

Effectiveness of dietary interventions on cardio-metabolic risk factors in patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background Dietary modification is considered as one of the main strategies in the management of nonalcoholic fatty liver disease (NAFLD). The objective of this study was to systematically investigate the effect of dietary interventions on the cardio-metabolic risk factors, including lipid profile and insulin resistance in this population.

Methods We searched electronic databases of PubMed and Scopus until January 2020 and included randomized controlled trials that compared the effect of dietary modifications vs. control on lipid profile and insulin resistance in patients with NAFLD. The random-effect analysis was performed to calculate pooled weighted mean differences (WMD).

Results Our finding showed that serum triglycerides (TG) (n=5, WMD -38.50 mg/dL, 95% confidence interval [CI] -61.68 to -15.31; P=0.001) and total cholesterol (TC) (n=4, WMD -18.70 mg/dL, 95%CI -34.85 to -2.53; P=0.023) decrease following diet intervention along with marginally significant weight reduction (n=5, WMD -3.61 mg/dL, 95%CI -7.25 to 0.04; P=0.053). There was no change in the homeostatic model assessment for insulin resistance, high- and low-density lipoprotein (LDL) levels (P>0.05). Subgroup analysis revealed that Mediterranean diet reduced TG (n=2, WMD -57.52 mg/dL, 95%CI -75.73 to -39.31; P<0.001) and weight (n=2, WMD -7.59 Kg, 95%CI -13.53 to -1.66; P=0.012), and also increased LDL level (n=2, WMD 29.73 mg/dL, 95%CI 13.82-45.65; P<0.001). However, standard hypocaloric diet improved TC (n=2, WMD -23.20 mg/dL, 95%CI -36.96 to -9.44; P=0.001) and LDL (n=2, WMD -16.82 mg/dL, 95%CI -29.44 to -4.19; P=0.009).

Conclusion Dietary modifications may improve serum TG, TC, and obesity in NAFLD.

Keywords Nonalcoholic fatty liver disease, dietary interventions, cardio-metabolic risk factors, insulin resistance, lipid profile

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is known as one of the most common chronic liver diseases worldwide [1]. It encompasses the vast spectrum of liver injury from simple steatosis to steatohepatitis, cirrhosis, and rarely hepatocellular carcinoma [1,2]. The estimated prevalence ranges from 6.3-33% in the general population, increasing to over 50% among obese and diabetic patients [3,4]. The pathophysiology of NAFLD is multifactorial and characterized by hepatic fat accumulation, oxidative stress, lipid peroxidation, and mitochondrial dysfunction [5]. This process is supposed to be triggered by insulin resistance which not only increases *de novo* hepatic lipogenesis, but also causes lipolysis and elevation of free fatty acids' level that subsequently induce hepatic steatosis [5,6].

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Cumulative evidence has shown that patients with NAFLD have a higher risk of cardiovascular events than the general population [7-9]. Inflammatory features of NAFLD mediate exacerbation of insulin resistance and also leads to atherogenic dyslipidemia; these factors are involved in the pathogenesis of cardiovascular diseases [10].

Lifestyle modification is deemed to be the most effective therapeutic modality for slowing down the progression of NAFLD [11,12]. In this way, dietary modifications and weight loss could reduce hepatic steatosis and improve disease activity [13,14]. However, there is inconsistent evidence regarding the effect of dietary interventions on cardio-metabolic risk factors, including insulin resistance and lipid profile in NAFLD. Mediterranean diet (MD) has been considered effective in controlling hepatic manifestations of NAFLD, though data on the impact of MD on dyslipidemia and insulin resistance indicators such as insulin level and homeostatic model assessment for insulin resistance (HOMA-IR) are conflicting [15]. On the other hand, multiple studies concentrated on low-fat/low-carbohydrate hypocaloric and ketogenic diets, although the effectiveness of these dietary patterns in improving hepatic and extra-hepatic complications of NAFLD is an area of dispute [14,16-18].

Recently, several systematic reviews have attempted to evaluate the effect of dietary modifications on the management of NAFLD although heterogeneity in the dietary pattern of the control groups limited the quality of the studies [15,19-22]. Therefore, in this systematic review and meta-analysis we aimed to summarize randomized controlled trials (RCTs) that assessed the effect of dietary interventions vs. controls, which has neither nutritional nor pharmacologic intervention on the cardio-metabolic risk factors, including lipid profile and insulin resistance in patients with NAFLD.

Materials and methods

This study was conducted in accordance with the systematic reviews and meta-analyses (PRISMA) guideline [23].

Search strategy

We systematically searched 2 electronic databases of PubMed-MEDLINE and Scopus-EMBASE to find relevant English published articles until January 2020. Keywords selected with 2 concepts of disease (NAFLD) and intervention (diet) (Appendix). Reviewers independently screened articles by title and abstract to find eligible studies and extracted data into a structured excel spreadsheet, and discrepancies were resolved by discussion.

Eligibility criteria

The entry requirement for the study was meeting the following criteria: (a) participants older than 18 years old with any sex or

ethnic origin; (b) proven NAFLD or nonalcoholic steatohepatitis based on liver biopsy or imaging; (c) using dietary intervention; (d) designed based on RCT; and (e) reporting at least 1 of the lipid profile components (triglycerides [TG], total cholesterol [TC], high-density lipoprotein [HDL], low-density lipoprotein [LDL], and/or insulin resistance surrogate marker HOMA-IR) as main outcomes. The data of weight change was also extracted from the included articles. In the case of 2 studies with duplicate data, we only included that with more complete information and a higher quality (according to the modified version of Cochrane tool [24]). We also excluded articles with: (a) insufficient data; (b) inappropriate (dietary change in control group) or no control group; and (c) investigation the effects of other interventions simultaneously along with diet intervention.

Data extraction

We appraised the full text of the included articles and extracted following data: (a) general information including the name of first author, origin country, year of publication, and the number of participants; (b) lipid profile (TG, TC, HDL, LDL), insulin resistance surrogate marker HOMA-IR, and weight; (c) predefined criteria including age (lower or more than 50 years old), body mass index (BMI) 25-29.9 and ≥ 30 kg/m² interpreted as overweight and obese, respectively, and type of diet (MD [low-calorie] and standard [low-calorie or high-fiber]) [25].

Risk of bias and quality assessment

The risk of bias was assessed using the modified version of Cochrane tool [24]. Studies were evaluated in 6 domains: random sequence generation; allocation concealment; blinding; missing outcome data; selective outcome reporting; and other sources of bias. Each domain was judged as low, probably low, probably high, and high. Two reviewers independently assessed the risk of bias, and any disagreements were solved by discussion.

Statistical analysis

In the current study, we used the mean and standard deviation (SD) of post-intervention data to compute the meta-analysis. The following formulas were used to calculate SD if the studies reported another kind of variation of means:

$$\text{SD from standard error (SE)} = \text{SE} \times \sqrt{n}$$

$$\text{SD from 95\% confidence interval (CI)} = \sqrt{n} \left(\frac{\text{upper level [UL]} - \text{lower level [LL]}}{3.92} \right)$$

$$\text{SD from interquartile range} = \frac{\text{UL} - \text{LL}}{1.35}$$

If a study had reported baseline and change of variables, post-intervention SD could not be calculated. In this case, we considered the SD with 70% cumulative frequency for it.

Random-effect analysis was performed to calculate pooled weighted mean differences (WMD). We used the 95% CIs to compare the results. If 95% CIs did not meet each other, the difference of WMDs was significant. We also considered

P-heterogeneity (P-h) with the value of <0.10 as significant between-study heterogeneity. Subgroup analysis of the predefined criteria was conducted to find the potential source of heterogeneity and the effect of each subgroup on the overall WMD. Finally, Egger's test was applied to reveal potential publication bias. We used STATA, version 14.0 (Stata Corp, College Station, TX) for all statistical analyses.

Results

Study selection

Fig. 1 briefly outlines the study selection process. 1976 unique articles were identified through PubMed and Scopus, of which 1966 articles were excluded after screening by title and abstract. The full texts of 11 relevant articles were reviewed to assess their eligibility. After excluding 6 articles due to implementing dietary intervention in control groups [17,26-29], and applying exercise intervention along with diet intervention in treatment group [30], only 5 studies met our inclusion criteria [16,31-34]. All cited references of the included studies and the relevant reviews were checked to find other potential eligible articles, but no other studies were included. Finally, 5 articles were used for data extraction and meta-analysis [16,31-34].

Characteristics of the included studies

Articles were published between 2015 and 2019. Two articles were performed in Italy [33,34], and the other 3 were conducted in Iran [16], China [32], and Brazil [31]. The overall sample size was 190 ranging from 20 to 60 participants, with mean age ranging from 42-56.47 years old. All the studies were done on both sexes.

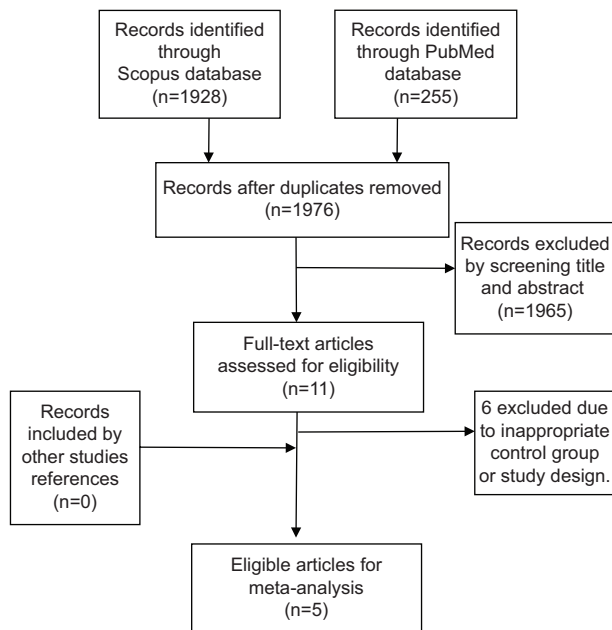


Figure 1 Flow diagram of study selection up to January 2020

Mean duration of intervention ranged from 3-8.6 months. Two articles had used low-calorie MD [33,34], 2 used standard low-calorie diet [16,31], and 1 used a high-fiber diet [32]. Table 1 briefly shows the characteristics of the included studies.

Supplementary Table 1 summarizes the risk of bias assessment. Insufficient reporting of allocation concealment, lack of blinding, and missing outcomes were the main sources of limitations of the included studies.

Effect of dietary intervention on TG level in patients with NAFLD

Combining 5 effect sizes with 190 participants demonstrated that serum TG significantly decreased in response to dietary intervention ($n=5$, WMD -38.50 mg/dL, 95%CI -61.68 to -15.31 ; $P=0.001$) with significant heterogeneity ($P-h=0.060$) (Fig. 2; Table 2). According to the subgroup analysis, type and duration of intervention as well as the participants' BMI and age were the potential sources of heterogeneity ($P-h>0.1$) (Supplementary Table 2). Moreover, subgroup analysis revealed that results for dietary intervention in overweight participants ($P=0.60$) and using a high-fiber diet ($P=0.67$) were insignificant (Table 3).

Effect of dietary intervention on TC level in patients with NAFLD

Pooling effect sizes from 4 studies showed a significant reduction in TC, without significant heterogeneity, in response to diet intervention ($n=4$, WMD -18.70 mg/dL, 95%CI -34.87 to -2.53 ; $P=0.023$ and $P-h=0.118$) (Fig. 3; Table 2). After applying subgroup analysis, results remained significant for obese patients ($n=3$, WMD -16.06 mg/dL, 95%CI -39.01 to 6.87 ; $P=0.005$), participants younger than 50 years old ($n=2$, WMD -23.20 mg/dL, 95%CI -36.96 to -9.44 ; $P=0.001$), using other diets than MD ($n=2$, WMD -23.20 mg/dL, 95%CI -36.96 to -9.44 ; $P=0.001$), and less than 3 months of intervention ($n=2$, WMD -23.20 mg/dL, 95%CI -36.96 to -9.44 ; $P=0.001$) (Table 3).

Effect of dietary intervention on HDL level in patients with NAFLD

The pooled estimate from the 3 effect sizes with 120 participants showed no effect of diet on HDL level ($n=3$, WMD -0.09 mg/dL, 95%CI -3.28 to 3.10 ; $P=0.955$) (Supplementary Fig. 1, Table 2). There was no heterogeneity between studies ($P-h=0.43$). Subgroup analysis also revealed no changes in the results for HDL (Table 3).

Effect of dietary intervention on LDL level in patients with NAFLD

According to data from 4 studies and 150 participants, there was no significant changes for serum level of LDL

Table 1 Characteristics of included studies

First author [Ref.]	Year	Country	NAFLD confirmation	Quality	Style of data report	Interested data report	Diet macronutrient distribution	Duration (Months)	Sample size of groups	
									Intervention	Control
de Faria Ghetti [31]	2019	Brazil	Biopsy	High	Before- After Mean \pm SD	HOMA-IR, TG, TC, HDL, LDL	Standard, low- calorie	3	20	20
Asghari [16]	2018	Iran	US	High	Before- After Mean \pm SD	HOMA-IR, TG, TC, HDL, LDL	Standard, low- calorie	3	30	30
Cheng [32]	2017	China	H-MRS	High	Before- After Mean (CIs)	TG	Modified, high fiber	8.6	22	18
Abenavoli [33]	2017	Italy	US	High	Before- After Mean (IQR)	HOMA-IR, TG, TC, LDL	Mediterranean, low-calorie	6	20	10
Abenavoli [34]	2015	Italy	US	Unclear	Before- After Mean (IQR)	HOMA-IR, TG, TC, HDL, LDL	Mediterranean, low-calorie	6	10	10

NAFLD, none alcoholic fatty liver disease; US, ultrasound; H-MRS, proton-magnetic resonance spectroscopy; SD, standard deviation; CI, confidence interval; IQR, interquartile range; HOMA-IR, homeostatic model assessment for insulin resistance; TG, triglycerides; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol

Table 2 Summary of results for cardio-metabolic risk factors

Variable	TG (mg/dL)	TC (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	HOMA-IR	Weight (Kg)
Study	5	4	3	4	4	5
Sample size	190	150	120	150	150	190
WMD	-38.497	-18.701	-0.093	6.909	-0.279	-3.607
95%CI	-61.685, -15.308	-34.875, -2.528	-3.284, 3.098	-20.254, 34.072	-1.015, 0.457	-7.254, 0.041
P- H	0.060	0.118	0.432	<0.001	0.954	0.325
P-W	0.001	0.023	0.955	0.618	0.456	0.053
P> t	0.131	0.821	0.039	0.130	0.520	0.063

TG, triglycerides; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; BMI, body mass index; HOMA-IR, homeostatic model assessment for insulin resistance

WMD, weighted mean difference; CIs, confidence intervals; P-W, P-Within test of WMD of subgroups with significance of <0.05; P-h, P-heterogeneity (test of heterogeneity between studies with significance of <0.1); P>|t|, test of small-study effects (with significance of <0.05)

(n=4, WMD 6.91 mg/dL, 95%CI -20.25 to 34.07; P=0.618) (Supplementary Fig. 2, Table 2). However, between study heterogeneity was significant (P-h=0.060), and subgroup analysis demonstrated that type and duration of intervention and participant's age were the potential sources of heterogeneity (P-h>0.1) (Supplementary Table 2). Subgroup analysis also revealed that the effect of diet in subgroups is completely reverse and significant; LDL level increased in the MD intervention (n=2, WMD 29.73 mg/dL, 95%CI 13.82-45.65; P<0.001), more than 3 months of intervention (n=2, WMD 29.73, 95%CI 13.82-45.65; P<0.001), and individuals over 50 years old (n=2, WMD 29.73 mg/dL, 95%CI 13.82-45.65; P<0.001), but decreased in the studies applying 3-month diet (n=2, WMD -16.82 mg/dL, 95%CI -29.44 to -4.19; P=0.009), other than MD (n=2, WMD -16.82 mg/dL, 95%CI -29.44 to -4.19; P=0.009), and in participants younger than 50 years old (n=2, WMD -16.82 mg/dL, 95%CI -29.44 to -4.19; P=0.001) (Table 3).

Effect of dietary intervention on HOMA-IR level in patients with NAFLD

There was no significant changes and heterogeneity for serum level of HOMA-IR (n=4, WMD -0.279, 95%CI -1.01 to 0.46; P=0.456 and P-h=0.954) according to data from 4 studies and 150 participants (Supplementary Fig. 3; Table 2). Subgroup analysis revealed no changes in the results for HOMA-IR (Table 3).

Effect of dietary intervention on weight changes in patients with NAFLD

All 5 included studies with 190 participants reported effect size for weight changes and our meta-analysis showed that dietary intervention was able to reduce weight, but marginally significantly (n=5, WMD -3.61 Kg, 95%CI -7.25 to 0.04; P=0.053) (Supplementary Fig. 4; Table 2). There was no heterogeneity

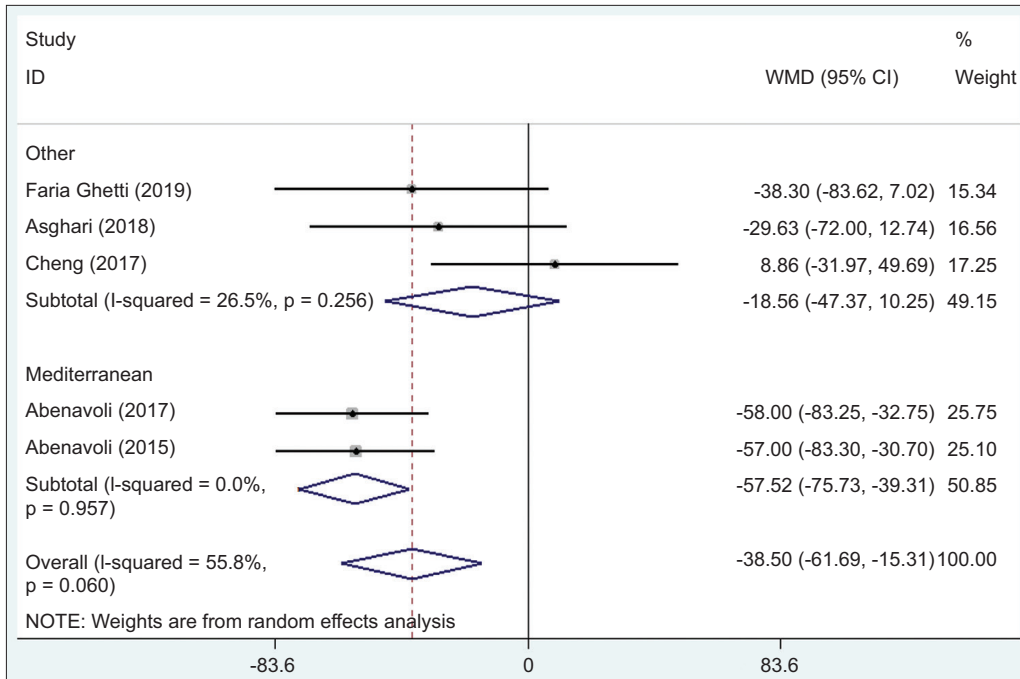


Figure 2 Forest plot for the pooled weighted mean differences of diet interventions on the level of triglycerides based on random-effect model WMD, weighted mean difference; CI, confidence interval

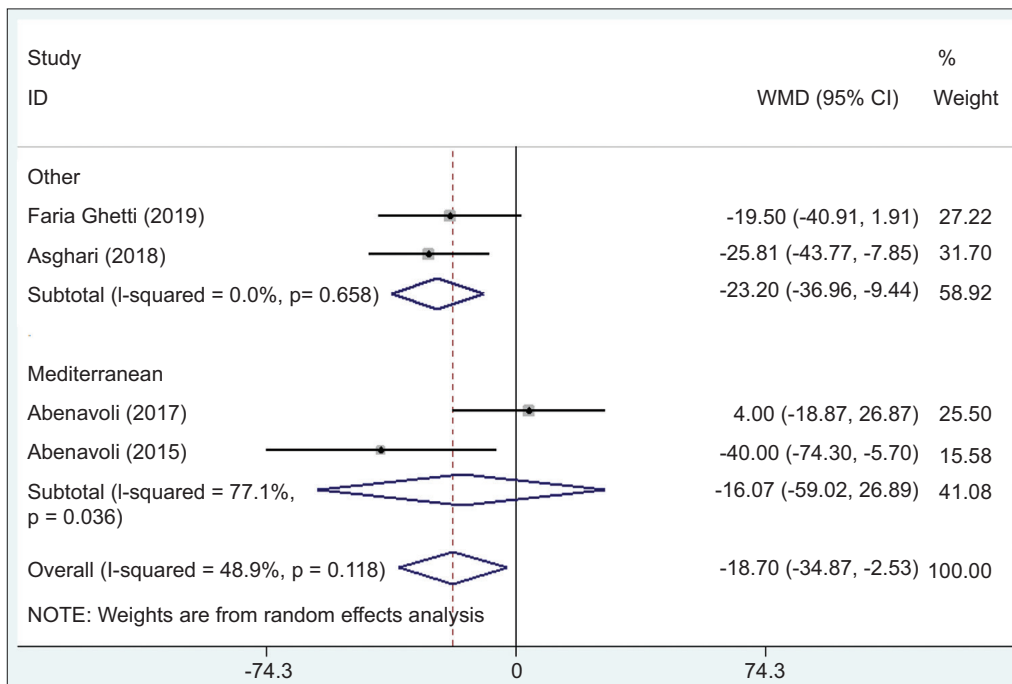


Figure 3 Forest plot for the pooled weighted mean differences of diet interventions on the level of total cholesterol based on random-effect model WMD, weighted mean difference; CI, confidence interval

among the studies (P-h=0.325). After applying subgroup analysis, the weight reduction turned to significant in MD (n=2, WMD -7.59 Kg, 95%CI -13.53 to -1.66; P=0.012), and obese participants (n=3, WMD -7.83 Kg, 95%CI -13.10 to -2.56; P=0.004) (Table 3).

Publication bias in the results

Eager’s test revealed publication bias only for HDL in response to dietary intervention (P=0.039) (Table 2).

Table 3 Subgroup analysis based on random-effect model for the effect of diet intervention on cardio-metabolic risk factor

Risk factors	TG (mg/dL)			TC (mg/dL)			HDL (mg/dL)			LDL (mg/dL)			HOMA-IR			Weight (Kg)			
	n	WMD	P -W	n	WMD	P -W	n	WMD	P -W	n	WMD	P -W	n	WMD	P -W	n	WMD	P -W	
Overall	5	-38.497	0.001	4	-18.701	0.023	3	-0.093	0.955	4	6.909	0.618	4	-0.279	0.457	5	-3.607	0.053	
Participants' age																			
≤50	2	-33.674	0.033	2	-23.203	0.001	2	-1.098	0.545	2	-16.820	0.009	2	-0.101	0.837	2	-3.385	0.337	
>50	3	-38.902	0.032	2	-16.067	0.463	1	4.000	0.275	2	29.733	<0.001	2	-0.532	0.362	3	-4.232	0.131	
Participants'																			
Overweight	2	-9.952	0.605	1	-25.810	0.170	1	-1.690	0.494	1	-21.200	0.010	1	-0.100	0.838	2	-0.448	0.838	
Obese	3	-54.847	<0.001	3	-16.065	0.005	2	1.135	0.600	3	16.891	0.243	3	-0.533	0.361	3	-7.829	0.004	
Type of diet																			
Mediterranean (low calorie)	2	-57.52	<0.001	2	-16.067	0.463	1	4.000	0.275	2	29.733	<0.001	2	-0.532	0.362	2	-7.595	0.012	
Standard (low calorie)	2	-33.674	0.033	2	-23.203	0.001	2	-1.098	0.545	2	-16.820	0.009	2	-0.101	0.837	2	-3.385	0.337	
High fiber	1	8.857	0.671	-	-	-	-	-	-	-	-	-	-	-	-	1	0	1	
Time (months)																			
≤3	2	-33.674	0.033	2	-23.203	0.001	2	-1.098	0.545	2	-16.820	0.009	2	-0.101	0.837	2	-3.385	0.337	
>3	3	-38.902	0.032	2	-16.067	0.463	1	4.000	0.275	2	29.733	<0.001	2	-0.532	0.362	3	-4.232	0.131	

There were only 2 studies for LDL, therefore subgroup analysis did not perform for this risk factor. All the studies of TC, HDL and HOMA-IR were done in short time, therefore subgroup analysis did not perform for these variables
 TG, triglycerides; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; BMI, body mass index; WMD, weighted mean difference; P-W, P-Within (Test of WMD of subgroups with significance of <0.05); HOMA-IR, homeostatic model assessment for insulin resistance

Discussion

In the present meta-analysis, we found that dietary intervention may reduce serum TG, TC, and weight in patients with NAFLD. There were no significant changes in LDL, HDL, and HOMA-IR levels following the intervention. According to our subgroup analysis, even though dietary intervention across both age groups was effective in improving TG, patients younger than 50 years old were more likely to benefit from diet regarding the reduction in the TC level. Furthermore, compared to overweight individuals, obese patients most benefited from dietary modification to reduce TG and TC. MD was effective in reducing TG and weight, though hypocaloric diet decreased TC. Moreover, the result showed that dietary modification for 3 months can be as effective as a prolonged intervention in lowering TG and TC.

It is well-known that lifestyle modifications, including nutritional changes, exercise and weight loss are the cornerstone of NAFLD management [11,12]. While numerous types of dietary approaches have shown to be effective in improving liver steatosis, the optimal diet is still unclear. The included studies in our analysis applied MD [33,34], calorie-restricted diet [16,31], and high-fiber diet [32]. Calorie restriction is a general dietary intervention in NAFLD that improves weight management and insulin sensitivity [14]. A meta-analysis of 3 randomized trials by Musso *et al* [13], emphasized the role of calorie restriction, regardless of macronutrient components, in improving TG and HOMA-IR. However, our results showed that standard hypocaloric diet was associated with a reduction in TC and had no effect on other cardio-metabolic risk factors.

According to the present meta-analysis, MD had a potential to reduce serum TG and weight in patients with NAFLD. MD is a less energy-dense diet, rich in monounsaturated fatty acids, omega-3 fatty acids, and antioxidants. These nutrients play an important role in modulating inflammatory cytokines, improving insulin sensitivity, and also regulating glucose and lipid metabolism [35]. A recent meta-analysis of 7 observational studies and 6 randomized trials reported that implementing MD was associated with reduction in TG, TC and HOMA-IR in NAFLD [21]. The effect of MD on improving TG, TC and HOMA-IR in NAFLD patients has been highlighted in other systematic reviews as well [20,22]. The aforementioned systematic reviews included trials in which patients in the control groups had some dietary modifications after the enrolment to the study compared to their baseline diet, while we included, as far as possible, RCTs that reported no dietary changes in the control groups after the study enrolment. Therefore, differences in inclusion criteria would be the main reason of conflict between their results and ours.

According to our data, the LDL level did not improve in response to dietary intervention, however, MD might increase it. This finding is inconsistent with previous meta-analyses in which adherence to the MD intermediated the LDL level [36] or MD intervention had no beneficial effect on the LDL level [21,22]. In the present meta-analysis, the data on LDL in response to MD was only extracted from 2 studies done by Abenavoli *et al* in which LDL level improved after both MD and control intervention with a 2-fold greater reduction in the control groups [33,34]. Since, we performed analysis on post-

intervention extracted data, the results related to these 2 RCTs, including the effects of MD intervention and a longer than 3 months period, showed an increase in the LDL level.

One of the included studies in this meta-analysis implemented a high-fiber diet in the management of NAFLD [32]. We extracted data on serum TG level from this study which demonstrated no significant effect of high-fiber diet on TG level. Dietary fiber regulates gut microbiota and prevents translocation of pathogenic bacteria to the systemic circulation [37]; pathogenic bacteria induce systemic inflammatory responses and lead to insulin resistance [38]. Moreover, a review of recent RCTs investigating the relationship between diet high in fiber, microbiota and cardio-metabolic risk factors, indicated that high-fiber diet-induced metabolic responses were associated with individual microbiota composition and diversity and abundance of specific bacteria [39].

Several limitations would afflict the results of this study. Primarily, there is serious concern regarding the risk of bias of the included studies. Second, inconsistency in the results of TG and LDL would lower the certainty of the estimated effects for these outcomes. Third, the number of the included studies was relatively low with small sample sizes which limited the precision of the estimated effects. Forth, dietary compositions in the included studies were variable that would question the accuracy of our categorization of dietary interventions and prevent from clear judgment about the association of dietary pattern and outcomes of interest. Fifth, a number of the included studies enrolled NAFLD subjects with normal cardio-metabolic variables at baseline that could intervene in the measured effect size for dietary intervention.

According to this systematic review, dietary modifications may improve serum TG, TC in NAFLD. However, the effectiveness of diet directly relates to the nutritional components, intervention follow up, as well as patients' age and BMI. Although our results showed that NAFLD patients were likely to benefit of dietary modification, both clinical and statistically significance indicated that there is more benefit to intermediate TG, TC and LDL from low-calorie standard diet intervention with a shorter follow up than 3 months, especially in young and obese patients. The results also showed marginal statistically significance for weight reduction in response to dietary intervention, however, the WMD of approximately 0.5-1 Kg achieved over trial periods, over 3-6 months, is minimal and therefore unlikely to be of clinical significance. RCTs with larger sample sizes and a longer duration of intervention are warranted to validate these findings.

In conclusion, this systematic review highlighted the benefit of nutritional modification in improving dyslipidemia in patients with NAFLD. Moreover, our findings emphasize the gap in identification of optimal diet and potential need for implementing individualized dietary approaches in NAFLD.

Acknowledgment

The authors would like to thank Misciagna *et al* [28] for providing additional data upon request.

Summary Box

What is already known:

- Patients with nonalcoholic fatty liver disease (NAFLD) have a higher risk of cardiovascular events than the general population
- Lifestyle modifications, including nutritional changes, exercise, and weight loss are the cornerstone of NAFLD management
- Adherence to the Mediterranean diet might intermediate the low-density lipoprotein (LDL) level in patients with NAFLD

What the new findings are:

- Nutritional modifications may improve serum triglycerides (TG) and total cholesterol (TC) in patients with NAFLD
- There is more benefit to intermediate TG, TC and LDL from low-calorie standard diet intervention with a shorter than 3 months follow up, especially in young and obese patients
- Our findings emphasize the gap in the identification of optimal diet and the potential need for implementing individualized dietary approaches in patients with NAFLD

References

1. Bellentani S. The epidemiology of non-alcoholic fatty liver disease. *Liver Int* 2017;**37**(Suppl 1):81-84.
2. Adams LA, Lymp JF, St Sauver J, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* 2005;**129**:113-121.
3. Vernon G, Baranova A, Younossi Z.M. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther* 2011;**34**:274-285.
4. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology* 2012;**55**:2005-2023.
5. Day CP. Pathogenesis of steatohepatitis. *Best Pract Res Clin Gastroenterol* 2002;**16**:663-678.
6. Liu W, Baker R.D, Bhatia T, et al. Pathogenesis of nonalcoholic steatohepatitis. *Cell Mol Life Sci* 2016;**73**:1969-1987.
7. Treeprasertsuk S, Leverage S, Adams LA, et al. The Framingham risk score and heart disease in nonalcoholic fatty liver disease. *Liver Int* 2012;**32**:945-950.
8. Pisto P, Santaniemi M, Bloigu R, et al. Fatty liver predicts the risk for cardiovascular events in middle-aged population: a population-based cohort study. *BMJ Open* 2014;**4**:e004973.
9. Hamaguchi M, Kojima T, Takeda N, et al. Nonalcoholic fatty liver disease is a novel predictor of cardiovascular disease. *World J Gastroenterol* 2007;**13**:1579-1584.
10. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. *N Engl J Med* 2010;**363**:1341-1350.
11. EASL-EASD-EASO. Clinical practice guidelines for the management of non-alcoholic fatty liver disease. *Obes Facts* 2016;**9**:65-90.
12. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the american association for the study of liver diseases. *Hepatology* 2018;**67**:328-357.
13. Musso G, Cassader M, Rosina F, et al. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. *Diabetologia* 2012;**55**:885-904.
14. Haufe S, Engeli S, Kast P, et al. Randomized comparison of reduced fat and reduced carbohydrate hypocaloric diets on intrahepatic fat in overweight and obese human subjects. *Hepatology* 2011;**53**:1504-1514.
15. Moosavian SP, Arab A, Paknahad Z. The effect of a Mediterranean diet on metabolic parameters in patients with non-alcoholic fatty liver disease: a systematic review of randomized controlled trials. *Clin Nutr ESPEN* 2020;**35**:40-46.
16. Asghari S, Asghari-Jafarabadi M, Somi MH, et al. Comparison of calorie-restricted diet and resveratrol supplementation on anthropometric indices, metabolic parameters, and serum sirtuin-1 levels in patients with nonalcoholic fatty liver disease: a randomized controlled clinical trial. *J Am Coll Nutr* 2018;**37**:223-233.
17. Properzi C, O'Sullivan TA, Sherriff JL, et al. Ad libitum Mediterranean and low-fat diets both significantly reduce hepatic steatosis: a randomized controlled trial. *Hepatology* 2018;**68**:1741-1754.
18. Kirk E, Reeds DN, Finck BN, et al. Dietary fat and carbohydrates differentially alter insulin sensitivity during caloric restriction. *Gastroenterology* 2009;**136**:1552-1560.
19. Parker A, Kim Y. The effect of low glycemic index and glycemic load diets on hepatic fat mass, insulin resistance, and blood lipid panels in individuals with nonalcoholic fatty liver disease. *Metab Syndr Relat Disord* 2019;**17**:389-396.
20. Saeed N, Nadeau B, Shannon C, et al. Evaluation of dietary approaches for the treatment of non-alcoholic fatty liver disease: a systematic review. *Nutrients* 2019;**11**:3064.
21. Akhlaghi M, Ghasemi-Nasab M, Riasatian M. Mediterranean diet for patients with non-alcoholic fatty liver disease, a systematic review and meta-analysis of observational and clinical investigations. *J Diabetes Metab Disord* 2020;**19**:575-584.
22. Asbaghi O, Choghakhori R, Ashtary-Larky D, et al. Effects of the Mediterranean diet on cardiovascular risk factors in non-alcoholic fatty liver disease patients: a systematic review and meta-analysis. *Clin Nutr ESPEN* 2020;**37**:148-156.
23. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;**6**:e1000097.
24. Higgins J.P.T, Altman D.G, Gotzsche P.C, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**:d5928.
25. Ardern C.I, Janssen I, Ross R, et al. Development of health-related waist circumference thresholds within BMI categories. *Obes Res* 2004;**12**:1094-1103.
26. Ryan MC, Itsiopoulos C, Thodis T, et al. The Mediterranean diet improves hepatic steatosis and insulin sensitivity in individuals with non-alcoholic fatty liver disease. *J Hepatol* 2013;**59**:138-143.
27. Katsagoni C.N, Papatheodoridis G.V, Ioannidou P, et al. Improvements in clinical characteristics of patients with non-alcoholic fatty liver disease, after an intervention based on the Mediterranean lifestyle: a randomised controlled clinical trial. *Br J Nutr* 2018;**120**:164-175.
28. Misciagna G, Del Pilar Díaz M, Caramia D.V, et al. Effect of a low

- glycemic index Mediterranean diet on non-alcoholic fatty liver disease: a randomized controlled clinical trial. *J Nutr Health Aging* 2017;**21**:404-412.
29. Marin-Alejandre B.A, Abete I, Cantero I, et al. The metabolic and hepatic impact of two personalized dietary strategies in subjects with obesity and nonalcoholic fatty liver disease: the fatty liver in obesity (FLiO) randomized controlled trial. *Nutrients* 2019;**11**:2543.
 30. Ueno T, Sugawara H, Sujaku K, et al. Therapeutic effects of restricted diet and exercise in obese patients with fatty liver. *J Hepatol* 1997;**27**:103-107.
 31. Ghetti FF, De Oliveira DG, De Oliveira JM, et al. Effects of dietary intervention on gut microbiota and metabolic-nutritional profile of outpatients with non-alcoholic steatohepatitis: a randomized clinical trial. *J Gastrointest Liver Dis* 2019;**28**:279-287.
 32. Cheng S, Ge J, Zhao C, et al. Effect of aerobic exercise and diet on liver fat in pre-diabetic patients with non-alcoholic-fatty-liver-disease: a randomized controlled trial. *Sci Rep* 2017;**7**:15952.
 33. Abenavoli L, Greco M, Milic N, et al. Effect of Mediterranean diet and antioxidant formulation in non-alcoholic fatty liver disease: a randomized study. *Nutrients* 2017;**9**:870.
 34. Abenavoli L, Greco M, Nazionale I, et al. Effects of Mediterranean diet supplemented with silybin-vitamin E-phospholipid complex in overweight patients with non-alcoholic fatty liver disease. *Expert Rev Gastroenterol Hepatol* 2015;**9**:519-527.
 35. Godos J, Federico A, Dallio M, et al. Mediterranean diet and nonalcoholic fatty liver disease: molecular mechanisms of protection. *Int J Food Sci Nutr* 2017;**68**:18-27.
 36. Tsartsou E, Proutsos N, Castana E, et al. Network meta-analysis of metabolic effects of olive-oil in humans shows the importance of olive oil consumption with moderate polyphenol levels as part of the mediterranean diet. *Front Nutr* 2019;**12**:6.
 37. Federico A, Dallio M, Godos J, et al. Targeting gut-liver axis for the treatment of nonalcoholic steatohepatitis: translational and clinical evidence. *Transl Res* 2016;**167**:116-124.
 38. Schnabl B, Brenner D.A. Interactions between the intestinal microbiome and liver diseases. *Gastroenterology* 2014;**146**:1513-1524.
 39. Schnabl B, Brenner D.A. Dietary fiber, gut microbiota, and metabolic regulation-current status in human randomized trials. *Nutrients* 2020;**12**:859.