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Mediterranean diet, gut microbiota, and type 2 diabetes: A systematic review and meta-analysis of intervention trials

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ABSTRACT

Aims: The Mediterranean diet (MedD) is associated with improved metabolic health and modulation of gut microbiota (GM), both relevant to preventing type 2 diabetes (T2D) and cardiovascular disease (CVD). This systematic review and meta-analysis evaluated the effects of MedD-based dietary interventions on metabolic outcomes and GM composition in individuals at increased risk of T2D and CVD.
Data synthesis: We searched PubMed, Embase, Web of Science, Cochrane CENTRAL, and Scopus up to October 11, 2024, for randomized controlled trials (RCTs) comparing MedD-based diets to control diets in adults. Studies reporting outcomes on glucose metabolism and GM composition were included. Random-effects meta-analyses were conducted on metabolic outcomes. GM findings were synthesized descriptively due to heterogeneity in sequencing methods and taxonomic reporting. Nine RCTs ($n = 1337$ participants) met the inclusion criteria. Compared with control diets, MedD interventions significantly reduced glycated hemoglobin (HbA1c) (mean difference −0.18, 95 % CI = −0.35, −0.01), LDL cholesterol (−0.10, 95 % CI = −0.19, −0.00), and triglycerides −0.20, 95 % CI = −0.28, −0.12). No significant effects were observed on fasting glucose, insulin, HOMA-IR, total cholesterol, or HDL cholesterol. A qualitative GM analysis showed increased α-diversity and enrichment of health-related taxa, including *Akkermansia muciniphila* and *Roseburia* spp.
Conclusions: Our findings suggest that MedD interventions improve HbA1c, LDL cholesterol, and triglycerides, and promote beneficial GM changes. These may contribute to the metabolic benefits of the MedD. Future research should focus on individualized approaches, longer intervention periods, and mechanistic insights using multi-omics data to better understand the diet–microbiota–host interaction.
Protocol registration: PROSPERO as CRD42023428016.

1. Introduction

The global prevalence of type 2 diabetes has increased significantly in recent decades, with the World Health Organization estimating that the number of diabetic patients rose from 108 million in 1980 to 422 million in 2014. By 2019, diabetes directly caused 1.5 million deaths and was responsible for approximately 460,000 kidney disease deaths and 20 % of cardiovascular deaths [1]. Lifestyle has a significant impact on disease burden, with unhealthy eating being a major contributor to type 2 diabetes due to enhanced accessibility of high-fat, high-sugar foods and ultra-processed products, which are characteristic of the Western diet [2]. Emerging evidence suggests that the Western diet negatively impacts the gut microbiome (GM), leading to increased inflammation and insulin resistance. This disruption is commonly associated with alterations in Firmicutes-to-Bacteroidetes ratio, with an increase in Firmicutes frequently observed in individuals with obesity and type 2 diabetes [3,4]. Perturbations in the eubiosis of the Bacteroidetes and Firmicutes phyla have been linked to increased intestinal permeability, enabling bacterial byproducts to cross a compromised gut barrier and trigger inflammatory responses characteristic of diabetes [5]. Conversely, several bacteria species have been shown to exert protective effects by reducing proinflammatory markers and

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maintaining intestinal barrier integrity. For instance, *Lactobacillus fermentum*, *Lactobacillus plantarum*, *Lactobacillus casei*, *Roseburia intestinalis*, *Akkermansia muciniphila*, and *Bacteroides fragilis* can enhance glucose metabolism and insulin sensitivity, while also reducing the production of proinflammatory cytokines [6,7].

Additionally, GM-derived metabolites, particularly the short-chain fatty acids (SCFAs) acetate (C2), propionate (C3), and butyrate (C4), exert profound effect on human health. Produced through the fermentation of dietary fiber and resistant starch, these SCFAs regulate key metabolic pathways implicated in obesity, insulin resistance, and type 2 diabetes [8,9]. Beyond their metabolic role, they exert anti-inflammatory effects, enhance gut barrier function integrity, improve insulin sensitivity, and paly a pivotal role in energy homeostasis and immune regulation [10].

The Mediterranean diet (MedD), characterized by a high intake of vegetables, fruits, whole grains, legumes, nuts, and olive oil, has been shown to significantly improve a range of cardiometabolic risk factors [11]. In particular, adherence to a MedD has been associated with higher levels of SCFAs, healthier GM and a reduced risk of metabolic disorders [12], specifically a lower incidence of type 2 diabetes [13–15].

The mechanisms linking adherence to the traditional MedD with better health outcomes are not fully understood. However, growing evidence suggests its benefits arise from combined effects, including cholesterol reduction, antioxidant and anti-inflammatory actions, and modulation of gut microbiota. Key contributors include monounsaturated fats (from extra-virgin olive oil), omega-3 fatty acids (from fish), and dietary fiber (from fruits, vegetables, legumes, and whole grains), which collectively improve blood lipids and lower LDL cholesterol [16].

Moreover, the abundance of polyphenols and other bioactive compounds in MedD has been shown to reduce oxidative stress and inflammation [17,18]. Recent studies emphasize the impact of the MedD in promoting a more diverse and resilient GM, which in turn influences host metabolic and immune functions. In particular, higher intake of dietary fiber and polyphenol-rich foods promotes the growth of beneficial microbial species and enhances the production of SCFAs. These metabolites help maintain gut barrier integrity and contributes to improved metabolic health, as previously mentioned [13,19].

To date, only few intervention studies have investigated the combined effect of the MedD on GM and key cardiometabolic risk factors. Therefore, this systematic review and meta-analysis aims to assess the benefits of MedD consumption on metabolic outcomes and GM composition in individuals at elevated risk of type 2 diabetes and cardiovascular disease.

2. Methods

2.1. Search strategy and selection of studies

This systematic review and meta-analysis followed the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [20,21]. We identified relevant articles published up to October 11, 2024, surfing the literature in PubMed/MEDLINE, EMBASE, ISI Web of Science, Scopus, and the Cochrane Library. Starting from a combination of free-text terms and controlled vocabulary related to MedD and glucose metabolism, the following search strategy strings were used: (Mediterranean diet) AND (diabetes or type 2 diabetes or impaired glucose tolerance or metabolic syndrome or fasting glucose or glucose metabolism or insulin resistance or insulin sensitivity or glycated hemoglobin or HbA1c or obesity or overweight) AND (microbiota or microbiome or alfa diversity or beta diversity or abundance or bacteria or SCFA or Short Chain Fatty Acids)".

We retrieved and assessed potentially relevant articles and examined the reference lists of all selected papers to identify additional relevant publications. All randomized intervention-controlled studies were included. The present study protocol was submitted to the International Prospective Register of Systematic Reviews database (PROSPERO) under registration number CRD42023469746.

2.2. Inclusion and exclusion criteria

Studies were considered eligible if they: 1) included original data from controlled dietary intervention trials comparing a diet resembling the features of the MedD to a control diet for which the same amount of energy was provided by foods characteristics of the Western diet; 2) included interventions lasting at least 2 weeks; 3) provided mean values after the intervention and control diets for at least one of the parameters of interest (i.e., fasting blood glucose, HbA1c, fasting insulin, systolic or diastolic blood pressure, total cholesterol, LDL cholesterol, HDL cholesterol, triacylglycerols) along with measures of dispersion or sufficient data to derive them; 4) assessed GM composition; 5) were conducted in humans; 6) were published in English; and 7) included adults aged over 18 years. Studies conducted in children and adolescents (<18 years), reviews, conference letters, notes, reports, short surveys, unpublished studies, and case reports were excluded. The population, intervention, comparison group, and outcome are shown in Table 1.

2.3. Study selection

Studies were selected by screening titles and abstracts, followed by individual assessment of all potentially relevant full-length articles by four authors (F.L., C.Q., M.V. and M.D.R.). Disagreements regarding the inclusion or exclusion of selected articles were resolved by consensus, discussion or involvement of two other researchers (A.F. and C.S.). Cohen's Kappa coefficient [22] was adopted to assess the agreement level of the reviewers with the result $K = 0.7894$ (substantial agreement). Studies were excluded if they did not meet the above criteria. When more than one study was published on the same cohort, only the most recent publication was included in the analysis. For studies with missing data, authors were contacted for data collection when possible.

2.4. Data collection and quality assessment

The following information was extracted: name of first author, year of publication, country, baseline characteristics of the study population (sex, age, BMI or body weight, and health status), number of subjects included, study design (crossover or parallel), intervention and control diets, duration of intervention, and body weights after the intervention and control diets. In addition, for each parameter of interest, we extracted the means after the intervention and control diets with corresponding standard errors (SEs), standard deviations (SDs), or 95 % confidence intervals (CIs), when available. If this information was unavailable, the corresponding authors were contacted for clarification.

Two authors separately assigned the quality scores to each study based on the risk of bias using the Cochrane Collaboration tool [23,24] for randomized trials, which assesses five domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported outcome. The risk of bias was assessed in each domain. Studies were classified as: 1) "low risk" when a low risk of bias was determined for all domains; 2) "some concerns", when one or more domains raised concerns but none were considered high risk; or 3) "high risk" when a high risk of bias was found for ≥ 1 domain or when multiple domains were judged to raise "some concerns".

2.5. Statistical analysis

Data was extracted from the included RCTs, and quantitative synthesis (meta-analysis) was performed if the studies were sufficiently homogeneous in terms of population, intervention, comparator, and outcome. Mean differences (MDs) and corresponding 95 % CIs were calculated for all continuous variables. Because of the large

Table 1
Main characteristics of the studies included in the review and meta-analysis.

First author, year (ref)	Country	Study design	No. and sex of subjects	Age, y	Health status	BMI, kg/m^2	Intervention diet	Control diet	Study duration
García-Gavilán JF, 2024	Spain	Parallel-design RCT	400 males and females' participants (Control Group, n 200; Intervention Group, n 200)	55–75 years	Obese and overweight	32.8 ± 3.6 kg/m^2	Er-MedD: energy reduction of 30 % of individual estimated energy requirements	Recommendations to improve their adherence to the MedD	1 year
Chooi YC, 2024	China	Double-blinded, parallel-design RCT	88 females' participants (Control Group, n 29; Intervention Group with C15:0 supplementation, n 31)	21–45 years	NAFLD	23–35 kg/m^2	Calorie-restricted diet with C15:0 supplementation	Standard hypocaloric control diet	12 weeks
Choo JM, 2023	Australia	RCT, cross-over design	34 males and females' participants (MedDairy, n 18 or LFD diet, n 16)	45–75 years	Metabolic syndrome	>25 kg/m^2	Fresh fruits, vegetables, legumes, fish, seafood, nuts, seeds, whole grain cereal products, selected white meats (poultry without skin), limited or non-consumption of red meat, processed meats, cream, butter, sugared beverages or bakery items, and the use of extra virgin olive oil (EVOO) for cooking or salad dressing. The recommended dairy consumption was 3–4 daily servings of dairy food based on the following: one serve = 250 mL low-fat milk, 40–120 g hard and/or semisoft to soft cheese, 200 g low-fat Greek yoghurt, or 200 g tzatziki.	Their habitual diet but reduce their total fat intake; participants were instructed to consume low-fat food (breads, cereals, lean meat, legumes, rice, vegetables, and fruits) and choose low-fat variations of food products (such as low-fat dairy) as a replacement to restrict or avoid high-fat foods, including cream, full fat dairy, processed meats, high fat meats, nuts, ice cream, and sugared bakery items, no more than 20 mL of any oil type.	8 weeks
Ben-Yacov O, 2023	Israel	Parallel-design RCT	200 males and females' participants (personalized postprandial glucose-targeting diet (PPT) n 113 or Mediterranean diet (MED) n 112	18–65 years	Metabolic syndrome		45–65 % of energy intake from carbohydrates, 15–20 % from protein and <35 % from fat, with <10 % from saturated fat. Including whole-wheat bread and grains, legumes, low-fat dairy products, fish, poultry, olive oil, fruits and vegetables. Discouraged foods included commercial bakery goods, sweets and pastries, fried foods and snacks, fatty and processed meat, and high-fat dairy products.	Recommendations in the PPT diet were tailored to participants based on their personal predicted glucose responses.	6 months
Rinott E, 2022	Israel	Parallel-design RCT	294 males and females' participants (Med Diet n 96 vs Healthy Diet n 97)	>30 years	Metabolic syndrome		Calorie-restricted Mediterranean diet rich in vegetables, with poultry and fish replacing beef and lamb intake. The diet also included 28g/day of walnuts.	Standard nutritional counseling based on the Harvard T. H. Chan School of Public Health`s "The Nutrition Source,".	6 months
Galié S, 2021	Spain	RCT, cross-over design	44 males and females' participants (Med diet n 23 vs Control diet n 21)	25–60 years	Overweight/obesity and metabolic syndrome	25–35 kg/m^2	Daily consumption of at least 2 servings of vegetables and 3 fruits, and weekly consumption of 3 servings of legumes, 5 servings of whole-grain cereals and pasta, 3 servings of fish and seafood and the use of extra virgin olive oil as the main culinary fat. A decreased consumption of red meat and processed foods to less than 1 serving/week, and reduced use of butter and margarine, white bread and sweetened beverages was recommended.	Did not provide any other dietary advice rather than the consumption of 50 g/day of mixed nuts.	2 months
Vitale M, 2021	Italy	Parallel-design RCT	29 males and females' participants (Med diet n 16 vs Control diet n 13)	20–60 years	Overweight/obese	25–35 kg/m^2	Fruit and vegetables (at least 5 portions, ~500 g/day) and nuts (30 g/day), refined cereal products replaced with wholegrain products (at least 2 portions, ~200 g/day between wholegrain pasta, bread and breakfast cereal), meat and derived meat products with legumes and fish (at least 2 portions, ~300 g/week of	Habitual diet unvaried during the intervention and did not consume extra virgin olive oil.	8 weeks

(*continued on next page*)

Table 1 (*continued*)

First author, year (ref)	Country	Study design	No. and sex of subjects	Age, y	Health status	BMI, kg/m^2	Intervention diet	Control diet	Study duration
							fish and 3 portions, ~300 g/week of legumes), butter and any other habitual condiments with extravirgin olive oil.		
Meslier V, 2020	Italy	Parallel-design RCT	82 males and females' participants (Med diet n 43 vs Control diet n 39)	20–60 years	Overweight/ obese	25–35 kg/m^2	Fruit and vegetables (at least 5 portions, ~500 g/day) and nuts (30 g/day), refined cereal products replaced with wholegrain products (at least 2 portions, ~200 g/day between wholegrain pasta, bread and breakfast cereal), meat and derived meat products with legumes and fish (at least 2 portions, ~300 g/week of fish and 3 portions, ~300 g/week of legumes), butter and any other habitual condiments with extravirgin olive oil.	Habitual diet unvaried during the intervention and did not consume extra virgin olive oil.	8 weeks
Davis CR, 2017	Adelaide	Parallel-design RCT	166 elderly males and females' participants (Med diet n 85 vs Control diet n 81)	≥65 years	Healthy		Traditional MedD, with wholegrain breakfast cereals, canned fish and legumes, some tropical fruits and Asian vegetables were allowed, although traditional foods were encouraged over these non-traditional foods. It comprised extra-virgin olive oil, vegetables, fruits, nuts, whole grains, legumes and fish as core foods. The diet was moderate in red wine and dairy foods (primarily cheese and yogurt) and contained small amounts of red meat, small goods and discretionary foods.	HabDiet groups were asked to continue their usual dietary intake without change, such as introducing new foods or ceasing consumption of regular dietary habits during the trial.	6 months

heterogeneity in the fixed-effects models, random-effects meta-analyses based on the I^2 cut-off were performed for all comparisons. The inverse variance method was used to determine the weights of the studies. Heterogeneity between studies was estimated using the Cochran Q test ($P < 0.05$, indicating statistically significant heterogeneity) and the I^2 statistic. It was suggested that I^2 statistics of 0–25 %, 25–50 %, 50–75 %, and 75–100 % indicate modest, modest-to-moderate, moderate-to- strong, and strong heterogeneity, respectively [25]. Additional sensi-tivity analyses were planned and performed in advance by systemati-cally omitting 1 study at a time and recalculating the summary association to test the robustness of the results and the impact of indi-vidual studies on heterogeneity.

For each parameter, we provided forest plots, in which a square was plotted for each study, with its projection on the underlying scale cor-responding to the study-specific mean difference. The area of the square is proportional to the inverse of the variance of the mean difference, giving a measure of the amount of statistical information available. A diamond was used to plot the summary weighted mean difference and the corresponding 95 % CI. Publication bias was evaluated by visually inspecting funnel plots and quantified by the Egger's regression sym-metry test, with significant bias detected at $P < 0.10$ [26]. Due to het-erogeneity in outcomes related to GM, stemming from differences in diversity indices, and functional endpoints, a meta-analysis of GM-related results was not feasible.

All statistical analyses were performed using RevMan 5.4 (Review Manager RevMan-Computer program; version 5.4; The Cochrane Collaboration, 2020) and R 4.1.0 (The R Project for Statistical Computing; version 4.1.0, 2021), and all tests were 2-sided with a sig-nificance level of 0.05 unless otherwise stated.

3. Results

We identified 401 articles from the original literature search in PubMed, EMBASE, ISI Web of Science, Scopus, and the Cochrane Li-brary. After excluding duplicate records, we screened 329 citations. During the initial screening of titles and abstracts, 267 records were excluded because they were based on animal studies, non-RCTs, re-views, comments, editorials or had unmatched populations, in-terventions, comparators, or outcomes. Subsequently, 62 articles were considered of interest based on their title and abstract, and their full texts were retrieved for detailed evaluation. Two additional studies were identified from the reference list of the retrieved papers. After a closer evaluation, 55 studies were additionally excluded for different reasons (i.e., unmatched populations, interventions, comparators, or outcomes), thus leaving 9 studies for this review and meta-analysis (Fig. 1).

3.1. *Study characteristics*

The studies included in the present work were published between 2017 and 2024. Among these, 2 each were conducted in Spain [27–29], Italy [30,31], and Israel [32–34], and 1 each in China [35], Australia [36], and Adelaide [17]. The total number of participants across the RCTs was 1337 and the sample size ranged from 29 to 400. One study exclusively recruited woman [35]. The participants' mean age ranged from 18 to 75 years. The BMI ranged from 23 to 35 kg/m^2. Among the 9 selected studies, 4 were conducted in overweight/ obese participants [27–31], 3 in subjects with metabolic syndrome [32–34,36], 1 each in healthy individuals [17], and in individuals with NAFLD [35]. The study duration ranged from 8 weeks to 1 year. Of the studies included, two were crossover RCTs [27,28,36], while the others followed a parallel-arm design. All the studies implemented dietary recommenda-tions aligned with the principles of the MedD. Three studies used a calorie-restricted MedD aimed at promoting weight loss [29,34,35]. The comparison groups varied across the RCTs and included a low-calorie diet, a nutritional balanced diet based on standard guidelines, or par-ticipants' usual dietary patterns. A summary of the key study

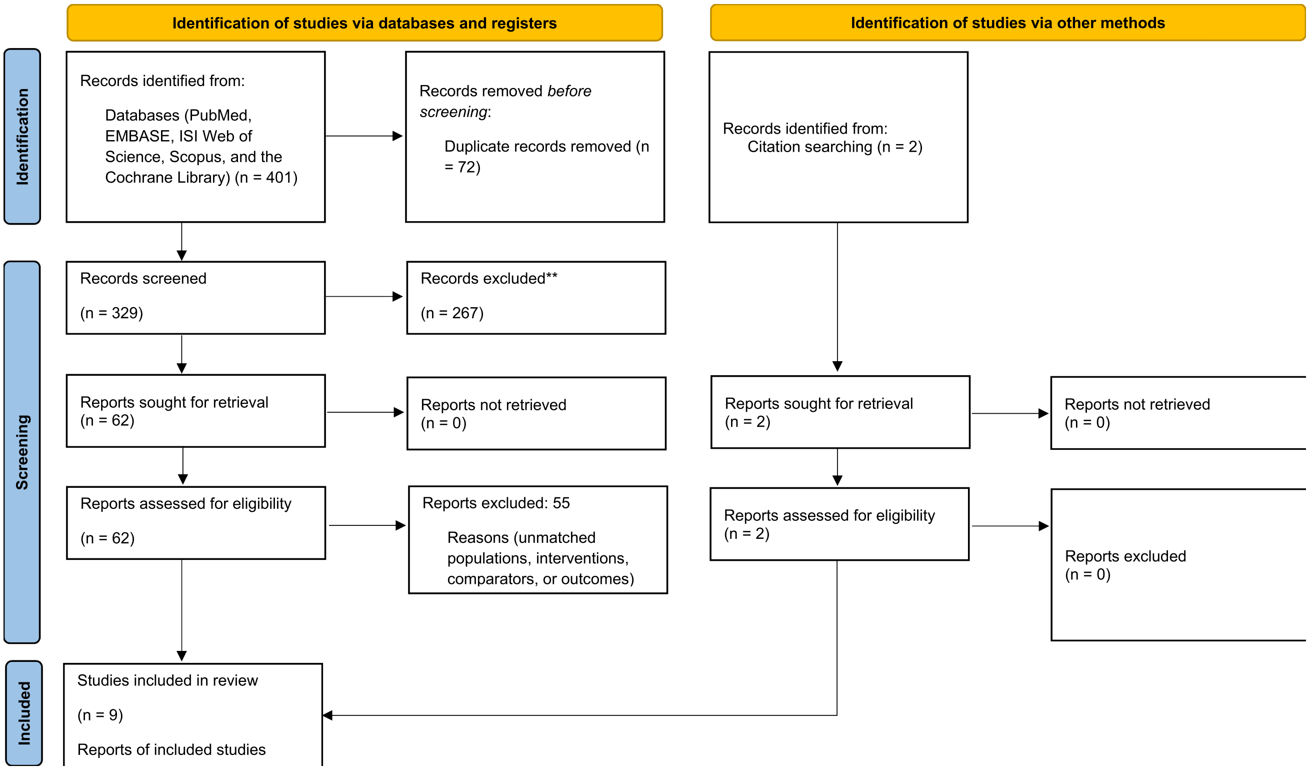

Fig. 1. PRISMA flowchart indicating the results of the search strategy.
From: M. J. Page, J. E. McKenzie, P. M. Bossuyt, I. Boutron, T. C. Hoffmann, C. D. Mulrow et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, BMJ 2021; 372:n71. https://doi.org/10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/
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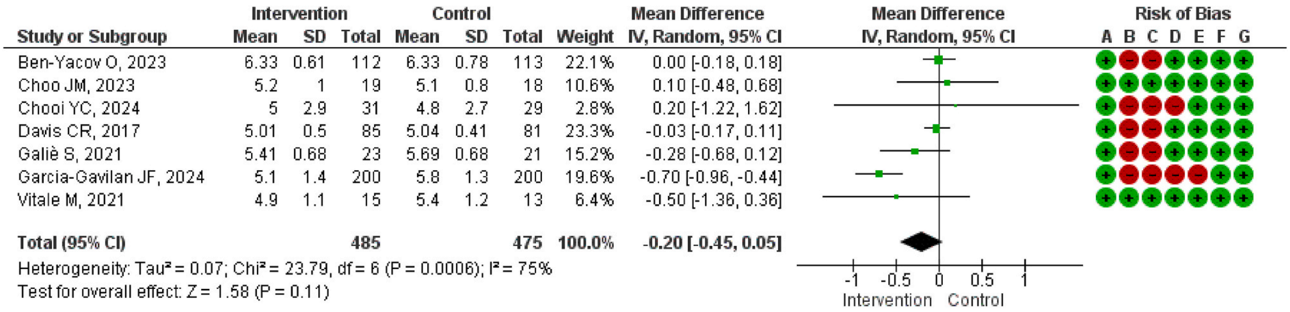
characteristics is presented in Table 1.

3.2. Overall effects of Mediterranean diet on glucose metabolism

Using the data pooled from the RCTs, we analyzed the effects of the MedD on blood glucose, HbA1c, insulin, and HOMA-IR (Figs. 2–5).

A total of 7 studies explored the effect of the MedD on glucose levels [17,27–30,32,33,35,36], showing a not significant reduction compared to the control group (MD = – 0.20, 95 % CI = – 0.45, 0.05) with strong heterogeneity (I^2 = 75 %, P = 0.0006) (Fig. 2). By systematically omitting 1 study at a time, heterogeneity was generated by 1 study [29]. Excluding this study did not alter the non-significant association and eliminated the heterogeneity. The mean study duration for pooled studies was 20 weeks (range 8 weeks to 1 year).

A total of 4 studies investigated the effect of the MedD on HbA1c [29,32,33,35,36], showing a significant reduction compared with the con-trol group (MD = – 0.18, 95 % CI = – 0.35, – 0.01) with strong het-erogeneity (I^2 = 88 %, P < 0.0001) (Fig. 3). By systematically omitting 1 study at a time, heterogeneity was generated by 2 studies [32,33,36]. Excluding these reports, the association remained statistically signifi-cant without significant heterogeneity. The mean follow-up time for pooled studies was 24 weeks (range 8 weeks to 1 year).

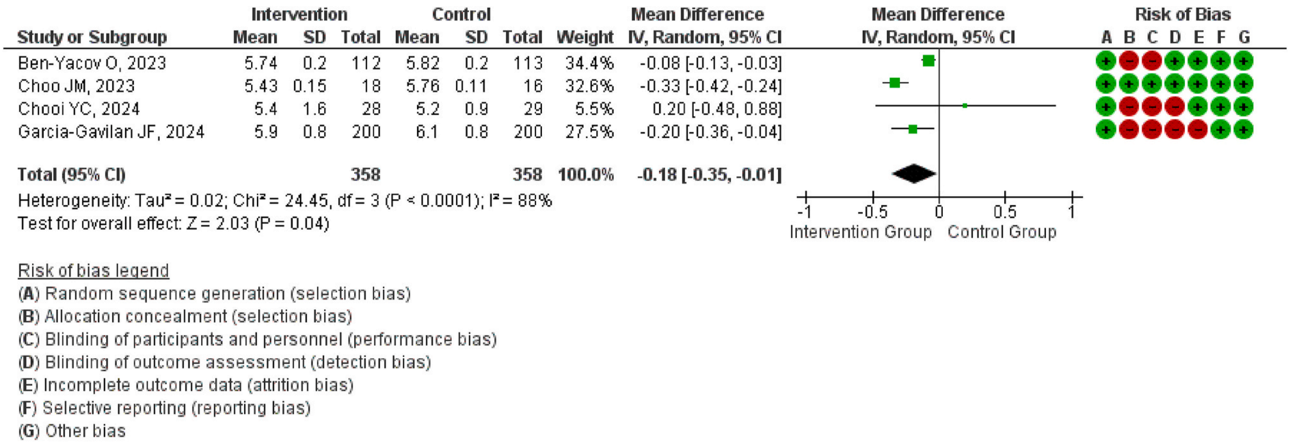


Study or Subgroup	Intervention Mean	Intervention SD	Intervention Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	A	B	C	D	E	F	G
Ben-Yacov O, 2023	6.33	0.61	112	6.33	0.78	113	22.1%	0.00 [-0.18, 0.18]	+	−	−	+	+	+	+
Choo JM, 2023	5.2	1	19	5.1	0.8	18	10.6%	0.10 [-0.48, 0.68]	+	+	+	+	+	+	+
Chooi YC, 2024	5	2.9	31	4.8	2.7	29	2.8%	0.20 [-1.22, 1.62]	+	−	−	−	+	+	+
Davis CR, 2017	5.01	0.5	85	5.04	0.41	81	23.3%	-0.03 [-0.17, 0.11]	+	−	−	+	+	+	+
Galiè S, 2021	5.41	0.68	23	5.69	0.68	21	15.2%	-0.28 [-0.68, 0.12]	+	−	−	+	+	+	+
Garcia-Gavilan JF, 2024	5.1	1.4	200	5.8	1.3	200	19.6%	-0.70 [-0.96, -0.44]	+	−	−	−	−	+	+
Vitale M, 2021	4.9	1.1	15	5.4	1.2	13	6.4%	-0.50 [-1.36, 0.36]	+	+	+	+	+	+	+
Total (95% CI)			**485**			**475**	**100.0%**	**-0.20 [-0.45, 0.05]**							

Heterogeneity: Tau² = 0.07; Chi² = 23.79, df = 6 (P = 0.0006); I² = 75%
Test for overall effect: Z = 1.58 (P = 0.11)

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Fig. 2. Effects of the Mediterranean diet on blood glucose.

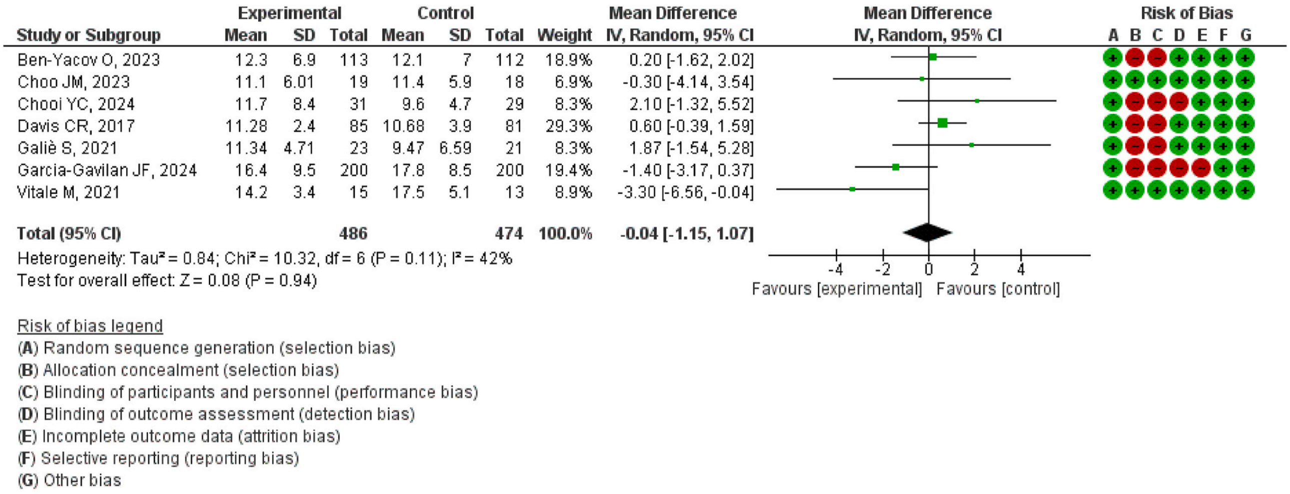


Study or Subgroup	Intervention Mean	Intervention SD	Intervention Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	A	B	C	D	E	F	G
Ben-Yacov O, 2023	5.74	0.2	112	5.82	0.2	113	34.4%	-0.08 [-0.13, -0.03]	+	-	-	+	+	+	+
Choo JM, 2023	5.43	0.15	18	5.76	0.11	16	32.6%	-0.33 [-0.42, -0.24]	+	+	+	+	+	+	+
Chooi YC, 2024	5.4	1.6	28	5.2	0.9	29	5.5%	0.20 [-0.48, 0.88]	+	-	-	-	+	+	+
Garcia-Gavilan JF, 2024	5.9	0.8	200	6.1	0.8	200	27.5%	-0.20 [-0.36, -0.04]	+	-	-	-	-	+	+
Total (95% CI)			**358**			**358**	**100.0%**	**-0.18 [-0.35, -0.01]**							

Heterogeneity: Tau² = 0.02; Chi² = 24.45, df = 3 (P < 0.0001); I² = 88%
Test for overall effect: Z = 2.03 (P = 0.04)

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Fig. 3. Effects of the Mediterranean diet on HbA1c.

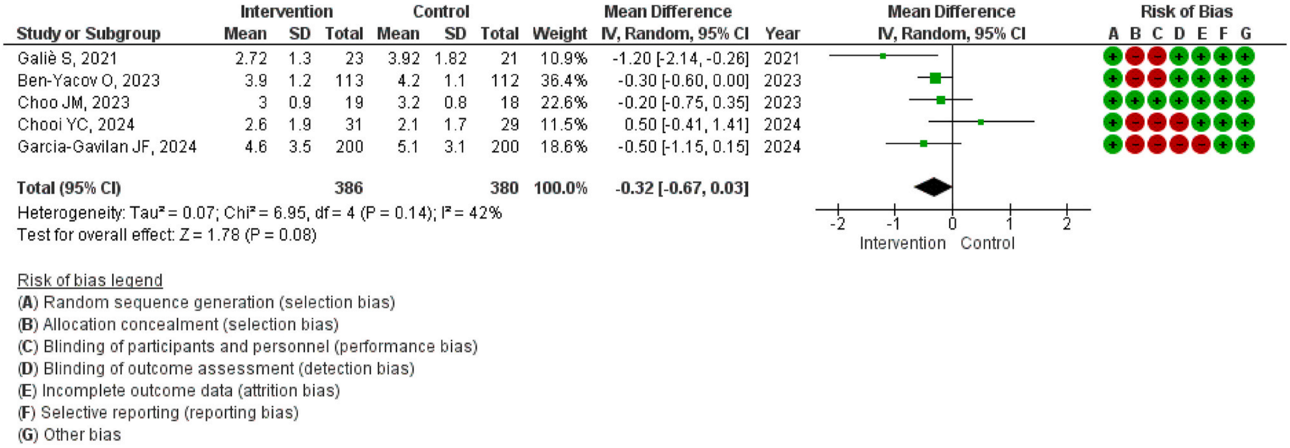


Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	A	B	C	D	E	F	G
Ben-Yacov O, 2023	12.3	6.9	113	12.1	7	112	18.9%	0.20 [-1.62, 2.02]	+	-	-	+	+	+	+
Choo JM, 2023	11.1	6.01	19	11.4	5.9	18	6.9%	-0.30 [-4.14, 3.54]	+	+	+	+	+	+	+
Chooi YC, 2024	11.7	8.4	31	9.6	4.7	29	8.3%	2.10 [-1.32, 5.52]	+	-	-	-	+	+	+
Davis CR, 2017	11.28	2.4	85	10.68	3.9	81	29.3%	0.60 [-0.39, 1.59]	+	-	-	+	+	+	+
Galiè S, 2021	11.34	4.71	23	9.47	6.59	21	8.3%	1.87 [-1.54, 5.28]	+	-	-	+	+	+	+
Garcia-Gavilan JF, 2024	16.4	9.5	200	17.8	8.5	200	19.4%	-1.40 [-3.17, 0.37]	+	-	-	-	-	+	+
Vitale M, 2021	14.2	3.4	15	17.5	5.1	13	8.9%	-3.30 [-6.56, -0.04]	+	+	+	+	+	+	+
Total (95% CI)			**486**			**474**	**100.0%**	**-0.04 [-1.15, 1.07]**							

Heterogeneity: Tau² = 0.84; Chi² = 10.32, df = 6 (P = 0.11); I² = 42%
Test for overall effect: Z = 0.08 (P = 0.94)

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Fig. 4. Effects of the Mediterranean diet on insulin.



Study or Subgroup	Intervention Mean	Intervention SD	Intervention Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	Year	A	B	C	D	E	F	G
Galiè S, 2021	2.72	1.3	23	3.92	1.82	21	10.9%	-1.20 [-2.14, -0.26]	2021	+	-	-	+	+	+	+
Ben-Yacov O, 2023	3.9	1.2	113	4.2	1.1	112	36.4%	-0.30 [-0.60, 0.00]	2023	+	-	-	+	+	+	+
Choo JM, 2023	3	0.9	19	3.2	0.8	18	22.6%	-0.20 [-0.75, 0.35]	2023	+	+	+	+	+	+	+
Chooi YC, 2024	2.6	1.9	31	2.1	1.7	29	11.5%	0.50 [-0.41, 1.41]	2024	+	-	-	-	+	+	+
Garcia-Gavilan JF, 2024	4.6	3.5	200	5.1	3.1	200	18.6%	-0.50 [-1.15, 0.15]	2024	+	-	-	-	-	+	+
Total (95% CI)			**386**			**380**	**100.0%**	**-0.32 [-0.67, 0.03]**								

Heterogeneity: Tau² = 0.07; Chi² = 6.95, df = 4 (P = 0.14); I² = 42%
Test for overall effect: Z = 1.78 (P = 0.08)

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Fig. 5. Effects of the Mediterranean diet on HOMA-IR.

A total of 7 studies analyzed the effect of the MedD on insulin levels [17,27–30,32,33,35,36], revealing a not significant reduction compared with the control group (MD = −0.04, 95 % CI = −1.15, 1.07) without significant heterogeneity (I^2 = 42 %, P = 0.11) (Fig. 4). The mean follow-up time for pooled studies was 20 weeks (range 8 weeks to 1 year).

A total of 5 studies explored the effect of the MedD on HOMA-IR [27–29,32,33,35,36], showing a not significant reduction compared with the control group (MD = −0.32, 95 % CI = −0.67, 0.03) without significant heterogeneity (I^2 = 42 %, P = 0.14) (Fig. 5). The mean follow-up time for pooled studies was 21 weeks (range 8 weeks to 1 year).

3.3. Overall effects of Mediterranean diet on lipid metabolism

Using data pooled from the RCTs, we analyzed the effects of the MedD on total cholesterol, LDL and HDL-cholesterol, and triglycerides (Figs. 6–9).

Five studies assessed the effect of the MedD on total cholesterol [17,27–31], revealing a not significant reduction in the MedD group compared to the control group (MD = −0.12, 95 % CI = −0.25, 0.01), without significant heterogeneity (I^2 = 15 %, P = 0.32) (Fig. 6). The mean follow-up time for pooled studies was 20 weeks (range 8 weeks to 1 year).

Similarly, 5 studies evaluated the effect of the MedD on LDL-cholesterol [17,27–31], demonstrating a significant reduction in the MedD group compared to the control group (MD = −0.10, 95 % CI = −0.19, −0.00) without significant heterogeneity (I^2 = 4 %, P = 0.39) (Fig. 7). The mean follow-up time for pooled studies was 20 weeks (range 8 weeks to 1 year).

The effect of HDL-cholesterol was examined in 5 studies [17,27–31], revealing a not significant increase in the MedD group compared to the control group (MD = 0.01, 95 % CI = – 0.02, 0.05) without significant heterogeneity (I^2 = 0 %, P = 0.44) (Fig. 8). The mean follow-up time for pooled studies was 20 weeks (range 8 weeks to 1 year).

Lastly, 5 studies assessed the impact of triglycerides [17,27–31], revealing a significant reduction in the MedD group compared to the control group (MD = – 0.20, 95 % CI = – 0.28, – 0.12) without significant heterogeneity (I^2 = 0 %, P = 0.70) (Fig. 9). The mean follow-up time for pooled studies was 20 weeks (range 8 weeks to 1 year).

3.4. Overall effects of Mediterranean diet on GM

This section provides a descriptive analysis of the impact of Mediterranean-based dietary patterns on GM diversity, as the heterogeneity in GM-related outcomes across studies precluded a quantitative meta-analysis. García et al. [29] reported beneficial changes in GM composition alongside cardiometabolic health. Specifically, after one year, the intervention group (IG) showed a reduction in the abundance of the *Eubacterium hallii* group (– 0.02 ± 1.1) and genus *Dorea* (– 0.2 ± 1.2) compared to the control group (CG) indicating a shift towards a healthier GM profile. Additionally, the authors reported an increase in alpha diversity indices, Chao1 (mean and SD: 5.5 ± 17.5) and Shannon (0.1 ± 0.5), after one year of follow-up among the participants in the IG compared with those in the CG (β = 6.376, p = 0.0005; β = 0.131, p = 0.013, respectively).

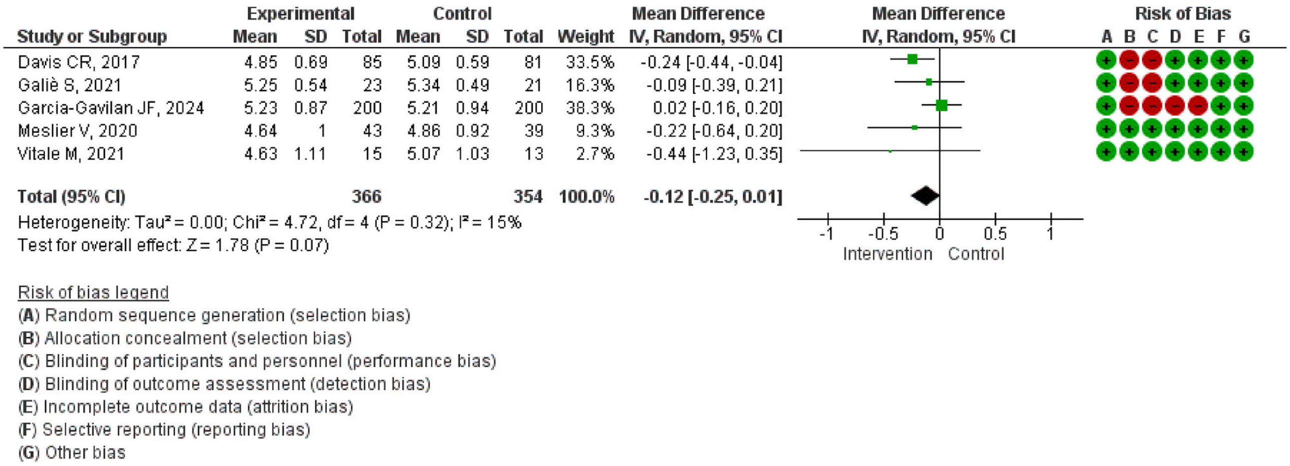
Similarly, Chooi et al. [35] found a significant increase induced by a MedD-like adapted for Asians (C15:0 supplementation) in *Bifidobacterium adolescentis* (β = 0.22 and β = 0.35 against Control and Diet without C15, respectively) whereas the abundance of *Bacteroides dorei* (β = 0.16) and *Bacteroides stercoris* (β = 0.19) was reduced.

Shoer et al. [37] showed that both interventions significantly influenced GM composition, metabolic profiles, and immune responses. Specifically, they reported an increase in *Bacteroides uniformis*, *Roseburia inulinivorans*, and *Faecalibacterium prausnitzii*, while observing a reduction in *Escherichia coli* and *Ruminococcus torques*.

Galiè et al. [27,28] identified two distinct microbial clusters linked to specific metabolites influenced by the MedD. The first blender, including *Lachnospiraceae* (uncultured genus), *Ruminococcaceae UCG002*, *Lachnoclostridium*, and various *Prevotellaceae* genera, was positively correlated with beneficial lipid metabolites such as triglycerides (TGs 56:6, 56:5) and cholesterol esters (ChoE 20:5), and negatively correlated with taurine. In contrast, the second cluster, consisting of *Christensenellaceae* family, *Oxalobacter,* Clostridiales family XII, *Ruminococcaceae UCG009*, and *Terrisporobacter*, showed the opposite pattern of associations.

Vitale et al. [30] reported that a MedD intervention led to increased alpha diversity compared to a control diet. The study also documented a decrease in the relative abundance of potentially harmful bacteria, including *Ruminococcus torques*, *Coprococcus comes*, *Streptococcus gallolyticus*, and *Flavonifractor plautii*, while promoting the growth of beneficial microbes like *Intestinimonas butyriciproducens* and *Akkermansia muciniphila*. Additionally, butyric acid levels increased, correlating positively with *Bacteroides xylanisolvens* and *Roseburia hominis*.

Meslier et al. [31] further supported the findings from Vitale et al. [30], demonstrating that adherence to the MedD enhanced microbial diversity and genetic richness. After 4 weeks, genetic richness increased by 8 % compared to baseline ($p < 0.05$) and by 10 % after eight weeks ($p < 0.01$). Additionally, the richness of Metagenomic Species Pangenomes (MSP) was measured at 230.9 ± 53.1. The authors observed an increase in anti-inflammatory species, including *Faecalibacterium prausnitzii*, *Roseburia*, and members of the Lachnospiraceae family alongside a reduction in pro-inflammatory bacteria like *Ruminococcus gnavus*. Additionally, microbial genes associated with carbohydrate degradation and butyrate metabolism were upregulated, emphasizing the MedD's influence on microbiota functionality beyond mere compositional changes. In contrast, Choo et al. [36] investigated the effects of a MedD supplemented with dairy foods (MedDairy) and found no substantial alterations in overall GM composition (PERMANOVA p = 0.573). However, specific bacterial taxa did exhibit notable shifts. Specifically, after eight weeks of intervention, the relative abundance of *Butyricicoccus*, *Lachnospiraceae NK4A136*, and *Streptococcus* increased, while *Collinsella*, *Veillonella*, two taxa from the *Oscillospiraceae* family (*Oscillospirales* uncultured, UCG-002), and *Ruminococcaceae UBA 1B19* decreased. Notably, a higher relative abundance of *Butyricicoccus* was significantly associated with greater adherence to a MedD and with

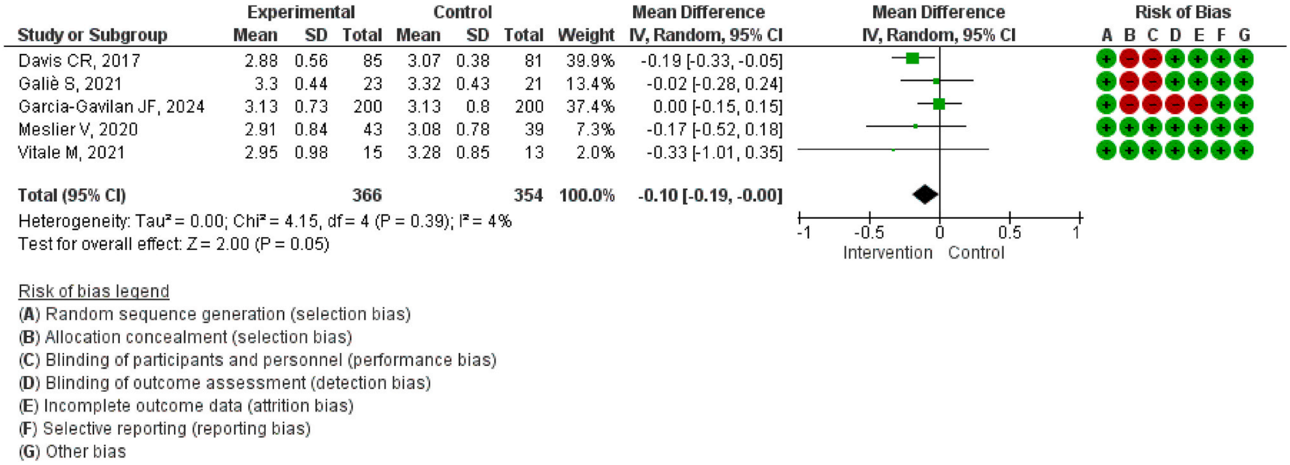


Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	Risk of Bias A	B	C	D	E	F	G
Davis CR, 2017	4.85	0.69	85	5.09	0.59	81	33.5%	-0.24 [-0.44, -0.04]	+	−	−	+	+	+	+
Galiè S, 2021	5.25	0.54	23	5.34	0.49	21	16.3%	-0.09 [-0.39, 0.21]	+	−	−	+	+	+	+
Garcia-Gavilan JF, 2024	5.23	0.87	200	5.21	0.94	200	38.3%	0.02 [-0.16, 0.20]	+	−	−	−	−	+	+
Meslier V, 2020	4.64	1	43	4.86	0.92	39	9.3%	-0.22 [-0.64, 0.20]	+	+	+	+	+	+	+
Vitale M, 2021	4.63	1.11	15	5.07	1.03	13	2.7%	-0.44 [-1.23, 0.35]	+	+	+	+	+	+	+
Total (95% CI)			**366**			**354**	**100.0%**	**-0.12 [-0.25, 0.01]**							

Heterogeneity: Tau² = 0.00; Chi² = 4.72, df = 4 (P = 0.32); I² = 15%
Test for overall effect: Z = 1.78 (P = 0.07)

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Fig. 6. Effects of the Mediterranean diet on total cholesterol.

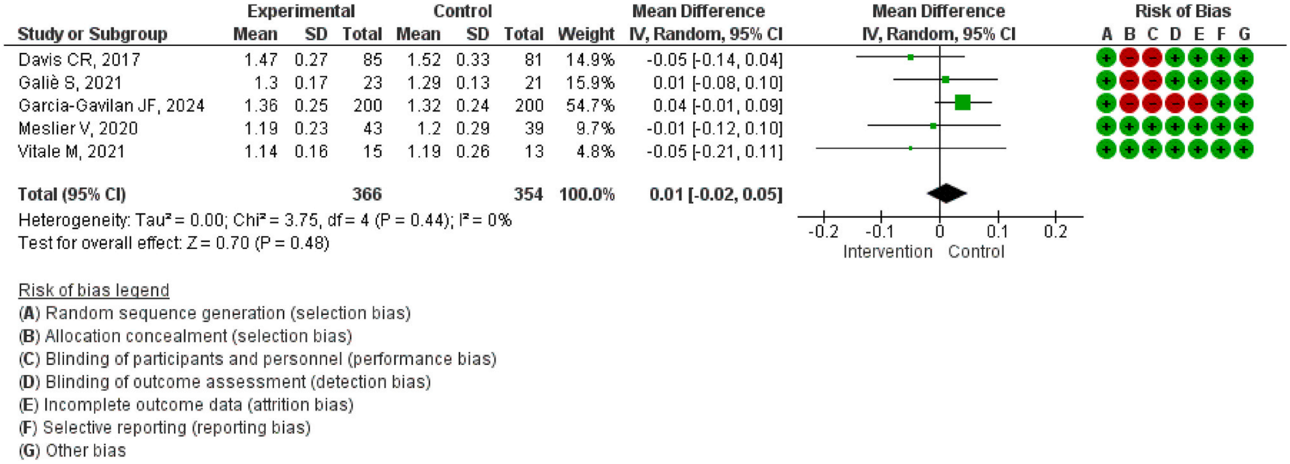


Study or Subgroup	Experimental			Control			Weight	Mean Difference	Risk of Bias						
	Mean	SD	Total	Mean	SD	Total		IV, Random, 95% CI	A	B	C	D	E	F	G
Davis CR, 2017	2.88	0.56	85	3.07	0.38	81	39.9%	-0.19 [-0.33, -0.05]	+	−	−	+	+	+	+
Galiè S, 2021	3.3	0.44	23	3.32	0.43	21	13.4%	-0.02 [-0.28, 0.24]	+	−	−	+	+	+	+
Garcia-Gavilan JF, 2024	3.13	0.73	200	3.13	0.8	200	37.4%	0.00 [-0.15, 0.15]	+	−	−	−	−	+	+
Meslier V, 2020	2.91	0.84	43	3.08	0.78	39	7.3%	-0.17 [-0.52, 0.18]	+	+	+	+	+	+	+
Vitale M, 2021	2.95	0.98	15	3.28	0.85	13	2.0%	-0.33 [-1.01, 0.35]	+	+	+	+	+	+	+
Total (95% CI)			**366**			**354**	**100.0%**	**-0.10 [-0.19, -0.00]**							

Heterogeneity: Tau² = 0.00; Chi² = 4.15, df = 4 (P = 0.39); I² = 4%
Test for overall effect: Z = 2.00 (P = 0.05)

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Fig. 7. Effects of the Mediterranean diet on LDL-cholesterol.

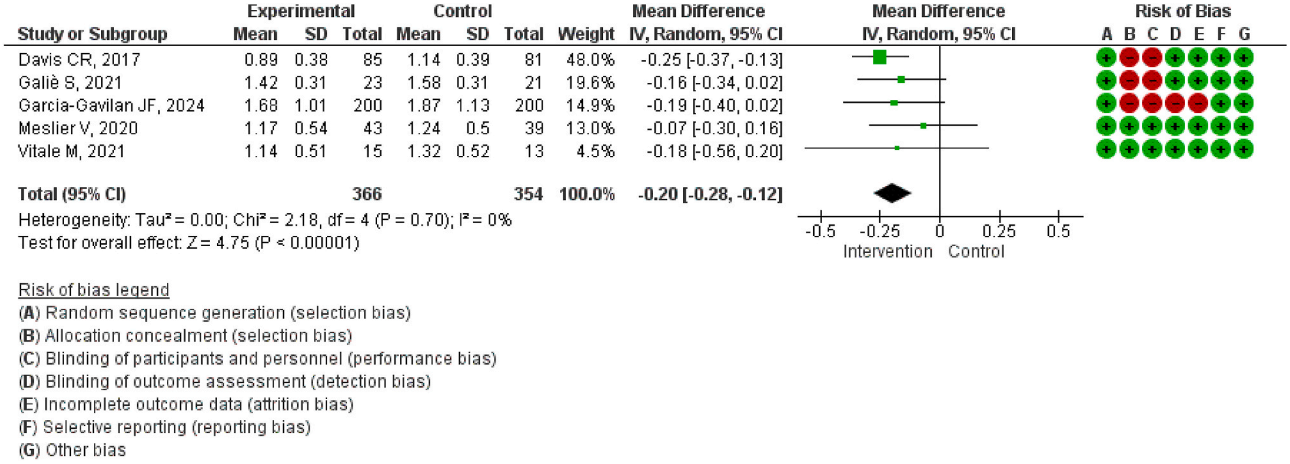


Study or Subgroup	Experimental			Control			Weight	Mean Difference	Risk of Bias						
	Mean	SD	Total	Mean	SD	Total		IV, Random, 95% CI	A	B	C	D	E	F	G
Davis CR, 2017	1.47	0.27	85	1.52	0.33	81	14.9%	-0.05 [-0.14, 0.04]	+	−	−	+	+	+	+
Galiè S, 2021	1.3	0.17	23	1.29	0.13	21	15.9%	0.01 [-0.08, 0.10]	+	−	−	+	+	+	+
Garcia-Gavilan JF, 2024	1.36	0.25	200	1.32	0.24	200	54.7%	0.04 [-0.01, 0.09]	+	−	−	−	−	+	+
Meslier V, 2020	1.19	0.23	43	1.2	0.29	39	9.7%	-0.01 [-0.12, 0.10]	+	+	+	+	+	+	+
Vitale M, 2021	1.14	0.16	15	1.19	0.26	13	4.8%	-0.05 [-0.21, 0.11]	+	+	+	+	+	+	+
Total (95% CI)			**366**			**354**	**100.0%**	**0.01 [-0.02, 0.05]**							

Heterogeneity: Tau² = 0.00; Chi² = 3.75, df = 4 (P = 0.44); I² = 0%
Test for overall effect: Z = 0.70 (P = 0.48)

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Fig. 8. Effects of the Mediterranean diet on HDL-cholesterol.



Study or Subgroup	Experimental			Control			Weight	Mean Difference	Risk of Bias						
	Mean	SD	Total	Mean	SD	Total		IV, Random, 95% CI	A	B	C	D	E	F	G
Davis CR, 2017	0.89	0.38	85	1.14	0.39	81	48.0%	-0.25 [-0.37, -0.13]	+	−	−	+	+	+	+
Galiè S, 2021	1.42	0.31	23	1.58	0.31	21	19.6%	-0.16 [-0.34, 0.02]	+	−	−	+	+	+	+
Garcia-Gavilan JF, 2024	1.68	1.01	200	1.87	1.13	200	14.9%	-0.19 [-0.40, 0.02]	+	−	−	−	−	+	+
Meslier V, 2020	1.17	0.54	43	1.24	0.5	39	13.0%	-0.07 [-0.30, 0.16]	+	+	+	+	+	+	+
Vitale M, 2021	1.14	0.51	15	1.32	0.52	13	4.5%	-0.18 [-0.56, 0.20]	+	+	+	+	+	+	+
Total (95% CI)			**366**			**354**	**100.0%**	**-0.20 [-0.28, -0.12]**							

Heterogeneity: Tau² = 0.00; Chi² = 2.18, df = 4 (P = 0.70); I² = 0%
Test for overall effect: Z = 4.75 (P < 0.00001)

Risk of bias legend
(**A**) Random sequence generation (selection bias)
(**B**) Allocation concealment (selection bias)
(**C**) Blinding of participants and personnel (performance bias)
(**D**) Blinding of outcome assessment (detection bias)
(**E**) Incomplete outcome data (attrition bias)
(**F**) Selective reporting (reporting bias)
(**G**) Other bias

Fig. 9. Effects of the Mediterranean diet on triglycerides.

lower systolic blood pressure (SBP), a clinical marker shown to be reduced following the MedDairy diet.

The DIRECT-PLUS study by Rinott et al. [34] explored different variations of MedD interventions, comparing the traditional MedD with the Green-MedD. Both diets significantly altered GM composition, with the Green-MedD, characterized by increased plant-based food intake and reduced meat consumption, induced more pronounced changes. Specifically, the authors noted an increase in *Prevotella* and a reduction in *Bifidobacterium*, supporting the notion that distinct dietary modifications within a Mediterranean framework can drive unique GM adaptations. Fig. 10 summarizes the key findings regarding GM changes across different MedD intervention studies.

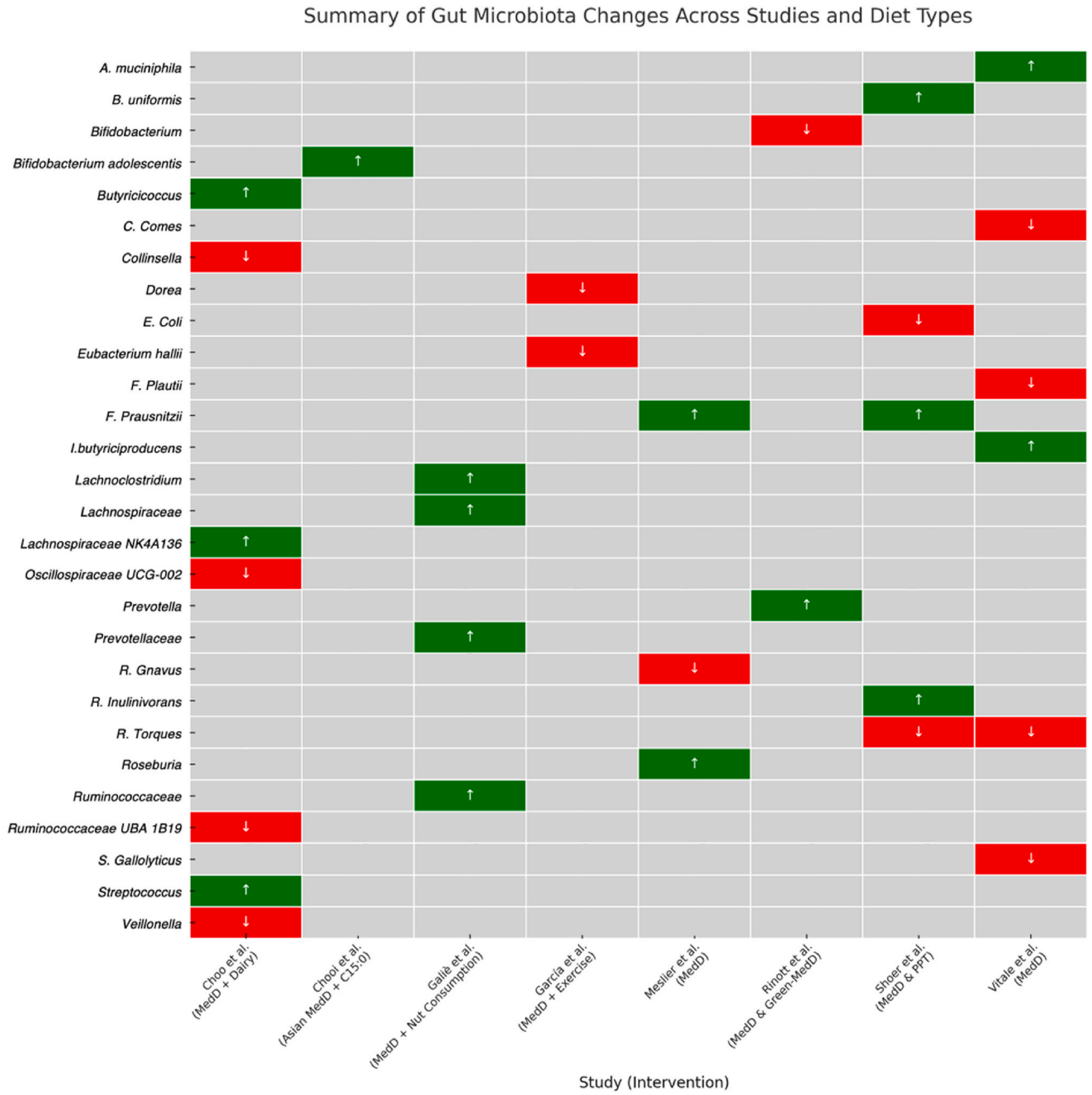


Fig. 10. Key findings regarding gut microbiota changes across different Mediterranean diet interventions.

4. Discussion

Earlier research confirmed by recent studies has provided strong evidence for the benefits of the MedD on cardiovascular health, including reduction in the incidence of cardiovascular outcomes as well as risk factors including obesity, hypertension, metabolic syndrome and dyslipidemia [16,38,39]. Adherence to the MedD is also linked to lower rates of type 2 diabetes and better glycemic control in diabetic patients compared to control dies [40,41]. However, the mechanisms underlying these benefits remain partially understood. It is still unclear whether the beneficial health effects associated with the MedD are driven by the diet itself or through accompanying changes in GM composition. Similarly, it is not completely clear whether better glycemic control by the MedD extends to both diabetic and non-diabetic populations.

To the best of our knowledge, this systematic review and meta- analysis is the first to evaluate the effects of a diet resembling the features of the MedD-like pattern on glucose and lipid metabolism in adults with overweight/obesity or metabolic syndrome, considering the potential mediation of GM composition. Our findings indicate that in individuals at high risk of developing type 2 diabetes and cardiovascular diseases, adherence to a MedD-style, in intervention trials, leads to reductions in HbA1c (− 18 %), LDL-cholesterol (− 10 %), and triglycerides (− 20 %) compared to a control diets. However, the estimate for LDL cholesterol was influenced by heterogeneity. Although negative trends of MedD on glucose, insulin, HOMA-IR, total cholesterol, and HDL-cholesterol cannot be ruled out, the evidence remains inconclusive, as these changes did not achieve statistical significance. Furthermore, the presence of publication bias further weakens the reliability of these estimates, underscoring the importance of unpublished negative results, which may undermine the scientific consensus and contribute to potential unsubstantiated conclusions [42].

The studies reviewed consistently emphasize the positive role of

Mediterranean-based dietary patterns in modulating GM composition [31]. Increased microbial diversity and beneficial shifts in specific taxa, such as *Faecalibacterium prausnitzii*, *Akkermansia muciniphila*, and *Butyricicoccus*, were frequently observed across interventions. These taxa are known for their anti-inflammatory properties and associations with improving metabolic and immune functions [13,43,44]. Addi-tionally, dietary variations, such as the C15:0 supplementation or the Green-MED diet, suggest potential avenues in further enhancing these microbiota-mediated benefits. However, some adaptations like Med-Dairy failed to induce significant microbiome changes, underscoring the need for further research to understand the nuances of diet-microbiome interactions [36]. It is noteworthy that changes in the abundance of specific bacteria, such as *Prevotella copri*, which are associated with metabolic dysfunction and increased cardiometabolic disease risk in a Western diet, were observed following a switch to a MedD-style [45,46]. Future studies should focus on long-term effects, inter-individual vari-ability, and the potential mechanistic pathways linking dietary compo-nents to microbiota-driven metabolic health improvements. To this end, the suggestion of personalized approaches aligns well with recent ad-vances in precision nutrition. For example, predictive models such as the one developed by Zeevi et al. [47] have demonstrated how gut micro-biome composition can be used to predict individual dietary responses. This work laid the foundation for microbiome-based, personalized di-etary recommendations. These models are currently undergoing refinement and validation with more diverse cohorts. In fact, large-scale interventions like the PREDICT studies [48] are actively exploring how individual glycemic, lipid, and inflammatory responses to food are shaped by a combination of microbiome profiles, genetic variants, and lifestyle factors. These studies underscore the potential of integrating multi-omic data for more effective and personalized dietary interventions.

Studies such as those by Chooi et al. [35], Shoer et al. [37], and Galè et al. [27,28] highlight the intricate interaction between diet, micro-biota, and host metabolism. In parallel, Vitale et al. [30] reinforced the notion that the MedD enhances gut microbial diversity, fostering a more metabolically beneficial microbiome. Nevertheless, further long-term studies are needed to clarify these relationships, especially in diverse populations and under different metabolic conditions.

The present meta-analysis has several strengths. First, it employs strict eligibility criteria that exclude studies without a control group (i. e., sequential studies), and those lacking GM data. Consequently, only high-quality studies were included. The absence of a detected effect may, however, reflect limited statistical power. Second, a comprehen-sive search for potential studies across multiple electronic databases was applied. Efforts were also made to contact the authors of the included RCTs for any missing data. Finally, four authors independently per-formed RCT selection, appraisal, and data extraction, minimizing bias.

Nonetheless, the present study has some limitations. Many of the original studies included small sample size and short duration, intro-ducing a potential bias. Approximately 50 % of the pooled results exhibited high statistical heterogeneity, likely attributable to variations in dietary interventions, baseline health characteristics, and sample size. To address this issue, we employed random-effects modeling to pool the data and applied sensitivity analysis to identify the impact of each in-dividual study on the pooled outcomes. Finally, a meta-analysis of GM- related outcomes was not feasible due to the lack of standardization in microbial endpoints and reporting. Future quantitative syntheses would benefit from adopting standardized protocols for sample collection, sequencing methods, and reporting of microbial diversity indices and taxa-level changes, ideally aligned with internationally recognized guidelines.

In conclusion, this meta-analysis does not provide definitive evi-dence that the MedD improves all metabolic risk factors for type 2 diabetes, particularly in the context of GM composition. It does, how-ever, confirm benefits on LDL cholesterol and triglycerides, supporting its role in cardiometabolic health. These findings highlight the need for further research on microbiota-mediated effects, individual response, longer intervention and mechanistic insights via multi-omics ap-proaches to better understand the diet–microbiota–host interaction. The MedD remains a sustainable and adaptable dietary framework deserving continued promotion in clinical and public health settings.

Author contributions

F.L., A.F., M.D.R., C.S., R.G., G.L.R. and M.V. drafted the original manuscript. F.L. conceived and designed the study. F.L., A.F., M.D.R., C. Q., C.S., and M.V. contributed to data collection. F.L., C.Q., M.V. and M. D.R. assessed all potentially relevant full-length articles. A.F. and C.S. resolved disagreements regarding the inclusion or exclusion of selected articles. M.V. performed the statistical analyses. All authors read and approved the final version of the manuscript.

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Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2025.104433.

Data availability

All data produced or analyzed during this study are available upon request.

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