3 m	MED + EVOO (15–45 ml/d)	HabDiet	hs-CRP ↔	NM
3b	Davis (2017), Australia (33)	137	Older adults	≥ 65 y	RCT Parallel	6 m	MED + EVOO (15–45 ml/day)	HabDiet	hs-CRP ↔	NM
4	Storniolo, (2015), Spain (43)	90	Older women	60–80	RCT Parallel	1y follow up	MED + VOO 52/72 ml/day	LFD	TAC ↑ MDA ↔	NM
5	Casas (2014), Spain (31)	109 (63/46)	At a High Risk for CVD	67.75 ± 6	Randomized	1y	MED + EVOO (50 ml/d)	LFD	IL-6 ↓ CRP ↓ sICAM-1↓ sVCAM-1↔ P-selectin ↓ E-selectin ↔	NM
6	Ceriello (2014), Spain (37)	24 (17/7)	T2DM	NR	Randomized	3 m	MED + EVOO (50 ml/d)	LFD	IL-6 ↓ sICAM-1↓	NM
7	Lasa (2014), Spain (39)	141 (61/80)	T2DM or ≥ 2 CVD risk factors	67.3 ± 6.5	RCT Parallel	1y	MED + VOO (1 L/Wk)	LFD	TNFα ↔	No adverse effect
8	Urpi-Sarda (2012), Spain (13)	341 (170/171)	T2DM or ≥ 3 CVD risk factors	66	RCT Parallel	1y	MED + VOO 143 ml/day	LFD	sICAM-1 ↓ IL-6 ↓	NM

Table 1 (continued)

ID	The first author (publication year), Country	Sample size (Male/Female)	Target Population	Mean Age (or range of age)	Study design	Duration	The intervention of the experimental group	The intervention of the control group	Main Results	Side Effects
9a	Urpi-Sarda (2012), Spain (36)	71	T2DM or ≥ 3 CVD risk factors	NR	RCT	3 m	MED + VOO (1 L/Wk)	LFD	CRP ↓ sICAM-1 ↓ sVCAM-1↓ IL-6 ↓	NM
9b	Urpi-Sarda (2012), Spain (36)	516	T2DM or ≥ 3 CVD risk factors	NR	RCT	1y	MED + VOO (1 L/Wk)	LFD	IL-6 ↓	NM
10	Konstantinidou, (2010), Spain (35)	59 (33/26)	Healthy	44 ± 11.54	RCT Parallel	3 m	Traditional MED + VOO	Habdiet	CRP ↓ P-selectin ↔ IFN-γ ↔	NM
11	Mena (2009), USA (30)	71 (36/35)	T2DM or ≥ 3 CVD risk factors	67.5 ± 8.8	RCT Parallel	3 m	MED + VOO	LFD	sICAM-1 ↓ IL-6 ↓ sVCAM-1 ↓ CRP ↓ P-selectin ↓ E-selectin ↔	No adverse effect
12	Corella (2009), Spain (32)	481	T2DM or ≥ 3 CVD risk factors	NR	RCT Parallel	3 m	MED + EVOO (1 L/Wk)	LFD	IL-6 ↓ sICAM-1↓ sVCAM-1↓ CRP ↔	NM
13	Razquin (2009), Spain (42)	124 (58/66)	T2DM or ≥ 3CVD risk factors	68.2 ± 5.9	RCT Parallel	3y follow up	MED-style diet + VOO 166 ml/day	LFD	BMI ↓ TAC ↑	NM
14a	Fuentes (2008), Spain (40)	20 (20/0)	Healthy	23·3 ± 1.5	Crossover	1 m	MED + VOO (%24 MUFA)	LFD enriched in ALA (%12 MUFA)	sVCAM-1 ↓ sICAM-1 ↔	NM
14b	Fuentes (2008), Spain (40)	20 (20/0)	Healthy	23·3 ± 1.5	Crossover	1 m	MED + VOO (%24 MUFA)	Western diet rich in SFA (%12 MUFA)	sVCAM-1 ↓ sICAM-1 ↔	NM
15a	Perez-Martinez (2007), Spain (41)	16 (16/0)	Healthy	NR	Crossover	1 m	MED + VOO (%24 MUFA)	Western diet rich in SFA (%12 MUFA)	sVCAM-1 ↓ sICAM-1 ↔ MCP-1 ↔ IL-6 ↔ TNFα ↔	NM
15b	Perez-Martinez (2007), Spain (41)	16 (16/0)	Healthy	NR	Crossover	1 m	MED + VOO (%24 MUFA)	LFD rich in ALA (%12 MUFA)	sVCAM-1 ↔ sICAM-1 ↔ MCP-1 ↔ IL-6 ↔ TNFα ↔	NM

Abbreviations: BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular disease; EVOO, extra virgin olive oil; m, month; HabDiet, habitual diet; hs-CRP, high sensitivity C-reactive protein; IFN-γ, Interferon gamma; IL-6, interleukin 6; LFD, low-fat diet; m, month; MCP-1, Monocyte Chemoattractant Protein-1; MED, Mediterranean diet; MUFA, mono unsaturated fatty acid; NM, not mentioned; NR, not reported; RCT, randomized clinical trial; SFA, saturated fatty acid; sICAM-1, soluble inter cellular adhesion molecule; sVCAM-1, circulating vascular cell adhesion molecule; TNFα, tumor necrosis factor α; T2DM, type 2 diabetes mellites; VOO, virgin olive oil; L/Wk, Liter per week; ml/d, milliliter per day; m, month; y, year

Fig. 2 Results of quality assessment. Risk of bias summary for included studies using the Cochrane risk-of-bias tool. The symbol "+" reports a low risk of bias, the symbol "–" reports a high risk of bias, and the symbol "?" reports an unclear risk of bias

challengeable problem in nutritional dietary trials, was evaluated as high for most of the included trials.

Outcome assessments

Systematic review findings

Overall, 9 out of 20 arms have reported CRP or hs-CRP that in 5 of them the levels of CRP have decreased significantly [13, 30, 31, 34, 35]. Considering IL-6, among 9 out of 15 interventions which reported this factor only in 1 study the results were notable [41]. Moreover, as shown in Table 1, MED supplemented with olive oils had positive impact on TNFα in 2 out of 4 studies [34, 38]. Regarding sICAM-1, in 6 out of 15 studies this parameter has remarkable reduction [13, 30–32, 36, 37]. Furthermore, the levels of sVCAM-1 in 5 out of 20 arms reduced significantly [13, 30, 32, 40, 41]. According to selectins, P-selectin levels have shown significant reduction among 2 out of 15 trials [30, 31], however, E-selectin levels was unchanged in all 4 out of 20 arms. In addition, between 4 out of 20 arms in which the MCP-1 was reported, only 1 study had significant outcomes [38] and finally, IFN-γ was reduced only in 2 out of 20 arms [38].

Meta-analysis findings

Overall, the results of our meta-analysis reviewed in Table 2.

Abbreviations: CRP, C-reactive protein; hs-CRP, high sensitivity C-reactive protein; IFN-γ, Interferon gamma; IL-6, interleukin 6; MCP-1, Monocyte Chemoattractant Protein-1; sICAM-1, soluble inter cellular adhesion molecule; sVCAM-1, circulating vascular cell adhesion molecule; TNFα, tumor necrosis factor α.

Table 2 Overall estimates of meta-analysis for the effect of MED enriched with Olive oils on inflammation and cell adhesion molecules

Variable	No. of study arms	Standardized Mean Difference (SMD)	*p* Value	Assessment of heterogeneity	
				I^2 (%)	Q-statistic *p* Value
IL-6	6	-1.854 (-3.694 to -0.013)	0.0484*	99.29	0.0000
CRP or hs-CRP	7	-0.968 (-1.496 to -0.440)	0.0003*	91.85	0.0000
TNFα	3	-0.746 (-1.612 to 0.121)	0.0919	87.61	0.0002
MCP-1	2	-1.51 (-1.421 to 1.120)	0.8160	89.94	0.0016
IFN- γ	2	-0.341 (-1.180 to 0.497)	0.4248	77.30	0.0358
sICAM-1	5	-2.366 (-4.336 to -0.395)	0.0186*	99.38	0.0000
sVCAM-1	4	-1.100 (-2.095 to -0.104)	0.0303*	94.96	0.0000
P-selectin	3	-0.651 (-1.179 to -0.124)	0.0155*	59.33	0.0866
E-selectin	2	0.093 (-0.295 to 0.482)	0.6378	00.00	0.5903

The effect of MED supplemented with Olive oils on inflammation

Considering Fig. 3, findings of 6 studies and combining their effect size have shown that.

following a MED enriched with olive oils can decrease the levels of IL-6 significantly *(SMD: -1.85; 95% CI: -3.69 to -0.01, I^2: 99.29%).* Moreover, this dietary pattern had a positive impact on the levels of CRP or hs-CRP *(SMD: – 0.96; 95% CI: -1.50 to -0.44, I^2: 91.85%).* However, our analyses did not show any significant effects on TNFα, MCP-1 and IFN- **γ** levels [*(SMD: – 0.75; 95% CI: -1.61 to 0.12, I^2: 86.61%), (SMD: – 0.15; 95% CI: -1.42 to 1.12, I^2: 89.94%) and (SMD: -0.34; 95% CI: -1.18 to 0.50, I^2: 77.30%), respectively.*]

The effect of MED supplemented with Olive oils on soluble adhesion molecules

Considering Fig. 4, our meta-analyses have shown favorable results for the levels of sICAM-1 and sVCAM-1 [*(SMD: -2.37; 95% CI: -4.34 to -0.40, I^2: 99.38%)* and *(SMD:-1.10; 95% CI: -2.10 to -0.10, I^2: 94.96%*, respectively] after combining their effect sizes. Moreover, we obtained remarkable findings for beneficial effect of following this enriched dietary pattern on P-selectin levels *(SMD: -0.65; 95% CI: -1.18 to -0.12, I^2: 59.33%).* However, combining the effect sizes of 2 studies for E-selectin, did not reveal any significant consequences *(SMD: -0.09; 95% CI: -0.30 to 0.48, I^2: 00.00%).*

Finding the sources of heterogeneity

Galbraith plot and sensitivity analysis

Considering to Galbraith plots in Appendix 2, for IL-6 *Corella et al., Bagheri et al., Mena et al. and Ceriello et al.* studies [30, 32, 34, 37] and for CRP or hs-CRP *Mena et al., Corella et al., Bagheri et al.* seem to be the sources of heterogeneity [30, 32, 34]. Moreover, for TNFα the studies of *Bagheri et al. and Lasa et al.* are out of the gray region and it would be possible that these studies are the regarding source of heterogeneity [34, 39]. According to the Galbraith plots for sICAM-1, *Ceriello et al., Mena et al., Casas et al., and Urpi-Sarda et al.* studies [30, 31, 36, 37] and for sVCAM-1, *Mena et al.* and *Corella et al.* can be heterogenic [30, 32]. For P-selectin none of the studies in Galbraith plot for P-selectin have revealed heterogeneity.

According to the findings of Sensitivity analyzes shown in Table 3, the level of each variable changed statistically significant after excluding the mentioned studies ($p < 0.05$). Therefore, these studies could consider to be the source of the heterogeneity.

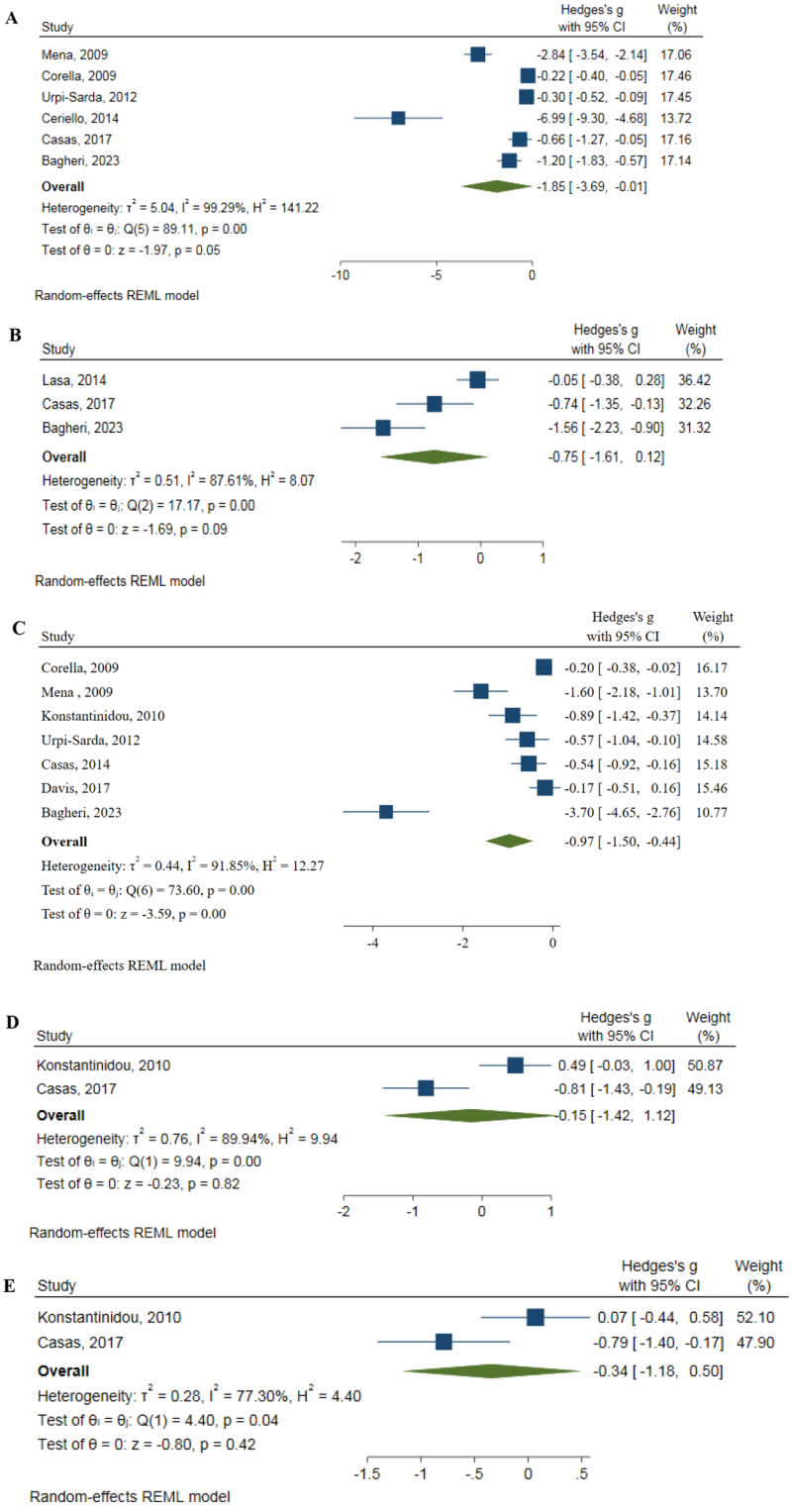

Fig. 3 Forest plot of the effect of Mediterranean diet supplemented with olive oils on Inflammatory biomarkers. (**A**) IL-6: Interleukin-6. (**B**)TNFα: Tumor Necrosis Factor α. (**C**) CRP or hs-CRP: C-reactive Protein or High-sensitive C-reactive Protein. (**D**)MCP-1: Monocyte Chemoattractant Protein-1. (**E**) IFN- γ: Interferon gamm

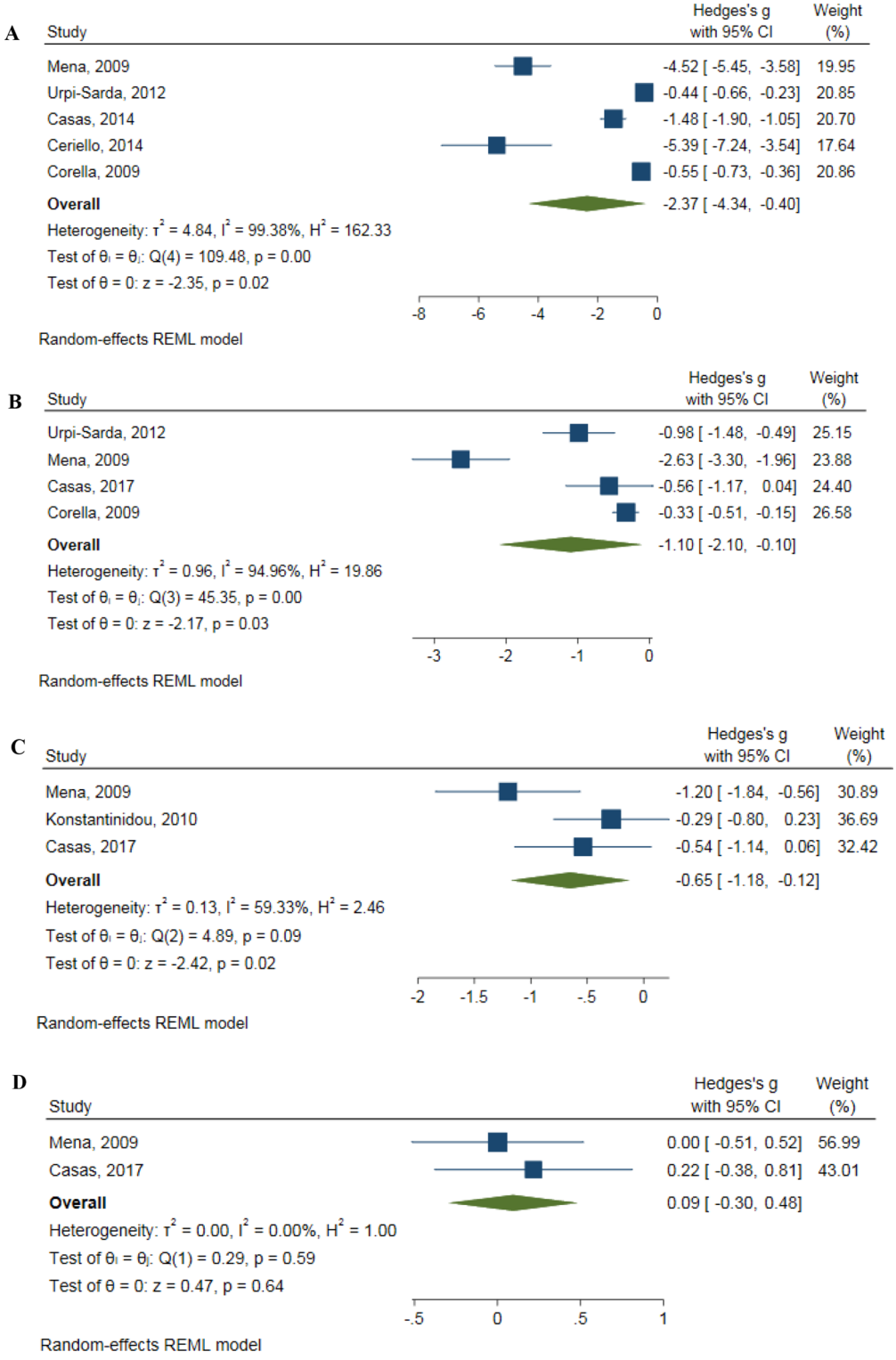

Fig. 4 Forest plot of the effect of Mediterranean diet supplemented with olive oils on Soluble Adhesion Molecules. (**A**) sICAM-1: Soluble Intercellular Adhesion Molecule-1. (**B**) sVCAM-1: Soluble Vascular Adhesion Molecule-1. (**C**) P-selectin. (**D**) E-selectin

Table 3 Results of sensitivity analysis

Variable	Omitted Study	Standardized Mean Difference (SMD)	*p* Value
IL-6	*Mena et al. (30)*	-1.691 (-3.947 to 0.566)	0.142
	Casas et al. (38)	-2.138 (-4.393 to 0.117)	0.063
	Bagheri et al. (34)	-2.034 (-4.348 to 0.279)	0.085
TNFα	*Casas et al. (38)*	-0.777 (-2.260 to 0.707)	0.305
	Bagheri et al. (34)	-0.344 (-1.014 to 0.327)	0.315
sICAM-1	*Ceriello et al. (37)*	-1.705 (-3.523 to 0.113)	0.066
	Mena et al. (30)	-1.816 (-3.907 to 0.275)	0.089
sVCAM-1	*Casas et al. (38)*	-1.284 (-2.610 to 0.043)	0.058
	Urpi-Sarda et al. (36)	-1.151 (-2.567 to 0.266)	0.111
P-selectin	*Casas et al. (38)*	-0.724 (-1.620 to 0.172)	0.113

Table 4 Results of meta-regression analysis

Meta-regression		Coefficient (SE)	*p* Value
IL-6	Mean Age	-0.036 (0.181)	0.840
	Duration	0.031 (0.048)	0.511
	Male percent	-0.103 (0.110)	0.352
CRP or hs-CRP	Mean Age	0.028 (0.047)	0.547
	Duration	0.121 (0.093)	0.198
	Male percent	-0.118 (0.048)	0.014*
sICAM-1	Duration	0.265 (0.216)	0.219

Table 5 Results of Egger and Begg's analyses

Variable	Egger test *p* Value	Begg's test *p* Value
IL-6	< 0.001	0.0242
CRP or hs-CRP	< 0.001	0.0027
TNFα	0.0128	0.2963
sICAM-1	< 0.001	0.2207
sVCAM-1	0.1847	0.3082
P-selectin	0.0612	0.2963

Table 6 Results of trim-and-fill analyses

Variable	No. of studies		Effect size (95% CI)	
	Observed	imputed	Observed	Observed + Imputed
IL-6	6	3	-1.854 (-3.694 to -0.013)	-0.317 (-2.525 to 1.891)
CRP or hs-CRP	7	3	-0.968 (-1.496 to -0.440)	-0.312 (-0.886 to 0.263)
TNFα	3	2	-0.746 (-1.612 to 0.121)	-0.048 (-1.063 to 0.967)
sICAM-1	5	2	-2.366 (-4.336 to -0.395)	-0.697 (-3.297 to 1.904)

Subgroup and meta-regression analyses

Regarding Table 4, after conducting meta-regression analysis we only observed a linear relationship between the percent of male and CRP or hs-CRP ($p = 0.014$). Moreover, as it has been shown in bubble plot, when the percent of men in the study population increased, the level of CRP or hs-CRP was decreased Appendix 3

Publication bias

According to Table 5, there are publication biases in the studies on IL-6, CRP or hs-CRP, TNFα, and sICAM-1 levels. Therefore, in order to improve our estimations, we performed trim-and-fill analysis on these variables (Table 6). Considering trim-and-fill results and related funnel plots (Appendix 4), apart from the presence of publication bias, there was a certain degree of asymmetry of the data distribution and an overestimation of the overall effect size of MED enriched with olive oils in IL-6, TNFα and sICAM-1. As a result, the number of probable missed studies for IL-6, TNFα, sICAM-1 and CRP or hs-CRP were 3, 2, 2 and 3 interventions, respectively

Discussion

As far as we know, the present meta-analysis is the first to analyze the effects of following a MED enriched by olive oils on systemic inflammation and soluble adhesion molecules

Systemic inflammation

The findings of present meta-analysis revealed that following a MED pattern which is supplemented with olive oils has positive impacts on inflammatory status. For assessing this effect, we analyzed CRP or hs-CRP, IL-6, TNFα, MCP-1 and IFN-γ data of 9 interventions. Although TNFα, MCP-1 and IFN-γ status did not reveal notable changes, our results demonstrated a remarkable improvement in the levels of major inflammatory biomarkers including CRP, hs-CRP and IL-6

Overall, in inflammatory conditions, IL-6 is one of the indispensable inflammatory cytokines which is released by T cells and macrophages. Liver in response to increased IL-6, is synthesizing CRP, an acute-phase protein and a general biomarker of inflammation [44]. Several previous in vitro and in vivo studies demonstrated that MED and its components, especially olive oils play a pivotal role in improving the Inflammation status. Regarding prior interventions, the anti-inflammatory effects of olive oils especially EVOO related to its major polyphenolic compounds including Oleocanthal, Oleuropein, and Hydroxytyrosol [45]. For instance, in a preclinical intervention, dietary Oleocanthal due to activating nuclear factor erythroid-2 related factor 2/heme oxygenase-1 (Nrf-2/HO-1) axis and inhibiting Janus kinase-signal transduction and activation of transcription (JAK-STAT) signaling pathway transducers and activators, mitogen-activated protein kinases (MAPKs) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathways leads to diminishing cyclooxygenase-2 (COX-2), Microsomal prostaglandin

E synthase-1 (mPGES-1) and inducible nitric oxide synthase (iNOS) protein expression and also Prostaglandin E_2 (PGE2) [46]. Another in vitro study demonstrated that adding phenolic fraction (PE) extracted from EVOO to peripheral blood mononuclear cells (PBMC) from inactive patients with systemic lupus erythematosus (SLE) and healthy donors by decreasing the frequency of cluster of differentiation 69 ($CD69^+$) cells can lead to modulating the production of inflammatory cytokines including IL-6, TNFα and IFN-γ. It seems that PE can increase the expression of the anti-inflammatory gene -I-kappa-B alpha (IκBα)- and decreased extracellular signal regulated kinase phosphorylation on PBMC [47]. Moreover, in a clinical intervention on elderly people, after consumption of a MED compared with saturated fatty acid rich (SFA-rich) and carbohydrate and polyunsaturated fatty acid rich (CHO-PUFA-rich) diets, the expression of inflammatory genes such as MCP-1 and TNFα decreased, respectively and the expression of IκBα increased [48]. Furthermore, according to *Yarla et al.*. a long-term olive oil consumption can modulate TNFα and IL-6, which are crucial in chronic low-grade inflammation associated with obesity-related conditions and frailty. In addition, olive oil has an anti-inflammatory effect through crosstalk between adipose tissue, liver, skeletal muscle, and brain and this positive property can enhance when consumes with a MED [49]

However, previous studies have demonstrated that MED or olive oils consumption have beneficial effects on the levels of TNFα, MCP-1 and IFN-γ we did not find any significant positive changes. Moreover, regarding a previous meta-analysis, although TNFα is a major biomarker in inflammatory responses, it has been rarely assessed in epidemiological clinical interventions conducted on olive oils and its levels were unchanged statically [50]

Soluble adhesion molecules

In total, the present study revealed that following a MED enriched and supplemented with olive oils can diminish the levels of sICAM-1, sVCAM-1 as well as P-selectin significantly. However, the level of E-selectin was unchanged

According to previous studies, on one hand, the soluble adhesion molecules such as sICAM-1, sVCAM-1, P-selectin and E-selectin by mediating inflammation, endothelial dysfunction, and development of micro and macrovascular complications are responsible for many disorders like T2DM [51]. On the other hand, the accumulation of soluble adhesion molecules can lead to endothelial dysfunction and thus appear in vascular lesions. The production of these molecules is stimulated by inflammatory cytokines such as TNFα. Therefore, one of the probable mechanisms as mentioned above, is associated with the polyphenolic capacity of olive oils and its anti-inflammatory role [52]. Other mechanisms that are worth mentioning are related to some preclinical studies. These in vitro interventions revealed that Oleocanthal by exhibiting a downregulatory effect on the gene expression of sICAM-1 can decrease the level of these molecules. Moreover, this component by decreasing the high mobility group box 1 (HMGB1), whose stimulation induced the expression of sICAM-1 and sVCAM-1 on the surface of endothelial cells has beneficial effects [53–55]. Regarding P-selectins, a previous study conducted on patients with severe obesity demonstrated that consumption of olive oil can reduce the unstimulated surface P-selectin expression as a marker of platelet activation [56]. Moreover, *Ed Nignpense et al.*, and *Ruina Zhang et al.*, formerly hypothesized that some of the polyphenols such as hydroxytyrosol which exist in olive oil can lead to decrease activation signaling inhibition, reduction of the degranulation, and suppress the surface P-selectin translocation due to blocking receptor-agonist interactions, such as protease activated receptor-1 (PAR1)-thrombin binding [56, 57]

Clinical implications of findings

Our significant findings provide clinicians and healthcare practitioners with valuable insights for recommending dietary interventions to patients suffering from metabolic conditions, especially those related to inflammation. For individuals with T2DM, CAD or CVD, adherence to a MED enriched with olive oils has shown potential in improving their clinical status. The observed reductions in key inflammatory biomarkers, such as CRP and IL-6, suggest that olive oil supplementation may play a crucial role in mitigating systemic inflammation and enhancing metabolic health

Furthermore, for healthy adults, the Mediterranean diet supplemented with olive oils serves as a powerful preventive strategy, significantly reducing the risk of developing chronic inflammatory conditions or CVD. The improvements in endothelial function, reflected in the decreased levels of soluble intercellular adhesion like sICAM-1 and sVCAM-1 as well as P-selectin, indicate protective effects against vascular dysfunction and atherosclerosis progression. Additionally, the absence of adverse effects on liver function and blood pressure highlights the safety and tolerability of this dietary approach across different populations

Clinicians should consider tailoring dietary recommendations based on individual patient characteristics to maximize therapeutic benefits. Optimizing olive oils intake within a Mediterranean diet framework may serve as both a treatment and preventive measure, contributing to better metabolic and cardiovascular outcomes

Strength and limitation

This systematic review and meta-analysis revealed that following an enriched MED with olive oils, has a great positive impact on Inflammation status and reinforces its role in improving cardiovascular health through aforementioned mechanism. A key strength of this study is its inclusion of multiple RCTs, which enhances the reliability and robustness of the findings. Additionally, the assessment of both pro-inflammatory biomarkers and soluble adhesion molecules offers a comprehensive evaluation of the diet's impact on inflammation and endothelial function. However, notable limitations exist. For instance, the high heterogeneity observed among studies for some outcomes. Despite using subgroup analysis and finding sources of heterogeneity in some subgroups, heterogeneity was still significant. It may stem from variations in study designs, sample sizes, intervention durations, and population characteristics. Moreover, the number of eligible trials for entering in the meta-analysis was limited and most of the studies were performed in Spain. Additionally, the number of interventions that evaluated TNFα, MCP-1, IFN-γ and E-selectin was relatively small (up to 3 studies). Furthermore, while the findings support the beneficial effects of olive oils supplementation, the relatively short follow-up periods in many included trials limit conclusions regarding long-term health outcomes. In addition, most of the studies had a high risk of bias, particularly in terms of randomization and blinding. As publication bias had a significant effect in our results and considering trim and fill analysis, the results may have not enough robustness and more studies are needed to clarify this association

Future research directions

While this meta-analysis highlights the anti-inflammatory effects of the MED supplemented with olive oils, future research should aim to address key gaps and limitations to enhance the understanding and applicability of these findings. Larger-scale, long-term randomized RCTs with standardized methodologies and diverse populations are needed to evaluate the sustained and positive impact of the MED enriched with olive oils on pro-inflammatory biomarkers and cardiovascular health. Standardized methodologies, including consistent dosages, duration of interventions, and biomarker assessments, would help reduce study heterogeneity and improve comparability across RCTs. Additionally, exploring potential synergistic effects of olive oils with other MED components -such as polyphenol-rich foods, seafood, nuts and whole grains- could provide deeper insights into its mechanistic pathways. Further investigations into genetic and metabolic variations influencing individual responses to the MED may also help personalize dietary recommendations for optimal health benefits. Ultimately, future research should integrate clinical, biochemical, and molecular approaches to solidify the role of olive oils-enriched MED in inflammation management and CVD prevention

Conclusion

MED exerts significant anti-inflammatory effects, notably reducing IL-6, CRP or hs-CRP, and sICAM-1, sVCAM-1 and P-selectin levels. These findings underscore the potential of the MED in mitigating cardiovascular risk and improving overall health outcomes. However, the observed high heterogeneity among studies, coupled with limitations such as small sample sizes and short follow-up durations, necessitate caution in interpreting the results. Future research should focus on larger-scale, long-term studies to explore the underlying mechanisms and assess the generalizability of these findings across diverse populations

Abbreviations

CVD	Cardiovascular disease
MED	Mediterranean diet
IL-6	Interleukin-6
CRP	c-reactive protein
hs-CRP	high-sensitivity CRP
TNFα	tumor necrosis factorα
MCP-1	monocyte chemoattractant protein-1
IFN-γ	interferon gamma
sICAM-1	soluble intercellular adhesion molecule-1
sVCAM-1	soluble vascular cell adhesion molecule-1
CHD	Coronary heart disease
WHO	World Health Organization
EFA	essential fatty acids
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
SMD	standardized mean difference
Nrf-2/HO-1	factor erythroid-2 related factor 2/heme oxygenase-1
JAK-STAT	janus kinase-signal transduction and activation of transcription
MAPKs	mitogen-activated protein kinases
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cells
COX-2	cyclooxygenase-2
mPGES-1	microsomal prostaglandin E synthase-1
iNOS	inducible nitric oxide synthase
PGE2	prostaglandin E_2
PE	phenolic fraction
EVOO	extra virgin olive oil
PBMC	peripheral blood mononuclear cells
SLE	systemic lupus erythematosus
$CD69^+$	cluster of differentiation 69
IκBα	I-kappa-B alpha
CHO-PUFA-rich diet	carbohydrate and polyunsaturated fatty acid rich diet
HMGB1	high mobility group box 1
PAR1	protease activated receptor-1
VOO	virgin olive oil

Supplementary Information

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Supplementary Material 1

Author contributions
M.K. Study design. Data collection. Data interpretation. Manuscript review. S.D.T. Study design. Data collection. Data interpretation. Manuscript writing. Manuscript review. N.D. Data collection. ARA. Data interpretation. Data analysis. Manuscript review. All authors read and approved the final manuscript.

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No ethical approval was required as this study did not involve human participants or laboratory animals.

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Competing interests
The authors declare no competing interests.

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