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Original article

Effects of the Mediterranean diet on cardiovascular risk factors in non-alcoholic fatty liver disease patients: A systematic review and meta-analysis

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SUMMARY

Background & aims: We aimed to investigate the effect of the Mediterranean diet (MedDiet) on cardiovascular risk factors in patients with non-alcoholic fatty liver disease (NAFLD).
Method: A systematic search was performed in Scopus, Web of Science, Cochrane library and PubMed databases to find randomized controlled trials (RCTs) related to the effect of the MedDiet in patients with NAFLD, up to July, 2019. There was no language and time limitation. Meta-analyses were performed using both the random and fixed effects model where appropriate, and I2 index was used to evaluate the heterogeneity.
Results: Primary search yielded 467 publications. Five RCTs were eligible. Our meta-analysis indicated that the MedDiet resulted in a significant decrease in serum levels of triglyceride and total cholesterol, and a decrease in body weight and HOMA-IR in comparison to a control diet, in NAFLD patients. Whereas, there were no significant improvement in the MedDiet group compared with the control group regarding other variables such as liver enzymes and blood pressure.
Conclusions: This meta-analysis indicated the advantageous effects of the MedDiet on some cardiovascular risks factors, as compared with a control diet. It seems that the MedDiet can be considered as an appropriate strategy to reduce cardiovascular risk factors in NAFLD patients.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is a developed metabolic stress-related liver disorder that was originally assumed to be largely confined to the people with Western lifestyles [1]. It is associated with an increased risk of hepatic and extra-hepatic complications such as cirrhosis and cardiovascular disease (CVD) [2]. Based on some population-based studies the global prevalence of NAFLD is 6%–35% of the general population [3]. Previous investigations have reported a relationship between NAFLD and CVD, which is the main causes of morbidity and mortality in these patients [4]. A meta-analysis of 16 observational prospective and retrospective studies with 34,043 adult individuals demonstrated that NAFLD is associated with an increased risk of CVD events [5]. It seems that NAFLD is correlated with factors such as dyslipidemia, central obesity, diabetes, and metabolic syndrome that may cause CVD [6]. The high morbidity, mortality, and health care costs associated with CVD in these patients, have led investigators to seek novel therapies, and early diagnosis and treatment of NAFLD is often aimed at reducing the complications of CVD [7].

The Mediterranean diet (MedDiet) is the generic name of the traditional dietary patterns of the individuals living in the Mediterranean region. It was first defined by Ancel Keys as a diet low in saturated fat and high in vegetable oils [8]. The MedDiet is characterized by a high intake of olive oil, fruit, nuts, vegetables, and cereals; a moderate intake of fish and poultry; a low intake of dairy products, red meat, processed meats, and sweets; and moderation

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wine consumption with meals [9]. In traditional MedDiet, plant foods constituted the core of the daily intake, while foods from animal were more peripheral. However, the MedDiet presented in the pyramid is not a vegetarian diet [9]. The beneficial effects of the MedDiet on health have been reported in numerous investigations [10]. Several cohort studies have reported that the MedDiet decreased the risk of CVD [11,12]. Among the different components of the MedDiet, olive oil, vegetable, fruit, and legumes seem to provide the strongest cardio-protective properties [13]. In regard to the NAFLD, a well-designed six-month randomized controlled trial (RCT) showed that adherence to the MedDiet could significantly reduce the fat content of the liver in patients with NAFLD, and this effect was independent of other lifestyle changes and weight loss [14].

Although, a recent meta-analysis reported the beneficial effects of MedDiet in patients with CVD [13], its beneficial effects in NAFLD patients are controversial. In 2017, a study indicated that the MedDiet improved anthropometric parameters and lipid profile in NAFLD patients, whereas it had no effect on insulin sensitivity [15]. However, a recent study concluded that adherence to the MedDiet in NAFLD patients had no significant effect on total cholesterol (TC), serum triglyceride (TG), and HbA1c in comparison to the control diet [16]. Therefore, we aimed to perform a systematic review and meta-analysis of RCTs to assess the effect of the MedDiet on cardiovascular risk factors including lipid profile like TG, TC, low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol, serum levels of liver enzymes including alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT), glycemic profile including fasting blood glucose (FBG), insulin, and homeostatic model assessment for insulin resistance (HOMA-IR), as well as, anthropometric parameters like body weight, body mass index (BMI), and waist circumference (CM), and both systolic blood pressure (SBP) and diastolic blood pressure (DBP) in patients with NAFLD.

2. Method

The present systematic review and meta-analysis adhered to the Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) statement guideline [17].

2.1. Search strategy

We systematically searched electronic databases including the Cochrane Library, PubMed, ISI Web of science and Scopus to detect RCTs that evaluated the effects of MedDiet on cardiovascular risk factors in patients with NAFLD, until July, 2019; without any language and date restriction. The merge of MESH and non-MESH terms were used as follows: “Mediterranean diet” AND (“Non alcoholic Fatty Liver Disease” OR “NAFLD” OR “Non-alcoholic Fatty Liver Disease” OR “Nonalcoholic Fatty Liver Disease” OR “Nonalcoholic Fatty Liver” OR “Nonalcoholic Fatty Livers” OR “Nonalcoholic Steatohepatitis” OR “NASH” OR “Nonalcoholic Steatohepatitides” OR “non-alcoholic steatohepatite” OR “non-alcoholic steatohepatitis” OR “non-alcoholic fatty liver disorders” OR “liver fat” OR “steatosis”). Also, we manually checked all reference lists of included articles and related reviews to avoid missing any relevant studies (Supplementary file 1, search strategy).

2.2. Eligibility criteria

The following criteria were considered as including criteria: 1) RCTs that were conducted on patients with NAFLD (regardless of previous CVD history), 2) RCTs included adult subjects (≥18 years old), 3) done on overweight or obese patients (BMI≥25), 5) RCTs that provided sufficient data on baseline and final measures of lipid profile, glycemic control, anthropometric indices, blood pressure and liver function enzymes in both MedDiet and control groups.

2.3. Excluded studies

Studies were excluded if they; 1) were done on children, animal and subjects without NAFLD, 2) were not RCT, 3) did not provide sufficient information for the outcomes in MedDiet or control groups.

2.4. Data extraction

Two investigators (OA and RC) individually screened the records. Two authors (OA and DA) extracted the data. Any disagreements in the inclusion of studies and data extraction were resolved under a chief investigator (AA). The following data were extracted from each study; first author's name, publication year, study design, region of the study, study duration, mean age and sex of the participants, sample size in each group, mean and SD of outcome measures at the baseline and the final stage of the study. All authors agreed with the studies included and most of the data extracted.

2.5. Quality assessment

We evaluated the quality of eligible studies by using the Cochrane scoring system [18]. This scoring system includes 7 criteria to evaluate the risk of bias: 1) random sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding of outcome assessment, 5) incomplete outcome data, 6) selective reporting, and 7) other source of biases. After evaluating the studies based on these items, each item takes one of the following points: (1) high risk, (2) low risk, and (3) unknown risk.

2.6. Data synthesis and statistical analysis

Effect sizes of all intended outcomes were expressed as weighted mean differences (WMDs) and 95% CI. The effect sizes were pooled exerting both random and fixed effects model where appropriate with DerSimonian and Laird method [19]. The mean net changes (mean values ± standard deviation) in the TG, TC, HDL-C, LDL-C, FBG, insulin, HOMA_IR, body weight, BMI, WC, SBP, DBP, ALT, AST and GGT for each study were calculated. Mean changes for the outcomes listed above were calculated by the difference between the final and initial values for each data, in both groups. Standard deviations (SDs) of the mean were calculated using the following formula: SD = square root [(SD pre-treatment) 2 + (SD post-treatment) 2 − (2 × 0.8 × SD pre-treatment × SD post-treatment)] [18]. When standard error of the mean (SEM) was reported, standard deviation (SD) was estimated by using the following formula: SD = SEM × sqrt (n) (n is the number of subjects) [20]. Heterogeneity between studies was evaluated by Cochrane's Q test (significance point at $p < 0.05$) and I^2 index. Publication bias was assessed using visual assessment of funnel plots, Beg test and Egger's regression asymmetry test. We performed the sensitivity analysis by conducting one-study remove (leave-one-out) approach, to estimate the impact of each trial on the pooled effect size. All statistical analyses were done using STATA software version 14 (STATA Corp, College Station, Texas). $P < 0.05$ was considered statistically significant. Funnel plots and egger tests.

3. Results

3.1. Selected studies

A total of 467 records were identified in primary search. After removal of duplicates (n = 222), title and abstract of 245 articles were assessed. After that, 240 articles were excluded due to: unrelated title and abstract, review studies and animal studies. Finally, 5 articles [15,16,21–23] were eligible for present systematic and meta-analysis. The flowchart of the searching process is indicated in the Fig. 1.

3.2. Studies characteristics

Among the eligible trials, one was a cross-over study [21], and other were parallel in design [15,16,22,23]. The included studies were conducted between 2013 and 2018, and included 167 patients. Trials duration ranged from 6 weeks [21] to 24 weeks [15,22,23]. All the studies were conducted on both sexes. These studies were conducted in Australia [16,21], Italy [15,22] and Greece [23]. The BMI of the participants ranged from 29 to 32 kg/m^2 and the age range was 33–56 years old. The main characteristics of the studies are shown in Table 1.

3.3. Findings from meta-analysis

Our meta-analysis indicated that the MedDiet resulted in a significant decrease in TG (n = 5, WMD: −39.77 mg/dl, 95% CI: −60.34, −19.20; $p < 0.001$) (Fig. 2, TC (n = 4, WMD: −23.93 mg/dl, 95% CI: −45.58, −2.28; $p = 0.030$) (Fig. 3), body weight (n = 5, WMD: −3.02 kg, 95% CI: −5.46, −0.57; $p = 0.045$) (Fig. 4) and HOMA-IR (n = 5, WMD: −0.80, 95% CI: −1.31, −0.29; $p = 0.002$) (Fig. 5) in comparison to a control diet. The MedDiet had no significant effect on the LDL, HDL, FBG, insulin, ALT, AST, GGT, BMI, WC, SBP and DBP (Table 2). On the other hand, there was no significant heterogeneity for HOMA-IR, WT, BMI, SBP, ALT, AST and GGT (Table 2). However, there were significant heterogeneities for TG, TC, LDL, HDL, FBG, insulin, WC and DBP (Table 2).

3.4. Quality assessment

All the studies [15,16,21–23] showed low risk of bias regarding the random sequence generation. Lack of allocation concealment was present in all the studies. Three trials [15,21,22] showed high risk of bias regarding the blinding of participants and personnel. All the trials [15,16,21–23] showed low risk of bias/unclear regarding

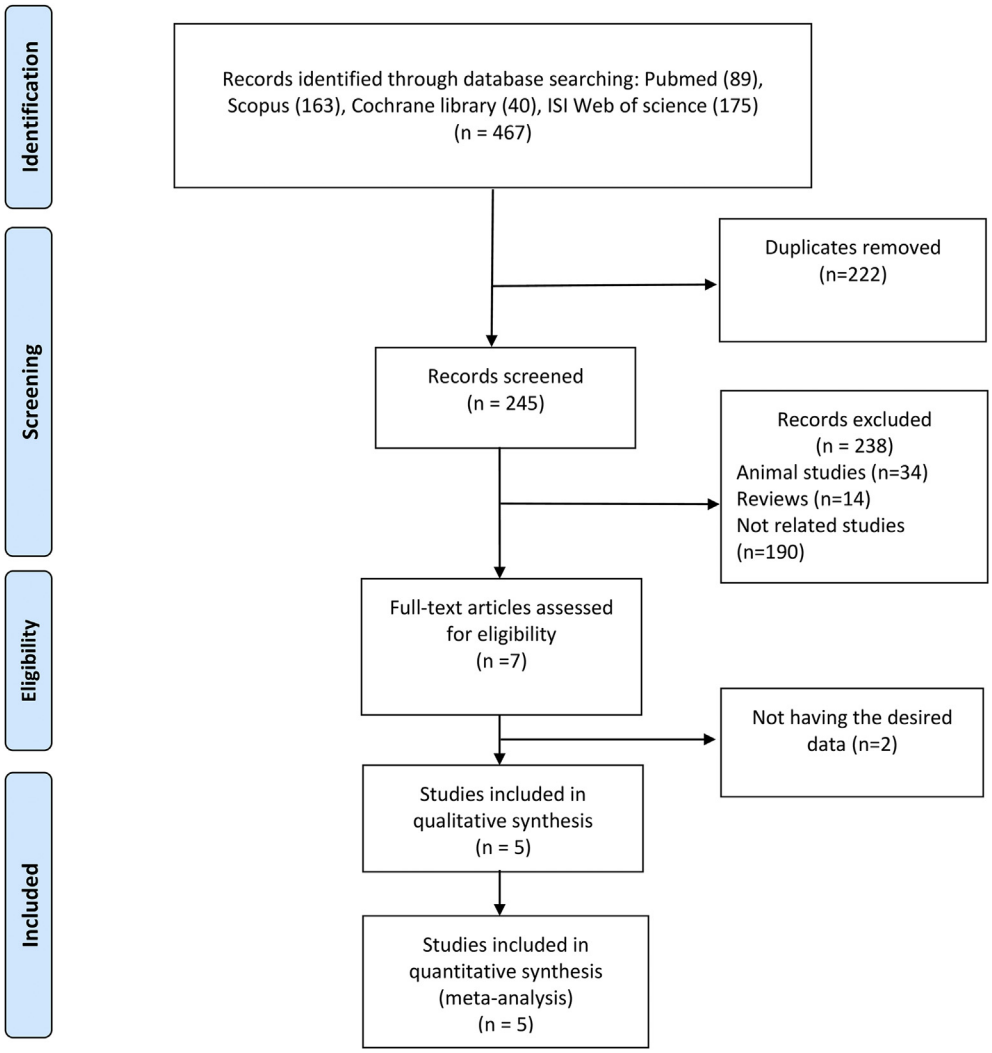

Fig. 1. Flow chart of selection of studies for inclusion in meta-analysis.

Table 1
Characteristic of included studies in meta-analysis.

Author	year	country	Study design	sex	Mean age (intervention /control)	Mean BMI (intervention /control)	Fatty liver disease status	Dietary intervention	Trial duration (week)	Sample size (intervention/ control)
MC Ryan	2013	Australia	R/C/CO	F/M	55/55	32/32	Steatosis≥33%	Traditional Cretan MD	6	12/12
L Abenavoli	2015	Italy	R/C/PA	F/M	56/33	32/29	NM	A personalized Mediterranean hypocaloric diet	24	10/10
L Abenavoli	2017	Italy	R/C/PA	F/M	52/33	31/29	NM	A personalized Mediterranean hypocaloric diet	24	20/10
CN Katsagoni	2018	Greece	R/C/PA	F/M	44/47	31.67/30.04	NM	Mediterranean food pattern, as described in the MD pyramid	24	21/21
C Properzi	2018	Australia	R/C/PA	F/M	51/53	31.5/30.2	Steatosis>5.5%	Traditional Cretan MD	12	26/25

R, randomize; C, control trial; CO, cross over; PA, parallel; F, female; M, male; NM, not mentioned; MD, Mediterranean diet.

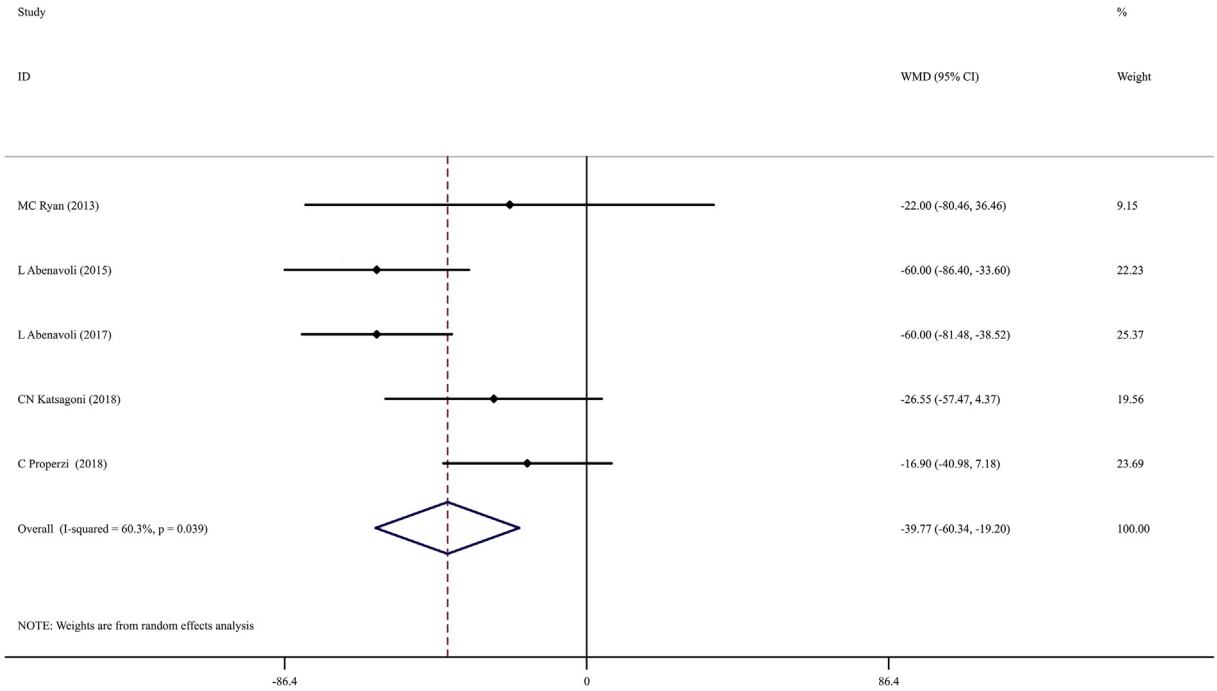

Fig. 2. Forest plot of the random-effects meta-analysis of the effect of the Mediterranean diet on serum levels of triglyceride.

the selective reporting and incomplete outcome data. More details are shown in Supplementary table 1.

3.5. Publication bias

Based on the egger's test, there is no publication bias for TG ($p = 0.186$), TC ($p = 0.071$), LDL ($p = 0.716$), HDL ($p = 0.261$), FBG ($p = 0.500$), insulin ($p = 0.856$), HOMA-IR ($p = 0.260$), WT ($p = 0.732$), BMI ($p = 0.444$), WC ($p = 0.224$), SBP ($p = 0.318$), DBP ($p = 0.845$), ALT ($p = 0.582$) and GGT ($p = 0.419$). In addition, the visual assessment of funnel plots revealed the same results (Supplementary file 2).

4. Sensitivity analysis

We found no significant effect of any trial on the overall effect sizes of TG, LDL, HDL, FBG, BMI, WC, SBP, DBP, AST and GGT. However by removing studies of L Abenavoli et al. [15] (WMD: −29.54 mg/dl, 95% CI: −59.57, 0.38) and Katsagoni et al. [23] (WMD: −24.58 mg/dl, 95% CI: −54.70, 5.53) effect of Mediterranean diet on TC, was significantly changed. Furthermore, by removing study of Properzi et al. [16] effect of Mediterranean diet on insulin was changed (WMD: −3.35 mIU/ml, 95% CI: −5.81, −0.89). Regarding HOMA-IR, after removing study of MC Ryan et al. [21] the result was significantly changed (WMD: −0.49, 95% CI: −1.09, 0.11). By removing study of MC Ryan et al. [21] (WMD: −6.52 IU, 95% CI: −12.77, −0.28) and C Properzi et al. [16] (WMD: −6.05 IU, 95% CI: −11.88, −0.21) effect of Mediterranean diet on ALT altered to significant. As well as, by removing both studies of L Abenavoli et al. [15,22] ((WMD: −2.21 kg, 95% CI: −4.97, 0.53), (WMD: −2.42 kg, 95% CI: −5.10, 0.24)) and study of CN Katsagoni et al. [23] (WMD: −2.55 kg, 95% CI: −5.24, 0.13) impact of Mediterranean diet on body weight was change to insignificant.

5. Meta-regression analysis

Meta-regression using the random-effects model was undertaken to investigate the potential association between a decrease in TG, TC, insulin and body weight, and study duration. Meta-regression analysis indicated a linear relationship between duration and changes in body weight ($p = 0.010$) (Table 3 and Supplementary file 3).

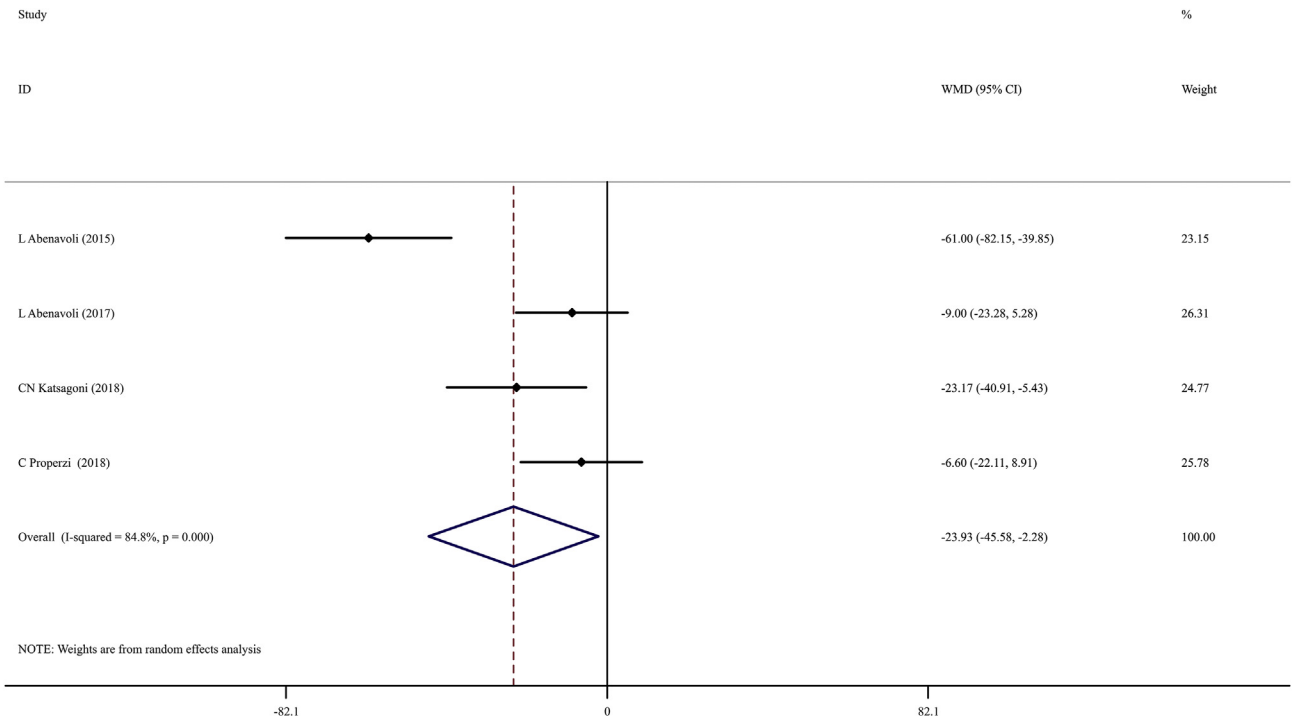

Fig. 3. Forest plot of the random-effects meta-analysis of the effect of the Mediterranean diet on serum levels of total cholesterol.

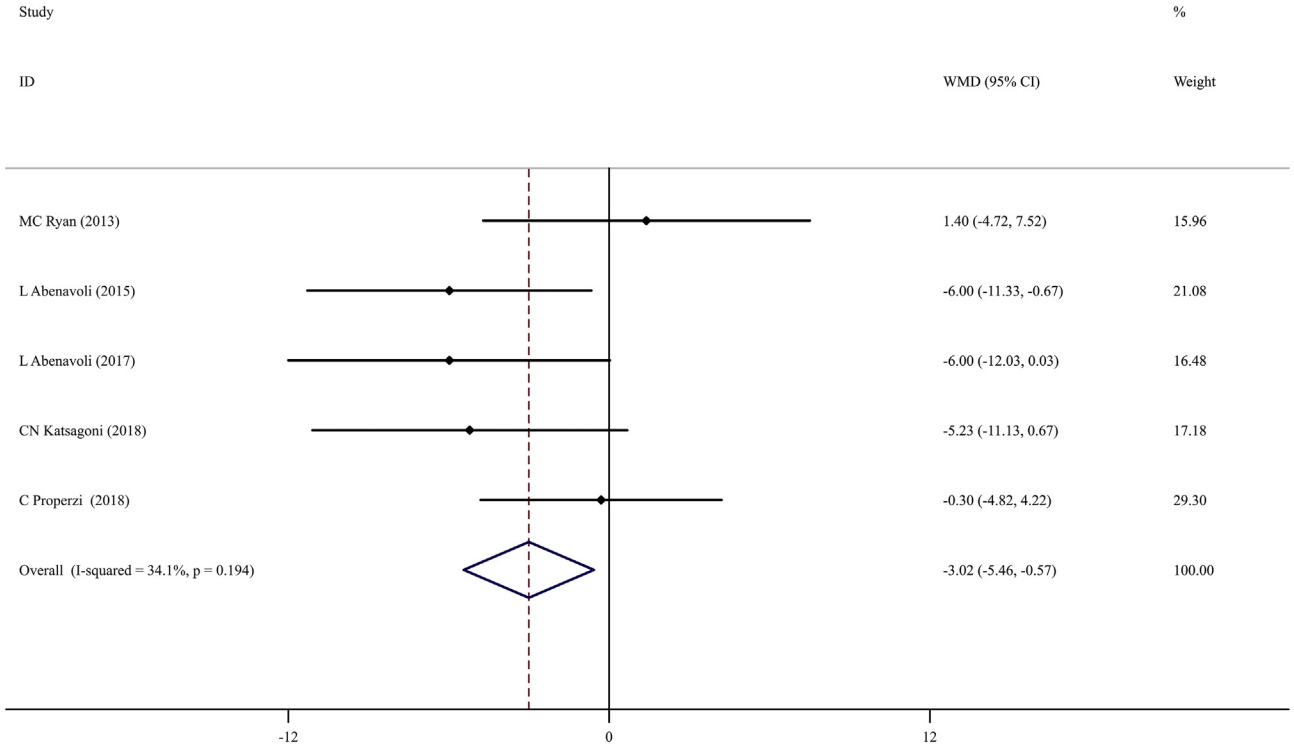

Fig. 4. Forest plot of the fixed-effects meta-analysis of the effect of the Mediterranean diet on body weight.

6. Discussion

This meta-analysis indicated that the MedDiet is associated with a greater improvement in TG, TC, body weight and HOMA-IR in NAFLD patients. Whereas, there were no significant improvement in the MedDiet group compared with the control group regarding other variables such as liver enzymes and blood pressure.

Previous investigations reported a relationship between NAFLD and CVD risk factors [6,24–26]. Obesity, type 2 diabetes, insulin resistance, hypertension and dyslipidemia are comorbidities associated with NAFLD [3,5]. Evidence suggest the role of dietary

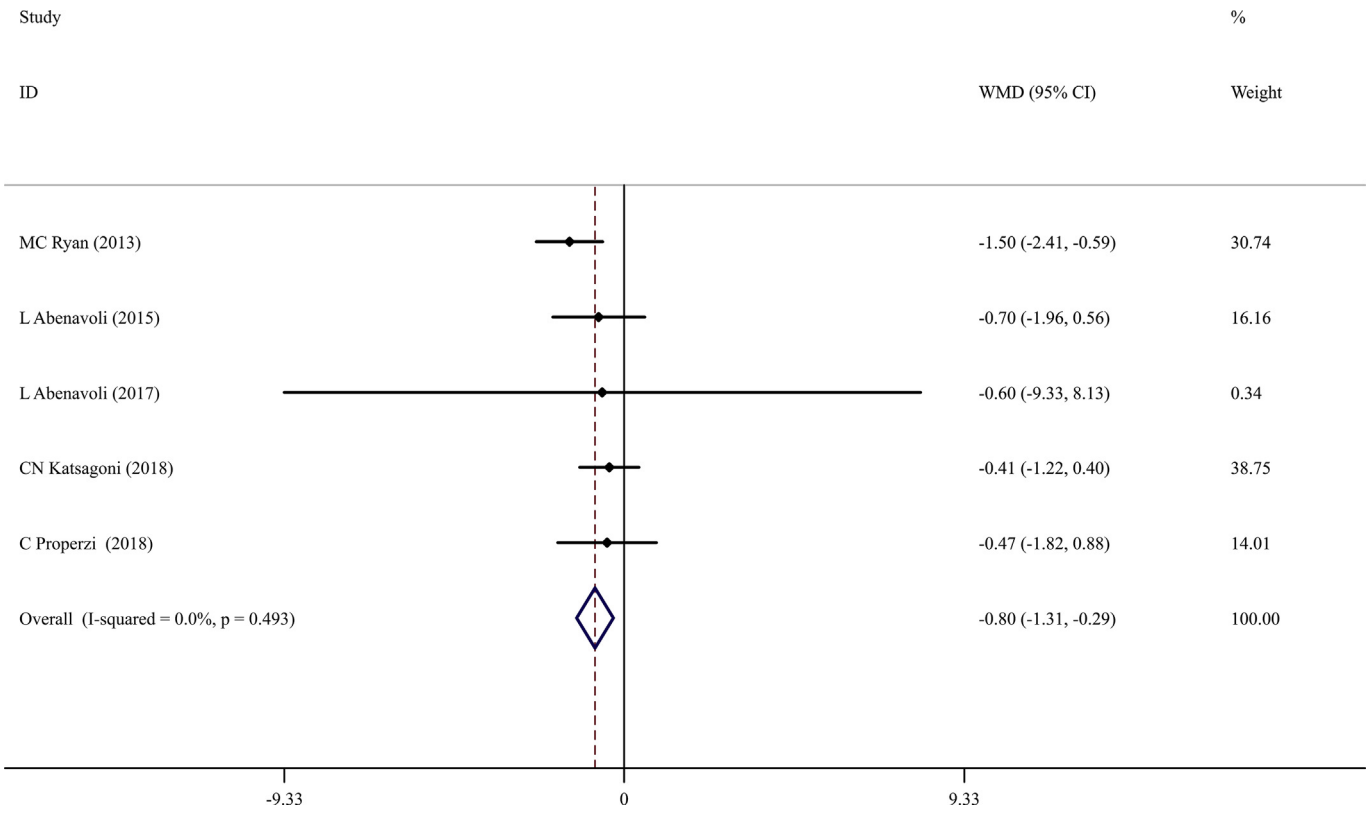

Fig. 5. Forest plot of the fixed-effects meta-analysis of the effect of the Mediterranean diet on HOMA-IR.

modifications in prevention and management of CVD risk factors. According to the latest American College of Cardiology/American Heart Association (AHA/ACC) guidelines, patients with CVD should follow dietary recommendations such as sodium reduction, and increasing intake of vegetables and fresh fruits [27]. Furthermore, it has been reported that the MedDiet can reduce the risk of CVD in different populations [28]. Epidemiologic, clinical, and experimental studies have shown that the frequent consumption of the main components of this dietary approach, such as olive oil, nuts, and red wine, is associated with a lower risk of CVD [29–31]. A systematic review reported that adherence to the MedDiet can improve the lipid profile as well as blood pressure, insulin

Table 2
The effects of Mediterranean diet on lipid profile, glycemic control, blood pressure, anthropometric measurements and liver function enzymes.

Variables	Number of effect sizes	Weighted mean difference	CI 95%	P- value	Heterogeneity	
					I^2 (%)	P- value heterogeneity
LDL	4	2.45	−16.72, 21.62	0.802	85.8	<0.001
HDL	4	2.58	−2.95, 8.10	0.361	74.1	0.009
FBG	5	−2.31	−6.81, 2.18	0.313	54.9	0.065
INSULIN	5	−1.38	−5.71, 2.95	0.532	84.2	0.001
BMI	3	−0.85	−2.01, −0.32	0.452	44.4	0.166
WC	4	−2.25	−5.82, 1.32	0.217	58.9	0.063
SBP	4	−2.20	−5.51, 1.10	0.198	8.6	0.350
DBP	4	−1.01	−6.21, 4.19	0.704	76.4	0.005
ALT	5	−5.25	−10.85, 0.35	0.121	25.3	0.253
AST	2	−3.00	−7.30, 1.30	0.172	0.0	1.000
GGT	5	−3.83	−8.32, 0.67	0.095	0.0	0.857

TG, triglycerides; TC, total cholesterol; HDL-C; high density lipoprotein cholesterol, LDL-C, low density lipoprotein cholesterol; FBG, fasting blood glucose; HOMA-IR, homeostasis model assessment-estimated insulin resistance; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, alanine aminotransferase; AST, Aspartate Aminotransferase, GGT.

Table 3
Findings from meta-regression on the effects of Mediterranean diet on TG, TC, HOMA-IR and boy weight by considering study duration.

	Effect sizes (n)	Beta	SE	Adj.R2	P-value	Heterogeneity I2%
TG	5	−0.24	0.32	–	0.505	0.00%
TC	4	−0.13	0.22	–	0.635	0.00%
HOMA-IR	4	13.32	7.94	98.97%	0.192	31.79%
Boy weight	5	−2.35	0.41	100%	0.010	0.00%

TG, triglycerides; TC, total cholesterol; HOMA-IR, homeostasis model assessment-estimated insulin resistance.

resistance, and serum markers of inflammation in patients with diabetes or metabolic syndrome [32]. Moreover, a network meta-analysis indicated that adherence to the MedDiet significantly reduced blood glucose levels, TC and LDL-C as compared to the control diet [33]. The findings of our meta-analysis regarding the beneficial effects of the MedDiet on cardiovascular risk factors are in line with previous systematic review and meta-analyses [32,33]. Furthermore, our findings regarding the effects of the MedDiet on weight is in line with the meta-analysis by Esposito et al. [34] which indicated that the MedDiet can be a useful tool to decrease body weight. One possible reason that our meta-analysis showed no change in liver enzymes following MD-based intervention in NAFLD patients may be that in most studies the baseline serum levels of AST and ALT were normal. As we explained in the method section, effect sizes of all intended outcomes were expressed as WMDs. For continuous variables, one simple approach to computing an absolute measure is the WMD, that is created by pooling results of RCTs which have used the same outcome measure in a manner that weights the results of each RCTs by the size of the trial. The WMD is readily interpretable, because it is on the same scale of measurement as the clinical outcome measure [35].

The MedDiet is high in legumes, fruits, vegetables, nuts, fish and unsaturated fats such as olive oil [9]. Cumulative evidence suggested that olive oil, as the principal source of the fat in the MedDiet, which is high in monounsaturated fatty acids (MUFA), may have a role in the prevention of CVD [36]. A rich-MUFA diet can help reduce the serum levels of TG, TC and LDL-C and raise the levels of HDL-C [37]. Olive oil is also riche in the phenolic compounds which has antioxidant properties [38]. Antioxidants have a proven role in reducing cardiovascular risk factors [39]. In addition to MUFA, the omega-3 fatty acids as a polyunsaturated fatty acid (PUFA), are another types of unsaturated fats in the MedDiet. One of the most important components of the MedDiet that is rich in unsaturated fatty acids is fish [40]. A multitude of studies have shown the beneficial effects of fish consumption in reducing the potential complications of CVD [41,42]. The beneficial effects of fish consumption on CVD-related risk factors, which include improving lipid profile and lowering blood pressure, are due to its high level of PUFA [43,44]. Another component recommended in the MedDiet is nuts, which are high in unsaturated fatty acids, as well as dietary fiber, minerals, vitamins, and other bioactive compounds [45]. In large prospective cohort studies, higher consumption of total and specific types of nuts were inversely associated with the lower risk of CVD [46]. A meta-analysis of 25 intervention trials showed that nut consumption improves blood lipid levels in a dose-related manner [47]. It has been shown that the TG-lowering effect observed in participants consumed the MedDiet might be related to the high intake of alpha-linolenic acid from walnuts [48]. Furthermore, several studies have suggested that the diet high in MUFA such as oleic acid (the primary component of olive oil) [49], and omega-3 fatty acids such as linolenic acid [50] decrease the accumulation of intrahepatic lipid, and improve TG levels in NAFLD patients, possibly by increasing peroxisomal activity [51], The AHA/ACC guidelines strongly recommend replacing mono- and polyunsaturated fats with saturated and trans-fatty acids for primary and secondary prevention of CVD [52]. In addition, the AHA/ACC guidelines strongly recommended that adherence to the MedDiet can reduce both the risk of coronary heart disease and the stroke [52]. It should be noted that the health benefits of the MedDiet are mainly due to the existence of biologic interactions between different components of it rather than to the effect of a single food group or nutrients [32].

It should be noted that there is a relationship between histological severity of NAFLD and response to a treatment [53]. As insulin resistance and fatty acid metabolism have shown to impact on NAFLD, medical managements targeting glucose or lipid metabolism have been evaluated for the treatment of NAFLD [54]. Some of the drugs used for the management of NAFLD such as thiazolidinediones, are peroxisome proliferator-activated receptor (PPAR) gamma agonists [55]. Previously, hepatoprotective effects of a dual PPARα/δ agonist were reported in rodent NASH-models [56]. PPARs belong to the superfamily of nuclear receptor. After binding to their ligands, PPARs form heterodimers with retinoid X receptors and these heterodimers control transcription of various target genes [57]. Metabolically active tissues express PPARα which regulates genes involved in fatty acid β-oxidation, although it further impacts on gluconeogenesis and inflammatory responses [57,58]. PPARβ/δ also seems to be an important metabolic regulator, which may also act on Kupffer cells to modulate NAFLD [59]. In 2015, a study reported that human liver PPARα gene expression negatively correlates with the severity of NAFLD, visceral adiposity and insulin resistance [53]. Therefore, it can be speculated that the response to a treatment may be different in different histological severity of NAFLD. One limitation of the included studies is that the response to treatment with the Mediterranean diet has not been investigated separately in different severity of NAFLD, which should be considered in future studies.

Moreover, the MedDiet is associated with increased consumption of fruits and vegetables [60]. Fruits and vegetables, as well as whole grains and legume are the good source of dietary fiber [52]. A large number of studies have revealed that a diet high in fiber is inversely associated with the risk of CVD [61]. Evidence suggest the beneficial effects of fiber for the management of NAFLD, and for reducing the risk of CVD in these patients [40]. In addition, modest wine consumption is the characteristic feature of the MedDiet [40]. Previous meta-analyses have addressed the beneficial effects of alcohol consumption on CVD outcomes [62]. A meta-analysis of 84 studies indicated that a light to moderate alcohol consumption is associated with a reduced risk of multiple cardiovascular outcomes [63]. It has been shown that, alcohol may improve CVD risks through improving lipid profile and blood pressure [64]. Result of Third National Health and Nutrition Examination Survey showed that the modest wine consumption is associated with a decreased prevalence of suspected NAFLD [65]. In addition, their investigations supports the safety of one glass of wine per day for cardioprotection in patients at risk for both NAFLD and CVD [65].

Present systematic review and meta-analysis has several strengths. First, this is the first meta-analysis to assess the effect of the MedDiet on cardiovascular risk factors in NAFLD patients. Second, we included RCTs which examined complementary endpoints, providing a comprehensive review on this topic. Third, this review is based on an up to date literature search from a large number of databases. An important limitation of our meta-analysis is the limited number of trials available, which limits the strength of the conclusion of the present meta-analysis. Furthermore, since all trials last no more than 6 months, our analysis unable to show the long-term effectiveness of the MedDiet on CVD risk in NAFLD patient. In addition, only one study has evaluated the histological changes in NAFLD. Analysis of the histological changes remains the gold standard for evaluating the effectiveness of a particular treatment in NAFLD [66]. Moreover, the fatty liver disease status of the patients was not reported except in two studies, which may be important in interpreting the results. Another limitation is that lack of allocation concealment was present in all the studies and three trials [14,20,21] showed high risk of bias regarding the blinding of participants and personnel. Allocation concealment is a method used to avoid selection bias by hiding allocation sequences from those who assign participants to intervention groups, until the assignment moment. Concealment of the allocation prevents researchers from influencing which participants are assigned to a

given intervention group. This process is critical to the success of any RCT. In addition, significant between study heterogeneities were observed for serum levels of lipid profile, FBG, insulin, WC and DBP, which can influence the results found regarding the effect of MedDiet on these variables. Therefore, this should be taken into account when interpreting the results. In addition, significant between study heterogeneities observed for some of the variables can influence the interpretation of the results. It should be noted that the results of the sensitivity analysis indicated that removing some studies impacts the results of body weight, ALT, TC, HOMA-IR and insulin, which may also influence the interpretation of the results. Furthermore, these studies were performed in tertiary centers with possibility of the selection bias. Therefore, further well designed RCTs addressing these issues are needed.

In summary, our meta-analysis suggests the advantageous effects of the MedDiet on some CVD risks factors, as compared with a control diet. Results of this meta-analysis indicated that adherence to the MedDiet can reduce the blood levels of both TG and TC, and decrease body weight and HOMA-IR. It seems that the MedDiet can be considered as an appropriate strategy to reduce CVD risk factors in NAFLD patients; however, further well-designed studies are needed to confirm the results of the present meta-analysis.

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There are no financial or other competing interests for principal investigators, patients included or any member of the trial.

Author contributions

AA and OA designed the study. RC and OA reviewed and selected the articles. DA and OA extracted needed data from articles. AA performed data analysis and interpretation. AA drafted the manuscript.

Declaration of Competing Interest

The authors declare that no conflict of interest exists.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2020.03.003.

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