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The Impact of Mediterranean Diet Intake on Carotid-Intima Media Thickness: A Meta-Analysis

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Keywords: Atherosclerosis; Carotid-intima media thickness; Mediterranean diet; Randomized controlled trials.

Abbreviations: CVD: Cardiovascular Disease; CIMT: Carotid Intima-Media Thickness; MedDiet: Mediterranean diet; UIN: Unique Identifier Number.

Abstract

Globally, cardiovascular disease is the leading cause of mortality. Lifestyle and dietary habits have significantly proven to influence cardiovascular risk. Studies have shown beneficial effects of Mediterranean diet in cardiovascular patients. However, few studies have reported inverse relation between Mediterranean diet and Carotid intima media thickness, a surrogate marker of atherosclerosis. This has created ambiguity regarding the benefits of Mediterranean diet in cardiovascular patients as it is recommended in guidelines for prevention of cardiovascular disease. Therefore, we aim to pool data from all the studies reporting on carotid intima-media thickness in cardiovascular patients and conduct meta-analysis to evaluate the effect of Mediterranean diet on carotid intima-media thickness. MEDLINE database was searched from inception to September 2021. Trials included were randomized controlled trials, studies which included participants above the age of 18 and not pregnant, studies reported changes in carotid intima-media thickness after consumption of Mediterranean diet as primary outcome. The results were reported using a random-effects meta-analysis, mean difference with 95% confidence interval. The subgroup analysis was done to investigate the influence of study-level factors like study duration. Results of this study demonstrate that consumption of Mediterranean diet was associated with a statistically significant reduction in carotid intima-media thickness (WMD: -0.03 mm; 95% CI: [-0.04, -0.01]; P < 0.0001). Subgroup results demonstrate that the studies reporting results with a minimum of 1 year intervention were significantly associated with reducing carotid intima-media thickness (-0.02 mm; 95% CI: [-0.04, -0.01]; P < 0.005). Mediterranean diet has a positive effect on carotid intima-media thickness; hence, this study demonstrates that Mediterranean diet is beneficial in diseases where carotid intima-media thickness is elevated such as atherosclerosis.

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Introduction

Cardiovascular disease (CVD) remains a principal cause of death globally [1]. Since the progressive development of atherosclerosis remains unnoticed for decades, preclinical indicators play an increasingly vital role in the prompt diagnosis and formulation of preventative efforts [2]. One such indicator is artery vessel wall enlargement, assessed using ultrasound measurements of Carotid Intima-Media Thickness (CIMT), which is a non-invasive, well-standardized, and verified imaging modality [3]. The common carotid artery is the most common site for intima-media thickness measurement due to it having easy visualization and reproducibility as compared to other segments of the carotid artery [4]. Lifestyle and dietary habits have been shown to significantly influence cardiovascular risk [5-6]. More recently, the Mediterranean diet (MedDiet) has become popular for its cardio protective effects [7-8]. The recommendations for this diet include a high intake of olive oil, fruits and nuts, moderate-to-high intake of fish, and low consumption of sweet products [9-10]. Multiple studies have evaluated this effect of the MedDiet. The PREDIMED study (Prevención con Dieta Mediterránea), has demonstrated the role of the MedDiet in providing long-term protection from CVD compared with a reduced-fat diet [11]. A secondary prevention clinical trial (the Lyon Diet Heart Study), based in France, also showed similar results [12]. In the context of intima-media thickness, a few observational studies have exhibited an inverse relationship between CIMT and adherence to diets rich in plant food and restricted to processed and saturated fat-rich foods [13-15]. This has created ambiguity regarding the benefits of using MedDiet in CVD patients and created a necessity to investigate the relationship between MedDiet and key indicator CIMT [16]. In this study, we aim to pool data from all the studies reporting on CIMT in CVD patients and conduct meta-analysis to evaluate the effect of MedDiet on CIMT.

Methods

Data sources and search strategy

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) and the American Heart Association guidelines for systematic reviews [17]. No ethical review board permission was required for this analysis as the data was widely available. Reviewers (AMR and SSJ) independently searched MEDLINE from inception till September 2021, without any time or language restrictions. A detailed search strategy has been provided in ***supplementary table S1***. The literature search also included bibliographies of identified articles, grey/unpublished literature, clinical trial registries, and reviews on the topic. The study was registered with the Research Registry, and the Unique Identifier Number (UIN) for this study is reviewregistry1549[18].

Study selection

Included studies satisfied the following eligibility criteria: (1) randomized controlled trials (double-blind, single-blind, open-label); (2) studies with adults aged 18 years or above; (3) MedDiet administered alone or in combination with any other intervention if placebo or comparable and valid active control group was present; and (4) studies reporting CIMT as a primary outcome. The exclusion criteria included the following: 1) reviews, case reports, conference abstracts and clinical trials with only abstract; 2) if trial size or study population was not clear.

Data extraction and quality assessment

All the selected studies were imported to EndNote X9 (Thomson Reuters, Toronto, Ontario, Canada) and duplicates were identified and removed. The remaining studies were examined on title and abstract by the reviewers, AMR and SSJ. The full text was appraised critically against the inclusion and exclusion for the final selection of studies. A third reviewer, UAAM, was consulted to review and resolve any discrepancies. Data were extracted by the first investigator (AMR) and then rechecked for accuracy by the second investigator (SSJ). Data extracted included study and population characteristics, and outcomes, including baseline and post-intervention values for CIMT. In addition, two reviewers (AMR and SSJ) assessed the quality of the RCTs as low, high, or unclear risk of bias according to the Cochrane risk of bias tool for randomized controlled trials [19]. Items were assessed as follows: i) adequate sequence generation; ii) allocation concealment; iii) blinding of participants and personnel; iv) blinding of outcome assessment; v) incomplete outcome data; vi) free of selective reporting; and vii) free of other bias. The study was then evaluated with the AMSTAR 2 critical appraisal tool for systematic reviews that included randomized or non-randomized healthcare intervention studies [20].

Statistical analysis

Data were analyzed using RevMan software (Review Manager Version 5.3.5, The Nordic Cochrane Centre, Copenhagen). For this study, sample size, and the mean and Standard Deviation (SD) of the CIMT measurements for pre- and post-intervention periods (for both MedDiet intervention and control) were extracted and used in the analyses. If the pre- and post-intervention mean were not given, then the mean change was considered. A forest plot was generated to evaluate the compound effect of MedDiet on CIMT (Figure 1). All data used in the meta-analysis is displayed in **Table 1**. Heterogeneity was assessed using the Cochrane Q statistic; $P < 0.1$ indicates significant heterogeneity. Heterogeneity across the trials was also evaluated by the I^2 test and the scale was set as a value <25% indicates low risk; 25–75% indicates moderate risk; and >75% indicates high risk [21]. All p-values were two sided and a p-value of <0.05 was considered significant in all cases. A random effects meta-analysis was performed.

Results

A systematic review was conducted, and 474 studies were discovered. 300 studies were eliminated after reading the title and abstract. Out of the remaining 174 studies, 170 articles were excluded after reading their full text. 4 studies satisfied the inclusion criteria and were included in this study. The PRISMA flowchart summarizes the selection process in **Figure 1**.

Study characteristics

Characteristics of the included trials are shown in **Table 1**. The total number of participants was 1505. The mean age was 54 (± 6.9) years. The mean BMI was 29.9. The median study duration was 118 weeks. Among the included trials, 2 trials reported included participants at increased cardiovascular risk [22-23]. One trial included participants with diabetes mellitus [24]. Similarly, one trial included participants with coronary heart disease [25]. In all the included studies, the cardiovascular risk was assessed by CIMT.

Effect of Mediterranean diet (MedDiet) on Carotid Intima-Media Thickness (CIMT)

Pooled analysis of 4 trials demonstrates that consumption of MedDiet was associated with a statistically significant reduction in CIMT (WMD: -0.03 mm; 95% CI: [-0.04, -0.01]; P < 0.0001; **Figure 2**). The heterogeneity among the trials was 0% (Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.20$, df = 5 (P = 0.82); $I^2 = 0\%$).

Subgroup analysis was performed based on study duration. Two subgroups were made, one study showed results within less than a year and 3 studies in the second subgroup reported results with a minimum intervention lasting more than a year. Results of this study demonstrate that the 3 trials, with 4 sets of data, reporting results with a minimum of 1 year intervention were significantly associated with reducing CIMT (-0.02 mm; 95% CI: [-0.04, -0.01]; P < 0.005). Similarly, the results in the subgroup with one trial, with 2 sets of data, also demonstrated significant reduction in CIMT (-0.04 mm; CI: [-0.06, -0.02]; P < 0.0007). There was no significant difference between the subgroups (Test for subgroup differences: $Chi^2 = 1.21$, df = 1 (P = 0.27), $I^2 = 17.2\%$). The results of the subgroup analysis are summarized in **Figure 3**. Due to the total number of studies being less than 10, egger's regression test for publication bias was not applicable.

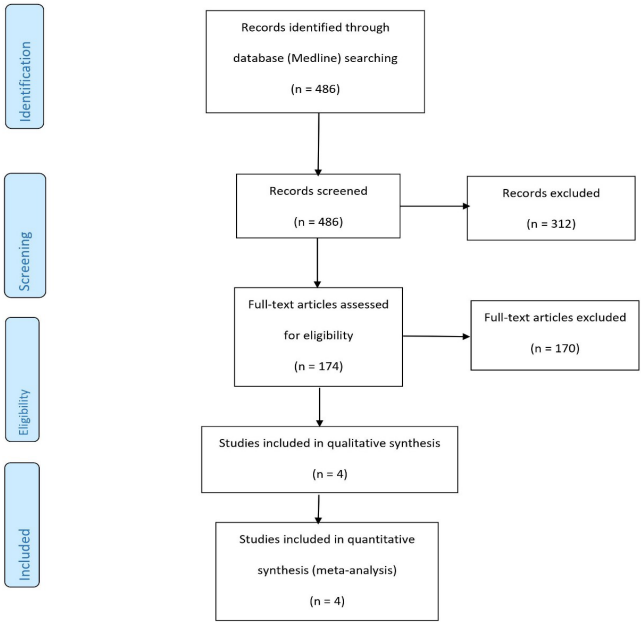
Study quality and publication bias

Overall, the quality of the trials was average. This is because only one study [24] reported random sequence generation, allocation concealment and blinding of participants and personnel. Two studies had high risk [23–24] due to incomplete outcome data (attrition bias) and other study had unclear bias. The summary of risk of bias assessment is given in ***supplementary figure 1***.

Table 1: Characteristics of the included trials

Author	Country	Study Design	Health Status	Outcome	Sample size	Age (years)	BMI (kg/m^3)	Duration (weeks)	Type of intervention	Type of control
Murie-Fernandez et al. 2011 [19]	Spain	Parallel	CVD risk	CIMT	187	67	29.4	48	G1: MedDiet + EVOO	Low-fat diet
									G2: MedDiet + nuts	
Sala-Vila et al. 2014 [20]	Spain	Parallel	CVD risk	CIMT	164	66	29.6	115	G1: MedDiet + EVOO	Low-fat diet
									G2: MedDiet + nuts	
Maiorino et al. 2017 [21]	Italy	Parallel	DM	CIMT	215	52	29.6	121	MedDiet	Low fat diet
Jimenez-Torres et al. 2021 [22]	Spain	Parallel	CHD	CIMT	939	59	31.1	364	MedDiet	Low fat diet

CHD: Coronary Heart Disease; CIMT: Carotid-Intima Media Thickness; CVD: Cardiovascular Disease; DM2: Diabetes Mellitus.

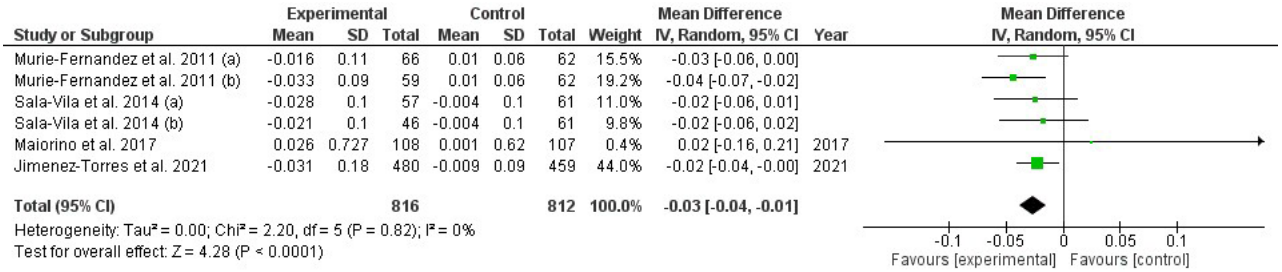


SFigure 1: PRISMA flowchart showing study selection process.

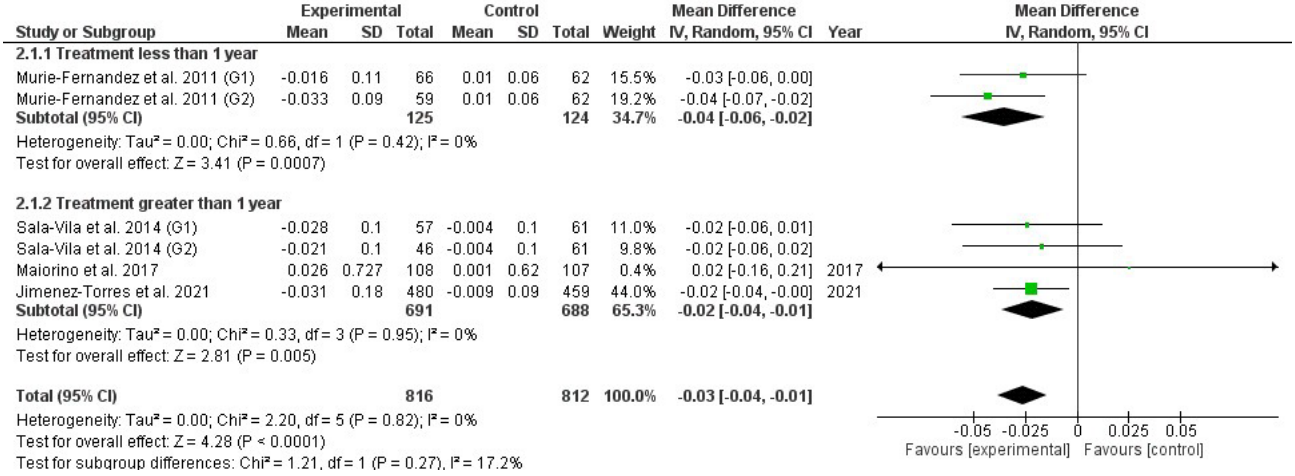
Discussion

This meta-analysis, which comprised 4 randomized controlled trials with a total of 1505 participants, provides evidence that MedDiet use may reduce CIMT levels in those at risk for cardiovascular events. To our best of knowledge, this meta-analysis is the first study to investigate the association between MedDiet and CIMT.

CIMT is a surrogate marker of atherosclerosis that is measured using B-mode ultrasound to determine the degree of carotid atherosclerotic vascular disease [26]. The findings of a meta-analysis performed by Lorenz et al. [27] revealed that CIMT levels are a significant predictor of CVD events, with a modest rise in CIMT leading to an increased risk of myocardial infarction and stroke. CIMT is linked to a number of risk variables, including age, gender, race, smoking, alcohol use, hyperglycemia, and hypertension [28–29]. Beneficial impact of MedDiet on cardiovascular health is attributed to its inhibitory effect on inflammatory markers in circulation [30-31] via down regulating genes involved in vascular inflammation [32], as well as the decrease in oxidative stress [33]. Furthermore, MedDiet may significantly lower LDL levels in the blood, which enhances endothelial function. By promoting inflammation and inducing fat accumulation in arteries, oxidized LDL raises the risk of endothelial dysfunction, which contributes to the development of atherosclerosis [34]. MedDiet slows the development of atherosclerosis by acting in the various stages of the disease [25]. Adherence to the MedDiet has also been linked to better balanced vascular hemostasis, according to the studies [35].



SFigure 2: Forest plot showing effect of Mediterranean diet on carotid-intima media thickness.



SFigure 3: Subgroup analysis showing effects of Mediterranean diet on carotid-intima media thickness for treatment duration of less than 1 year or greater than 1 year.

The preponderance of the studies included in this meta-analysis was performed in the same country, Spain, there was no heterogeneity in the research. Another explanation for the lack of heterogeneity in the previous research may be because treatment techniques were homogeneous or very similar. There is currently a lack of studies investigating the link between Med-Diet and CIMT, therefore further research, including young and healthy people, will be needed in the future to confirm the therapeutic advantages of MedDiet on cardiovascular health and its involvement in CIMT reduction. As CIMT is related to atherosclerosis, which is major health risk, trials demonstrating the influence of MedDiet on patients with different comorbidities is also considered necessary.

This research has a number of limitations. First, since the bulk of studies included took place in the same country, generalizability may be restricted. Another drawback of this study is that the participants' average age was 54, thus it only included a small portion of our community. Another drawback of this research is that it only included individuals with comorbidities such as increased CVD risk, congenital heart defects or diabetes and no healthy participants were involved in the analysis.

Conclusion

The findings from this analysis suggest that consumption of MedDiet was associated with statistically significant reduction in CIMT. The effect was seen to be significant in patients who had incorporated MedDiet for less than a year as well as in participants with minimum of 1 year intervention. Thus, long-term treatment of MedDiet reduces CIMT values in individuals with CVD comorbidities and may also delay atherosclerosis development. Due to small number of studies available on the association between MedDiet and CIMT, more trials are needed to investigate the effectiveness of this diet in reducing CIMT and its preventative role with regards to CVDs in different patient populations.

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