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Effects of the Mediterranean Diet on Gut Microbiota Composition and Diversity in Overweight and Obesity: A Scoping Review of Randomized Controlled Trials

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Abstract

Background: *The Mediterranean diet (MedDiet) is widely associated with anti-inflammatory and metabolic benefits, and gut microbiota modulation has been proposed as a critical mechanistic pathway. However, evidence from randomized controlled trials (RCTs) remains fragmented, and it is unclear whether MedDiet produces consistent microbiome changes in overweight and obese populations.*

Objective: *To systematically map and synthesize evidence from RCTs evaluating the effects of MedDiet interventions on gut microbiota composition, inflammatory biomarkers, and metabolic outcomes in adults with overweight or obesity.*

Methods: *A scoping review was conducted following PRISMA-ScR guidelines. PubMed, Embase, and Scopus were searched through May 2025 for RCTs evaluating MedDiet interventions in adults with BMI $\geq$ 25 kg/m^2 without the use of microbiota-targeted supplementation. Primary outcomes included gut microbiota composition and diversity. Secondary outcomes included inflammatory biomarkers (CRP, IL-6, TNF-α) and anthropometric or metabolic measures. Risk of bias was assessed using the RoB 2 tool.*

Results: *Eight RCTs met inclusion criteria, of which four evaluated gut microbiota directly. MedDiet interventions were associated with selective enrichment of metabolically favorable taxa, including short-chain-fatty-acid–producing genera such as Roseburia, Faecalibacterium, and Akkermansia, supporting biologically plausible pathways linking diet to metabolic and inflammatory regulation. However, global diversity metrics—including alpha diversity and Firmicutes/Bacteroidetes ratio—showed inconsistent or non-significant changes across studies. Improvements in inflammatory markers and anthropometric outcomes were more consistently observed than microbiota diversity shifts. Notably, comparator diets—including low-fat, ketogenic, and low-carbohydrate regimens—also produced microbiome changes, highlighting the difficulty in isolating MedDiet-specific microbial effects. Substantial heterogeneity in intervention design, duration, microbiome analysis methods, and outcome prioritization limited cross-trial comparability.*

Conclusion: *Evidence from randomized trials suggests that the Mediterranean diet may exert metabolically relevant effects through selective modulation of specific microbial taxa rather than uniform changes in global microbiome diversity. While inflammatory and metabolic improvements are consistently observed, microbiota-mediated mechanisms remain incompletely characterized. Future RCTs should incorporate standardized microbiome endpoints, longer follow-up, and mechanistic analyses to clarify causal pathways and distinguish MedDiet-specific effects from broader dietary influences.*

Introduction

The gut microbiome plays an essential role in maintaining host health, contributing to nutrient metabolism and regulation of the immune system. It has emerged as a key mediator in the development of chronic diseases characterized by low-grade systemic inflammation, such as obesity and metabolic syndrome (Gill et al., 2022). Obesity affects more than one billion people worldwide and is a major contributor to chronic disease and premature death (Brauer et al., 2024). In these patients, the gut microbiome is disrupted, with reduced diversity and enrichment of pro-inflammatory species linked to insulin resistance and metabolic dysfunction (Gill et al., 2022).

Dietary interventions are known to influence gut microbiota composition, and diet quality has been increasingly recognized as an independent factor modulating inflammation and gut health, beyond caloric restriction (The GBD 2015 Obesity Collaborators, 2017). Among the various dietary patterns investigated, the MedDiet is one of the most consistently studied anti-inflammatory dietary patterns, often associated with improvements in metabolic health and favorable microbial profiles (Ciobârcă et al., 2020; Rinninella et al., 2023). A systematic review and meta-analysis by Koelman et al. identified the MedDiet as the dietary pattern with the most prominent anti-inflammatory effects, with significant reductions in biomarkers such as IL-6, IL-1β, and CRP (Koelman et al., 2022).

The MedDiet was first defined in the 1960s in Greece and southern Italy as being low in saturated fat and rich in vegetable oils (Martínez-González & Sánchez-Villegas, 2004). General descriptions of the MedDiet are similar across publications, emphasizing the same main components: high intake of extra virgin olive oil, vegetables, fruits, cereals, nuts, and legumes; moderate intake of fish and other meats, dairy products, and red wine; and low intake of eggs and sweets (Willett et al., 1995). The frequency and quantities of these foods vary depending on the indications for their use.

When we associate diet with obesity issues, several studies have reported reduced microbial diversity and richness in obesity, often accompanied by an increased Firmicutes/Bacteroidetes ratio, a feature commonly associated with obese phenotypes (Ciobârcă et al., 2020; Koelman et al., 2022; Rinninella et al., 2023). Certain taxa are frequently inversely correlated with obesity, supporting their potential probiotic role (Martínez-González & Sánchez-Villegas, 2004).

Despite growing interest, evidence on how the MedDiet modulates the gut microbiome and inflammatory pathways in obesity remains inconsistent. Many randomized controlled trials (RCTs) have combined the MedDiet with additional interventions such as physical activity programs, caloric restriction, or supplementation, or there are results that relies mainly on observational studies making it difficult to isolate the diet's independent effects (Galié et al., 2021; Meslier et al., 2020). Furthermore, studies vary widely in their definitions of the MedDiet, duration of intervention and methods used to assess microbiota and inflammatory biomarkers, limiting comparability and reproducibility (Khavandegar et al., 2024; Perrone & D'Angelo, 2025). This scoping review aimed to systematically map available RCTs, clarifying the effects of the MedDiet on gut microbiota composition, systemic inflammatory biomarkers and metabolic outcomes in adults with overweight and obesity.

Materials and Methods

This scoping review was conducted in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines. The review aimed to map and summarize clinical evidence on the effects of the MedDiet on gut microbiota composition, inflammatory biomarkers, and anthropometric or metabolic outcomes in adults with overweight or obesity. The protocol was developed a priori following the Population–Concept–Context (PCC) framework. A comprehensive search was performed across electronic databases (PubMed, Scopus and Embase) from April 17, 2025, with the last update conducted on May 4, 2025, using a combination of controlled vocabulary (e.g., MeSH terms) and free-text keywords related to "Mediterranean diet," "microbiota," "obesity," and "inflammation." The search strategy was adapted for each database. Reference lists of relevant articles were manually screened to identify additional studies.

Search strategy

A combination of keywords and Medical Subject Headings (MESH) terms was employed using Boolean operators. The following search string was developed using keywords and MeSH Terms:

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Editor: Felipe Fregni
Reviewers: Ingrid Galvis, Lavinia Rech, Fernando Camacho-Palma, Olivier Clerc
Keywords: mediterranean diet, gut microbiota, obesity, inflammation, randomized controlled trial, dietary intervention
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((obes*[tw]) OR (abdominal obesity[MeSH Terms]) OR (central obesity[MeSH Terms]) OR (obesity [MeSH Terms]) OR (obesity, abdominal [MeSH Terms])) AND ((diet, mediterranean [MeSH Terms]) OR (diets, mediterranean [MeSH Terms]) OR (Mediterr*[tw])) AND ((microbiota[MeSH Terms]) OR (microbiotas[MeSH Terms]) OR (human microbiome[MeSH Terms]) OR (Gastrointestinal Microbiome[Mesh]) OR (Cytokines[MeSH]) OR (Interleukins[MeSH]) OR (Inflammation Mediators[MeSH]). Results: PubMed: 146 results; Embase: 1,480 results; Scopus: 692 results.

Inclusion and exclusion criteria

Full texts of potentially relevant studies were assessed for inclusion. Discrepancies were resolved by discussion and consensus. Studies were included if they were (1) clinical trials or intervention studies in adults ($\geq$ 18 years), (2) conducted in participants with BMI $\geq$ 25, (3) evaluated adherence to or the effects of a Mediterranean dietary pattern, including both isocaloric and hypocaloric interventions, with or without caloric restriction, and (4) reported outcomes related to gut microbiota, inflammation, or metabolic/anthropometric parameters. Studies combining MedDiet with supplements, pre/probiotics, or other dietary regimens were excluded. Studies were excluded if they combined the MedDiet with supplements, pre/probiotics, or other dietary regimens, if participants had a BMI $\leq$ 25, or if they involved animal models, participants under 18 years of age, or pregnant individuals. Although our initial focus was on randomized controlled trials (RCTs) to assess the specific effect of the MedDiet, the limited number of available RCTs led us to adopt a scoping review approach. Nevertheless, we included only studies that were RCTs to ensure methodological rigor while capturing all relevant evidence. The primary outcome of interest was changes in gut microbiome composition, including shifts in the Firmicutes/Bacteroidetes ratio and other measures of microbial diversity. Secondary outcomes encompassed inflammatory biomarkers, such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), as well as anthropometric and metabolic parameters, including weight, body mass index (BMI), and insulin sensitivity. All articles were screened and selected according to these eligibility criteria to ensure consistency and reproducibility.

Selection of studies

All identified records were imported into Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia, 2025; available at www.covidence.org) for management, screening, and deduplication. Three researchers independently searched all databases to ensure comprehensive coverage. After automatic and manual removal of duplicates, two reviewers independently screened titles and abstracts for relevance. Records that met the inclusion criteria during this initial screening were then assessed in full text according to predefined inclusion and exclusion criteria.Disagreements at either stage were resolved by consensus with a third reviewer. The study selection process is detailed in Figure 1 (PRISMA flow diagram).

Data extraction

Data extraction was performed independently by two reviewers using a standardized form within Covidence (Veritas Health Innovation, Melbourne, Australia, 2025). Extracted information included study characteristics (author, year, country, design, sample size), participant profile, dietary interventions and comparators, follow-up duration, and reported outcomes. The extracted dataset was exported to a spreadsheet and manually standardized (terminology, units, and variable categories).

Findings were summarized descriptively and organized into three thematic domains: (1) gut microbiota, (2) inflammation, and (3) anthropometric–metabolic outcomes. Two reviewers verified all extracted data and resolved any discrepancies by consensus.

Data Synthesis

Given the heterogeneity across studies design, populations, definitions, and reporting formats a qualitative narrative synthesis was undertaken. Discrepancies were resolved by consensus.

Risk of Bias Assessment

The methodological quality of included studies was appraised using the Revised Cochrane Risk-of-Bias tool for Randomized Trials (RoB 2) (Sterne et al., 2019). Two reviewers independently assessed each study across the five domains: Randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, selection of reported results.

Each domain was rated as low risk, some concerns, or high risk of bias. Discrepancies were resolved through consensus or by consulting a third reviewer. Results were visualized using the Robvis online tool

for graphical representation of bias assessments.

Results

Description of the studies

The search across the 3 databases identified a total of 2395 records. After eliminating duplicates, 1623 records were screened based on titles and abstracts, and 153 full-text articles were further assessed for eligibility. Ultimately, 8 studies (Buscemi et al., 2009; Deledda et al., 2022; Esposito et al., 2003; Georgoulis et al., 2021; Haro et al., 2016, 2017; Urpi-Sarda et al., 2012; Vitale et al., 2021) were included in this scoping review. The study selection process is outlined in the flow chart in Figure 1. The key characteristics of the included studies are summarized in Table 1.

Population

The included RCTs enrolled adults with overweight or obesity in free-living/outpatient settings. Reported ages ranged from approximately 18 to 80 years, predominantly middle-aged. No sex restrictions were prespecified; included trials enrolled men, women, or both. BMI was typically $\geq$ 25 kg/m^2, with study-specific upper ranges up to approximately 40 kg/m^2 when reported.

Two studies (Deledda et al., 2022; Urpi-Sarda et al., 2012) included individuals with type 2 diabetes or high cardiovascular risk, while others enrolled metabolically healthy participants (Buscemi et al., 2009; Vitale et al., 2021). Georgoulis et al. focused on patients with obstructive sleep apnea, and Haro et al. investigated participants with coronary heart disease or metabolic syndrome (Georgoulis et al., 2021; Haro et al., 2016, 2017). In the CORDIOPREV studies, Haro et al. (2016) and Haro et al. (2017) enrolled independent cohorts with different sample sizes and follow-up durations; thus, Haro et al. (2017) is not a continuation of Haro et al. (2016).

Regarding sex distribution, two studies included only women (Buscemi et al., 2009; Esposito et al., 2003), one enrolled only men (Haro et al., 2016), and the remaining studies included both sexes.

In addition, comorbidity profiles and medication use differed: several studies included drug-naïve participants (Deledda et al., 2022), while others recruited individuals under standard therapy for chronic conditions (Haro et al., 2016; Urpi-Sarda et al., 2012).

Intervention characteristics

Across studies, MedDiet interventions shared core features, including emphasis on minimally processed foods, EVOO as the principal fat, and high intake of vegetables, fruits, legumes, whole grains, nuts, and fish, yet differed in energy targets, fat distribution, delivery, and follow-up. Comparators included low-fat diets, very-low-carbohydrate/ketogenic protocols, Atkins-type hypocaloric diets, habitual Western-type diets, or standard care.

Several trials aimed to match or control total energy intake (e.g., Vitale isocaloric; Buscemi fixed kcal/kg; Deledda matched restriction across intervention/control; Esposito prespecified calorie targets for the intervention), but this was not consistently reported by Haro and Georgoulis. Delivery modes ranged from structured meal plans and provision of foods (EVOO/nuts or low-fat staples) to intensive behavioral counseling. Adherence was variably assessed by dietary diaries, counseling visits, or was not reported.

In most trials, the MedDiet was contrasted with a low-fat or low-carbohydrate/ketogenic control, creating clear macronutrient and fat-quality contrasts; Vitale minimized confounding by matching energy and macronutrients at the meal level, while Esposito and Georgoulis layered behavioral components (activity/sleep) onto diet, testing diet-only versus diet-plus-lifestyle effects. Provision of EVOO/nuts (Urpi-Sarda et al., 2012) and olive-oil standardization (Haro et al., 2016) improved fidelity to MedDiet principles and internal validity.

Follow-up ranged from very short durations of 2–3 months (Buscemi et al., 2009; Deledda et al., 2022; Vitale et al., 2021) to intermediate durations of 6–12 months (Georgoulis et al., 2021; Haro et al., 2016; Urpi-Sarda et al., 2012) and long-term durations of 24 months (Esposito et al., 2003; Haro et al., 2017).

Comparator description

In this review, we defined that the MedDiet would be compared against any other dietary pattern, regardless of caloric content or macronutrient composition, to capture the full range of potential contrasts. Across the included studies, control interventions varied considerably, reflecting different dietary models used for comparison with the MedDiet. Deledda compared it to a very low-calorie ketogenic diet (VLCKD), characterized by severe carbohydrate restriction, marked caloric deficit, and gradual carbohydrate reintroduction after two months, transitioning to a Mediterranean pattern. Vitale used a habitual Western diet as control, matched for total energy and macronutrients but differing in protein source (animal vs. plant-based), saturated fat, fiber content, and glycemic index/load. Haro (2016) reported that participants in the low-fat,

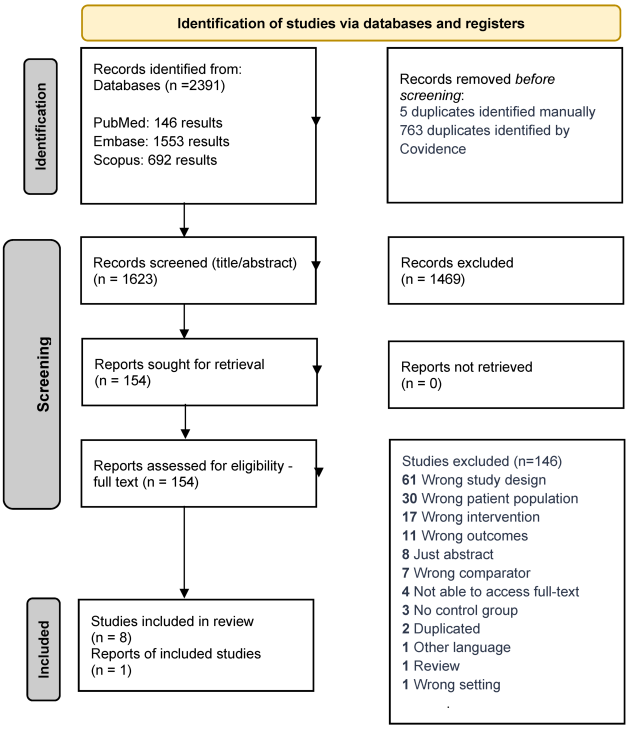

Figure 1: *PRISMA flow diagram of study selection process.*

Author	Title	Population	Sample size	Dropout	Intervention	Control	Follow up	Timepoints	Number of arms	Subgroup of another study	Outcomes
Deledda 2022	Dynamics of Gut Microbiota and Clinical Variables after Ketogenic and Mediterranean Diets in Drug-Naïve Patients with Type 2 Diabetes Mellitus and Obesity	Aged 45-65 years; newly diagnosed and not complicated T2DM; BMI≥28 Kg/m2; drug-naïve patients for T2DM	12	1	MedDiet	Very low-calorie ketogenic diet (VLCKD)	3 months	T0, T2M, T3M	2	No	Gut microbiome (Firmicutes/Bacteroidetes ratio, microbial diversity), Body composition, Biochemical improvements (glucose, insulin, HbA1c)
Vitale 2021	Acute and chronic improvement in postprandial glucose metabolism by a diet resembling the traditional Mediterranean dietary pattern: Can SCFAs play a role?	Adults aged 20–60 years; overweight/obesity (BMI 25–35 kg/m²)	33	4	Isocaloric compared to their habitual diets but had the features of the traditional MedDiet	Maintained their habitual diets, which had the typical features of a western diet	8 weeks	T0, T2M	2	No	Gut microbiome (SCFAs, microbial diversity), Body composition, Biochemical improvements (glucose, insulin, lipid profile)
Haro 2016	Two Healthy Diets Modulate Gut Microbial Community Improving Insulin Sensitivity in a Human Obese Population	Obese men aged 20-75 years, with coronary heart disease; BMI 32.2 ± 0.5 kg/m²	20	0	MedDiet or a low-fat	LFHCC diet	1 year	T0, T1Y	2	CORDIOPREV study	Gut microbiome (composition and relative abundance), Biochemical improvements (insulin sensitivity, lipids)
Haro 2017	Consumption of Two Healthy Dietary Patterns Restored Microbiota Dysbiosis in Obese Patients with Metabolic Dysfunction	Obese men aged 20-75 years; with severe metabolic disease; obese patients without metabolic dysfunction	106	0	MedDiet	LFD	2 years	T0, T2Y	3	CORDIOPREV study	Gut microbiome (dysbiosis, diversity), Biochemical improvements (glucose, insulin, lipid profile)
Buscemi 2009	Effects of hypocaloric very-low-carbohydrate diet vs. Mediterranean diet on endothelial function in obese women	Female sex, aged 30–50 years; BMI range 27–39.9kg/ m2; with no metabolic comorbidities and no medication use	25	5	MedDiet hypocaloric	Atkins low- carbohydrate	2 months	T0, T5D, T60D	2	No	Body composition, Inflammatory markers (CRP, IL-6, TNF-α), Biochemical improvements (lipids, glucose)
Esposito 2003	Effect of Weight Loss and Lifestyle Changes on Vascular Inflammatory Markers in Obese Women: A Randomized Trial	Premenopausal obese woman, aged 20-46, BMI > 30kg/ m2	120	8	Low energy MedDiet and increase physical activity	Was given general information about healthy food choices and exercise	2 years	T0, T2Y	2	No	Body composition, Inflammatory markers (CRP, IL-6, TNF-α), Biochemical improvements (lipids, glucose)
Georgoulis 2021	A weight-loss Mediterranean diet/lifestyle intervention ameliorates inflammation and oxidative stress in patients with obstructive sleep apnea: results of the “MIMOSA” randomized clinical trial	Adults aged 18–65; overweight or obese (BMI≥ 25 kg/ m2) otherwise healthy individuals with moderate or severe OSA.	187	60	Low-calorie MedDiet	Mediterranean lifestyle group (MLG), Standard care (SCG)	6 months	T0, T6M	3	MIMOSA randomized clinical trial	Body composition, Inflammatory markers (CRP, IL-6, TNF-α), Oxidative stress, Gut microbiome (composition, diversity)
Urpi-Sarda 2012	The mediterranean diet pattern and its main components are associated with lower plasma concentrations of tumor necrosis factor receptor 60 in patients at high risk for cardiovascular disease	Men aged 54–79 and women aged 58–79, BMI> 25kg/m²	516	0	MedDiet-VOO and MedDiet-Nuts	LFD	1 year	T0, T1Y	3	PREDIMED trial	Inflammatory markers (TNFR60, IL-6, CRP), Biochemical improvements (lipids, glucose)

AHI, apnea-hypopnea index; BMI, body mass index; LFHCC, low-fat high-complex carbohydrate diet; LFD, low-fat diet; MedDiet, Mediterranean diet; MedDiet-VOO, Mediterranean diet supplemented with virgin olive oil; MLG, Mediterranean lifestyle group; OSA, obstructive sleep apnea; SCFA, short-chain fatty acids; SCG, standard care group; T2DM, type 2 diabetes mellitus; VLCKD, very low-calorie ketogenic diet.
T0, baseline; T2M, 2 months; T5D, 5 days; T6M, 6 months; T60D, 60 days; T1Y, 1 year; T2Y, 2 years.

Table 1: *Summary of study characteristics, interventions, and outcomes.*

Author	Gut microbiome	Body composition	Inflamatory markers (IL-6 / us-CRP / TNF alfa)
Deledda 2022	Alpha diversity: (shannon index) No stastistically significant between groups and time points. Beta diversity: No statistically significant difference. F/B ratio: No differences between diets Akkermansia: increase in the VLCKD group, with no changes in MedDiet group	After two months (T2) and three months (T3): Mean weight (kg): −9.4 ± 2.8 in VLCKD vs −5.2 ± 2.1 in MedDiet Mean BMI (kg/m²): −3.2 ± 0.9 in VLCKDvs −1.8 ± 0.7 in MedDiet Mean ±SD Body weight (kg) T0 (MedDiet): 82.2 ± 11.7. T0 (WD): 81.8 ± 11.8 P-value (MedDiet vs WD): 0.914	Not evaluated in this study
Vitale 2021	Alpha diversity: (Shannon index) A significant increase in the MedDiet compared to WD was observed at the end of treatment. Beta diversity: Not mentioned F/B ratio: MedDiet was associated with a reduction of the F/B, while control diet showed no difference from baseline. Akkermansia: a statistically significant increase occurs in the MedDiet group, with no improvement in the control diet group.	T2M (MedDiet): 82.3 ± 12.0 T2M (WD): 81.3 ± 12.0 P-value (MedDiet vs WD): 0.824 BMI (kg/m2) T0 (MedDiet): 28.9 ± 2.3 T0 (WD): 29.3 ± 3.5 P-value (MedDiet vs WD): 0.703 T2M (MedDiet): 28.9 ± 2.4 T2M (WD): 29.2 ± 3.6 P-value (MedDiet vs WD): 0.831	Not evaluated in this study
Haro 2016	Alpha diversity: (Chao1 index) No differences between diet at baseline and 1 year follow up. Beta diversity: Not mentioned. F/B ratio: not mentioned Akkermansia: not mentioned	Not evaluated in this study	Not evaluated in this study
Haro 2017	Lower abundance of Actinobacteria and Bacteroidetes phyla in the MetS-OB group compared with the NonMetS-NonOB group (p = 0.008 Q = 0.032 and p = 0.018 Q = 0.032, respectively) Higher F/B ratio in the MetS-OB group than in the NonMetS-NonOB group (p = 0.019) at baseline. Low-fat diet reduced the F/B ratio (p <0.001), but MedDiet did show a significant difference after 2 years of the intervention	Not evaluated in this study	Not evaluated in this study
Buscemi 2009	Not evaluated in this study	Mean ± SEM BMI (kg/m2) MedDiet: 34± 1.0 BMI (kg/m2) AL: 34,5± 1.8 / P-value (MedDiet vs AL): NS Weight (kg) T0 MedDiet: 83.6 ± 2.6 T0 AL: 87.1 ± 3.8 / P-value (MedDiet vs AL): NS T5 MedDiet: 81.9 ± 2.6 T5 AL: 84.6±3.8 / P-value (MedDiet vs AL): NS T60 MedDiet: 78.8±2.6 T60 AL: 79.6 ±3.8 / P-value (MedDiet vs AL): NS	Mean ± SEM IL-6 (pg/mL) T0 MedDiet: 45±4.9 T0 AL: 57.5±9.0 / P-value (MedDiet vs AL): NS T5D MedDiet: 48.9±6.6 T5D AL: 878.1±10.9 / P-value (MedDiet vs AL): 0.034 T60D MedDiet: 41.6±5.6 T60D AL: 56.6±6.8 P-value (MedDiet vs AL): NS
Esposito 2003	Not evaluated in this study	Mean (SD): BMI (kg/m2) T0 MedDiet: 35±2.3 T0 (Control): 34±2.4 T2Y MedDiet: 30±2.1 T2Y (Control): 34±2.4 P value after 2 years < 0.001 Weight (kg) T0 MedDiet: 95±9.4 T0 (Control): 94 ± 9.2 T2Y MedDiet: 81±7.6 T2Y (Control) : 91±9.0 P value after 2 years < 0.001	Mean (SD): IL-6 (pg/mL) T0 MedDiet: 4.3 (1.0-9.0) T0 (Control): 4.1 (2.0-9.0) T2Y MedDiet: 2.9 (1.1-6.5) T2Y (Control) : 3.8(2.1-8.9) P value after 2 years < 0.009 CRP (mg/L) T0 MedDiet: 3.2 (1.5-8.4) T0 (Control): 3.4 (1.4-8.3) T2Y MedDiet: 2.1 (0.9-7.1) T2Y (Control): 3.1 (1.3-8.2) P value after 2 years < 0.008
Georgoulis 2021	Not evaluated in this study	T6M: SCG :+0.3 ± 3.6% → no significant weight loss, including a slight average gain MedDietG: −7.4 ± 4.1% → significant weight loss MLG: −10.6 ± 5.8% → even greater weight loss Both intervention groups (MedDietG and MLG) lost significantly more weight than the control group (SCG) (P < 0.001). Furthermore, the MLG group had greater weight loss than the MedDiet group (P = 0.004)	Median (first, third quartile) hsCRP mg/dL T0 hsCRP (SCG): 2.45 (1.24,5.17) T0 hsCRP (MedDietG): 2.65 (1.00, 5.31) T0 hsCRP (MLG): 3.14 (1.26, 5.29) T6M hsCRP (SCG): 2.51 (1.84, 5.61) T6M hsCRP (MedDietG): 1.96 (1.35, 3,36) T6M hsCRP (MLG): 1.81 (0.92, 3.27)
Urpi-Sarda 2012	Not evaluated in this study	Not evaluated in this study	T1Y: MedDiets: there were reductions in IL-6, TNFR60, and TNFR80 (P < 0.05) LFD: IL-6 tended to increase (P = 0.14) In between-group comparisons (ANCOVA), the two MedDiets showed 1–34% lower plasma concentrations of ICAM-1, IL-6, TNFR60, and TNFR80 than the LFD (P < 0.028)

BMI, Body Mass Index; LFHCC, low-fat high–complex-carbohydrate diet; LFD, low-fat diet; MedDiet, Mediterranean diet; MedDiet-VOO, Mediterranean diet supplemented with virgin olive oil; MLG, Mediterranean lifestyle group; SCG, standard care group; VLCKD, very low-calorie ketogenic diet; AL, Atkins low-carbohydrate diet; M (SD), mean (standard deviation); Mean ± SEM, mean ± standard error of the mean.

T0, baseline; T2M, 2 months; T5D, 5 days; T6M, 6 months; T60D, 60 days; T1Y, 1 year; T2Y, 2 years.

Table 2: *Summary of main outcomes reported across included trials.*

Figure 2: *Summary of risk of bias using Cochrane RoB 2 tool and risk of bias graph generated with the Robvis tool (RoB 2: Risk of bias tool 2, Robvis: Risk of bias visualization tool).*

high-complex carbohydrate diet (LFHCC) group consumed 28% of total fat, distributed among mono-, poly-, and saturated fats, with low-fat foods provided by the researchers to ensure cost equivalence with the MedDiet arm. Similarly, Haro (2017) compared the MedDiet to a low-fat diet (LF) consistent with the National Cholesterol Education Program and American Heart Association guidelines (< 30% total fat, < 10% saturated fat). Buscemi compared the MedDiet to an Atkins low-carbohydrate diet, with an initial extreme carbohydrate restriction (5%) followed by gradual reintroduction up to 20% at the study's end. Esposito provided only general guidance on healthy eating and exercise to the control group, without a structured dietary plan. In Georgoulis' trial, two comparators were used: a Mediterranean lifestyle group (MLG) and a standard care group (SCG); the latter received only a hypocaloric plan and general health advice, whereas the MLG included behavioral components. Finally, Urpi-Sarda used a low-fat diet (LFD) following American Heart Association recommendations to reduce all types of dietary fat.

Outcomes

The outcomes assessed across the included studies showed considerable variability in terms of domains, including gut microbiome, inflammatory biomarkers, BMI, weight, and waist circumference, as well as timing of assessment (T0, T2M, T3M, T1Y, T2Y, etc.).

Only four distinct trials (Buscemi et al., 2009; Deledda et al., 2022; Haro et al., 2016, 2017) focused on the gut microbiome, while others examined secondary outcomes. Specifically, four studies described inflammatory biomarkers and five studies evaluated changes in body composition. In addition, differences were observed in whether outcomes were designated as primary or secondary, affecting interpretation.

We extracted and reported within-trial intervention-versus-control results for each study. When comparable numerical data were unavailable or reported heterogeneously, we conducted narrative qualitative comparisons across studies to describe the direction and approximate magnitude of effects.

Primary outcome: Gut microbiome

Regarding gut microbiota, four studies (Deledda et al., 2022; Haro et al., 2016, 2017; Vitale et al., 2021) evaluated microbial changes following dietary interventions. At the genus level, Deledda et al. observed a marked increase in *Akkermansia*, Christensenellaceae, and *Eubacterium* species after a very low-calorie ketogenic diet, accompanied by a reduction in Firmicutes, Actinobacteriota, and *Alistipes*, suggesting a more favorable metabolic profile. In contrast, the MedDiet induced only modest microbiota shifts, mainly slight increases in Actinobacteriota and Firmicutes. Similarly, Vitale

et al. reported that the MedDiet led to greater abundance of *Akkermansia muciniphila* and *Intestinimonas butyriciproducens*, aligned with higher fiber intake and butyrate production. Haro et al. (2016) found significant diet-dependent microbial changes, with the MedDiet increasing *Roseburia*, *Oscillospira*, and *Parabacteroides distasonis*, whereas the low-fat, high-complex-carbohydrate diet increased *Prevotella* and *Faecalibacterium prausnitzii*. Haro et al. (2017) did not detect significant diversity differences after two years of intervention. Regarding microbiota diversity, three studies reported an alpha diversity index; two used the Shannon index and one used the Chao1 index (Haro et al., 2016). Deledda et al. and Haro et al. found no significant difference between groups at baseline or at the end of each study, while Vitale et al. found a statistically significant increase in the MedDiet group compared with the control group at study completion. Only Deledda et al. reported beta-diversity outcomes, with no significant differences among interventions. Finally, the Firmicutes/Bacteroidetes ratio was reported in three studies. Vitale et al. found that the MedDiet was associated with a reduction in this ratio, while Deledda et al. and Haro et al. found no statistically significant difference between MedDiet and control diets. Interestingly, Haro et al. did find a reduction of the ratio in the low-fat diet group after two years of follow-up. Among the included trials, Haro et al. (2017) presented methodological limitations leading to a high risk of bias, which warrants cautious interpretation of its findings.

Secondary outcomes

Concerning inflammatory markers, five studies included biochemical endpoints. Esposito et al. observed significant reductions in IL-6 (T0 MD: 4.3; T2Y MD: 2.9; $p = 0.009$), IL-18, and CRP (T0 MD: 3.2; T2Y MD: 2.1; $p = 0.008$), as well as an increase in adiponectin levels in the Mediterranean intervention group, whereas Buscemi et al. found lower IL-6 levels in the Mediterranean group than in the low-carbohydrate group ($p = 0.034$ at day 5). Georgoulis et al. reported that combining a MedDiet with behavioral and lifestyle changes significantly reduced hsCRP (T6M MedDiet group: 1.96, MLG: 1.81 vs. SCG: 2.51 mg/dL; $p < 0.001$) and the oxidative stress marker 8-isoPGF2α, with effects mainly mediated by weight loss ($p < 0.001$). Similarly, Urpi-Sarda et al. demonstrated that both Mediterranean diets supplemented with EVOO or nuts reduced plasma IL-6, ICAM-1, TNFR60, and TNFR80 concentrations compared with a low-fat diet ($p \leq 0.028$). In contrast, Deledda et al., Haro et al. (2016, 2017), and Vitale et al. did not evaluate inflammatory biomarkers.

As for body composition, most trials reported improvements in anthropometric parameters favoring Mediterranean-based interventions or energy-restricted regimens. Deledda et al. found greater reductions in weight (VLCKD: -9.4 ± 2.8 kg vs. MD: -5.2 ± 2.1 kg), BMI (VLCKD: -3.2 ± 0.9 vs. MD: -1.8 ± 0.7 kg/m^2), and waist circumference in the ketogenic group compared with the Mediterranean group, though both achieved significant decreases ($p < 0.001$). In Buscemi et al., both Mediterranean and low-carbohydrate (Atkins) diets reduced weight (T60 MD 78.8 ± 2.6 kg vs. AL: 79.6 ± 3.8 kg) and BMI (MD: 34 ± 1.0 vs. AL: 34.5 ± 1.8), but the Atkins group achieved greater total weight loss after two months. Georgoulis et al. demonstrated significant weight reduction after six months in both the MedDiet ($-7.4 \pm 4.1\%$) and Mediterranean lifestyle ($-10.6 \pm 5.8\%$) groups compared with standard care ($+0.3 \pm 3.6\%$; $p < 0.001$), with the lifestyle arm showing superior outcomes ($p = 0.004$). Esposito et al. also reported significant improvements after two years, with greater reductions in body weight, BMI, and waist-to-hip ratio in the MedDiet and physical activity group compared with controls. Haro et al. (2016, 2017) and Urpi-Sarda et al. did not assess body-composition parameters. Among all included studies, only Esposito et al. (2003) assessed insulin resistance/sensitivity, and even then indirectly, using the HOMA-IR index.

Assessment of risk of bias in individual studies

The overall risk of bias of six included studies was classified as having some concerns (Buscemi et al., 2009; Deledda et al., 2022; Esposito et al., 2003; Georgoulis et al., 2021; Haro et al., 2016; Haro et al., 2017; Vitale et al., 2021), mainly due to limited information or methodological concerns regarding the randomization process, deviations from intended intervention, and selection of reported results. For instance, Buscemi et al. did not describe the randomization procedure, which could lead to selection bias; Deledda et al. and Vitale et al. lacked detailed adherence monitoring, raising concerns about deviations from the intended intervention; Esposito et al. and Georgoulis et al. selectively reported outcomes, potentially inflating the perceived benefits; and Haro et al. (2016) did not clearly describe blinding of outcome assessors, increasing the risk of detection bias. Urpi-Sarda et al. was judged to have a low risk of bias across all domains. This study clearly described randomization, monitored adherence, used blinded outcome assessment, and reported all prespecified outcomes, providing confidence in the validity of

its findings. Haro et al. (2017) was rated as having an overall high risk of bias due to high risk in three domains: deviations from intended interventions, measurement of the outcome, and selection of the reported result. Specifically, the open-label design without blinding of participants or investigators, together with limited information on adherence monitoring, increases the likelihood that differences in participant behavior or researcher expectations may have influenced the observed effects. Moreover, the lack of a clear description of blinding in outcome assessment raises the possibility of detection bias, and incomplete reporting of prespecified outcomes suggests selective reporting. These biases may have inflated the apparent effectiveness of the dietary intervention, meaning the findings from this study should be interpreted cautiously and given less weight when synthesizing evidence on the impact of diet on gut microbiota and metabolic outcomes.

Discussion

This scoping review synthesized evidence from eight randomized controlled trials in adults with overweight or obesity, with a primary focus on gut microbiota. Of these, four trials profiled the gut microbiome, four assessed systemic inflammatory biomarkers, and five reported body-composition outcomes. Across studies, MedDiet interventions were associated with modest, consistent improvements in weight/BMI and inflammatory markers. Importantly, the pattern observed across trials suggests that the Mediterranean diet may exert its effects through selective modulation of specific microbial taxa rather than uniform alterations in global microbiome diversity. While enrichment of metabolically relevant taxa such as Akkermansia, Roseburia, and Faecalibacterium was observed in several studies, consistent improvements in global diversity metrics—including alpha diversity and Firmicutes/Bacteroidetes ratio - were not demonstrated. This distinction suggests that functional and taxonomic specificity, rather than broad ecosystem restructuring, may underlie microbiota-mediated metabolic benefits. These findings highlight the importance of focusing on functional microbial pathways and taxa-specific responses rather than relying solely on global diversity indices as markers of microbiome improvement.

Across interventions, MedDiet patterns shared core features, abundant plant-based foods, EVOO, nuts, and fish, yet differed in caloric goals, comparators, and follow-up durations. Despite this heterogeneity, a coherent trend emerges: MedDiet interventions were consistently linked to improvements in body composition, attenuation of inflammatory biomarkers, and enrichment of beneficial microbial taxa such as Akkermansia, Roseburia, and Faecalibacterium prausnitzii. These bacteria are known producers of short-chain fatty acids that regulate host metabolism and inflammation. Alpha diversity is described as the evaluation of the richness and evenness of an individual microbiome, which has been described as reduced in obese individuals (Duan et al., 2021). Our review couldn't fail to show consistently an improvement from MedDiet, as only one study showed significant improvement after the intervention. Nevertheless, the other three reports compared MedDiet vs other specific diets. This only can be interpreted as lack of evidence that MedDiet is superior to ketogenic and low-fat diets regarding alpha diversity. Likewise, only Vitale et al. found a reduction in the F/B ratio. Interestingly, there are conflicting results in the literature regarding the status of F/B in obese patients (Duan et al., 2021), with some reports suggesting a decreased ratio in obesity. Collectively, these findings support the biological plausibility that Mediterranean-style dietary patterns improve metabolic health through microbiota modulation and reduction of systemic inflammation. These conclusions are consistent with evidence in healthy adults showing that greater adherence to a MedDiet enriches short-chain–fatty-acid–producing taxa and increases fecal SCFAs, supporting a microbiota-mediated pathway to metabolic improvement.

This review faced a fundamental evidence constraint at the intersection of our three prespecified features, adults with BMI > 25, Mediterranean-diet interventions, and gut microbiota outcomes. Identifying randomized trials that simultaneously met all three criteria proved challenging and limited the pool of eligible studies. As a trade-off to preserve scope, we did not further standardize additional design elements (e.g., minimum follow-up duration or a uniform comparator), which reduced cross-trial comparability. Moreover, participant populations were heterogeneous, including individuals with and without comorbidities, and using or not using medications—a profile that likely contributed to variability in inflammatory and metabolic responses. Collectively, these issues constrain the precision of inferences and underscore the need for future RCTs that couple clear eligibility for overweight/obesity with standardized follow-up, harmonized comparators, and consistent microbiome, inflammatory, and body-composition endpoints.

Future studies should include longer follow-up durations ideally between 12 and 24 weeks to better capture sustained microbial and metabolic adaptations to dietary change.

Methodological differences across studies including variations in sample size, adherence measure-

ment, lack of blinding, and different microbiome analysis techniques further limit comparability and may explain inconsistencies in reported outcomes. Additionally, potential risks of bias, such as dietary self-reporting and publication bias, are inherent challenges in nutrition research.

Finally, due to the exploratory nature of a scoping review and the small number of eligible studies, a formal quality appraisal or meta-analysis was not feasible. As a result, our findings offer a descriptive summary rather than definitive conclusions on the Mediterranean diet's impact on gut microbiota in obesity.

Despite these limitations, this review highlights important implications for research and practice, generally associated with modest weight loss and anti-inflammatory effects, even when microbiome outcomes are not systematically reported. Overall, the evidence supports the Mediterranean diet as a promising, biologically plausible dietary approach for improving metabolic health in individuals with overweight and obesity.

Conclusion

This scoping review identified some trends suggesting MedDiet may beneficially modulate gut microbiota composition, reduce systemic inflammation, and improve metabolic outcomes in adults with overweight or obesity. However, methodological heterogeneity and limited microbiota data across trials constrain the strength of these findings.

Future randomized controlled trials should adopt longer follow-up durations ($\geq$ 6 months to allow for microbiota stabilization and initial metabolic changes, or ideally 12–24 months to assess long-term adherence, sustained effects, and clinical outcomes), with standardized microbiota and biomarker assessments and clearly defined Mediterranean diet (MedDiet) protocols to enhance comparability and reproducibility. Such studies are essential to clarify the mechanisms by which the MedDiet influences host metabolism and to inform clinical strategies for obesity management through dietary modulation of the gut microbiome.

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Conflicts of Interest

The authors declare no conflict of interest.

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