Effects of the Mediterranean Diet on Type 2 Diabetes' Incidence and Treatment: A Systematic Review

Panayota Kailatzi[1], Margarita Matte[2] and Styliani G. Tziaferi[3]

Abstract

The incidence of Type 2 diabetes is increasing rapidly worldwide, bringing about an enormous economic burden for societies. Dietary habits play an important role in the manifestation and treatment of this disease. Results from epidemiological studies and clinical trials, suggest that adherence to the Mediterranean diet may exert beneficial influence on glycemic control and prevention of this condition. We conducted a systematic review aiming to determine the impact of the Mediterranean diet on glycemic control and diabetes incidence. Electronic databases, PubMed and Google Scholar, were searched for available publications that assessed the effect of the Mediterranean diet on type 2 diabetes. Thirty nine studies met the inclusion criteria, sixteen explored the impact of the Mediterranean diet on type 2 diabetes incidence, fifteen explored the impact of the Mediterranean diet on type 2 diabetes treatment, nine explored the impact of the Mediterranean diet on diabetes indices, as components of Metabolic syndrome and four examined the impact of the Mediterranean diet on cardiovascular risk factors, including type 2 diabetes. Current guidelines and recommendations from all the major scientific associations, strongly encourage a Mediterranean-like dietary pattern for primary and secondary prevention of major chronic diseases, including type 2 diabetes.

Keywords: Mediterranean diet, type 2 diabetes, glycemic control, HbA1c, insulin resistance, glucose homeostasis, cardiovascular disease, metabolic syndrome

1 Introduction

Type 2 diabetes (T2D) remains the major cause of morbidity and mortality world-wide. According to International Diabetes Federation, 382 million people suffered from diabetes

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[1]National and Kapodistrian University of Athens.
[2]National and Kapodistrian University of Athens.
[3]University of Peloponnese.

in 2013, while this will rise to 592 million by 2035 [1] Individuals with T2D have a potent risk for a range of complications that can lead to disability and premature death such as renal failure, neuropathy, blindness, hypertension, peripheral vascular and cardiovascular diseases (CVD) [2, 3]. As a result, the management of diabetes mellitus poses a huge medical and economic burden, making it a current public health priority [4].

Although genetic predisposition and environmental influences seem to be the most important factors responsible for the development of T2D, the increased prevalence of this condition seems to result mainly from the lifestyle changes in modern societies. It is well established that diabetes is a nutrient- gene- interaction disease [5-8]. The westernized dietary patterns, physical inactivity, and the raising rates of overweight and obese people are some of the modifiable factors that contribute to the increasing incidence of T2D. Behavior change interventions such as dietary habits may promote healthful lifestyles, reducing the incidence of T2D and improve glycemic control [9]. Diet quality plays an important role to the disease manifestation. High- quality diets with low glycemic index and glycemic load and rich in fruits and vegetables are associated with reduced risk of chronic diseases such as MetS, CVD and T2D. This is attributed to weight balance, low insulin response, lower blood lipids, blood pressure, blood glucose and inflammation [10-14].

Foods are rarely eaten in isolation but, instead, in combination with other food groups, thus the combined effect of food groups may create an additive effect on health [15]. Analyses of the overall diet rather than of individual food groups takes this potential food synergy into account. The Mediterranean diet (MeDiet) is the traditional dietary pattern of Mediterranean region residents [16]. This diet is comprised of abundant plant foods(vegetables, fruits, seeds, nuts and cereals), high consumption of whole grains, olive oil, legumes, moderate to high consumption of fish, moderate to low consumption of meat, meat products, milk and dairy products and moderate intake of alcohol (red wine) [16-19]. The MeDiet is one of the best known dietary patterns for its beneficial effects on human health. Adherence to the MeDiet is usually measured with MeDiet scores, including a variety of components, with higher values in these scores reflecting higher adherence to the MeDiet. Recent studies have shown that conformity to the MeDiet protects individuals from major chronic diseases like heart disease, cancer, Parkinson and Alzheimer. Results from epidemiological studies and clinical trials demonstrate the beneficial role of the MeDiet regarding the development of T2D and its treatment. High consumption of vegetables, fruits, whole grain cereals and moderate consumption of alcohol provide antioxidants, anti-inflammatory factors and dietary fiber, which have been implicated in improvements in glucose regulation and the progression of complications associated with diabetes. Moreover, high consumption of fish and olive oil provides a high intake of polyunsaturated and monounsaturated fatty acids that beneficially influence insulin resistance [20-29].

Nevertheless, urbanization and globalization have altered the diet and nutrition towards the opposite direction despite the nutritional recommendations for a healthy diet and lifestyle [30]. Even in Mediterranean countries, dietary habits have partially changed into a more Westernized dietary pattern. Therefore, diet evaluation for the prevention of T2D is of significant public health importance [1, 22, 25-29, 31]. The aim of this study was to systematically review all the available studies that have evaluated the impact of the MeDiet in human T2D, including diabetes prevention, treatment and metabolic and cardiovascular outcomes.

2   Methods

We searched Pubmed and Google Scholar databases for relevant articles about the effect of the MeDiet on T2D incidence and treatment from February 2014 to May 2014. We used the keywords Mediterranean diet, type 2 diabetes, glycemic control, HbA1c, insulin resistance, glucose homeostasis, cardiovascular disease, metabolic syndrome, as well as combinations of these. In addition, the reference lists of the retrieved articles helped us to find relevant articles that did not allocate through database searching procedure. We narrowed the search to studies published in English between 2003 and 2014, and limited to those conducted in humans. We excluded studies that analyzed adherence to a non-specific dietary pattern. We also excluded studies with less than 3 months follow- up and those with gestational or type 1 diabetes population. We focused the search on articles referring to the MeDiet as a whole dietary pattern and excluded studies that only investigated one aspect of the MeDiet. Moreover, reports with restricted calorie intake or those that aimed to reduce body weight, were discarded.

3   Results

A total of 129 articles were identified in the initial search, of which we excluded 41 on the basis of the title or abstract due to the deliberation of only one of the two aspects (T2D or MeDiet). Of the remaining 88 articles were discarded 49 for the following reasons: a non specific dietary pattern instead of a MeDiet was evaluated (n=8), the study population had gestational or type 1 diabetes (n=3), the follow-up was less than 3 months (n=3), including 2 studies that were published before 2003, studies with restricted calories or those aimed to reduce body weight (n=8), studies regarding specific foods of MeDiet (n=25) and those that were not written in English (n=1).   Thirty nine studies met the inclusion criteria (Figure 1). Of these, we identified 18 observational studies (7 prospective cohort studies, 8 cross-sectional studies, 1 retrospective study, 1 case- cohort prospective study and 2 both cross-sectional and prospective studies), 12 intervention studies (2 of them were cross- over and 10 randomized trials), and 8 reviews.

From the total of 39 studies (Table 1), 31 took place in European countries, of them, 26 conducted in the Mediterranean region, four in north Europe and one was multicenter. Five studies conducted in USA, two in Australia and one in Asia. The number of subjects ranged from 12 to 41.614 participants. Greater adherence to the MeDiet was associated with older age [32, 46, 57, 58], being female [34, 35, 46, 57, 58], better education [33,35], higher incomes [36], smaller waist circumference [36], non- smoking [36, 46, 57, 58], more physically active individuals [57], multivitamin users [46], ERT users [46], slightly greater BMI [58], hypertension [58] and previous acute myocardial infarction [58]. In contrast, the study of Panagiotakos et al [55], found no difference between the two sexes, while in another study [34], age, physical activity, education and consumption of antiplatelet β- blocker agents had no difference between conformity groups.

3.1 Diabetes Incidence

Given the dramatic increase of T2D prevalence nowadays, strategies aiming to prevent the disease manifestation are of major public health priority. The association between MeDiet adherence and the incidence of T2D was assessed in 7 prospective studies [32, 33, 35, 37,

49, 50, 58], three cross- sectional studies [25, 55, 62], one case- cohort prospective study [39], three reviews [44, 28, 64] and two randomized controlled trials [65,42].

The most available prospective studies support the protective role of the MeDiet against T2D development. The protecting reduction risk ranges from 9% to 83% for patients closely adhered to the MeDiet, compared to those with the lowest adherence, after adjustment for several confounding factors such as smoking, BMI, age, sex, family history of T2D, physical activity, etc. [33, 34, 37, 39, 50, 58]   Moreover a high MeDiet score together with a low GL, offer protection of about 20% against diabetes. Interestingly, the MeDiet not only has a beneficial effect on healthy adults, but also on individuals with recent myocardial infarction. Specifically, Mozzaffarian et al [58], found that prevention of weight gain, smoking cessation and consumption of the MeDiet, offer a protective effect on T2D incidence on this patient group. It should be noted that dietary pattern scores such as the alternative HEI (Healthy Eating Index), the DASH (Dietary Approaches to Stop Hypertenson) [37] and the Healthy eating pattern [49] scores were associated with a lower risk on T2D incidence, emerging that a common dietary pattern characterized by plant based foods, fruits, whole- meal bread, low- fat dairy, moderate alcohol and low intake of red meat may beneficially influence the T2D odds.

Cross- sectional evidence regarding the association between adherence to MeDiet and the likelihood of T2D, demonstrate the beneficial role of MeDiet to T2D incidence. It is noteworthy that both Panagiotakos et al [55] and   Sanchez- Tainta et al [25] discovered that following the MeDiet is inversely associated not only with the clustering of diabetes, but also with hypertension, obesity, and hypercholesterolemia among high cardiovascular risk and elderly individuals. In another cross-sectional study of Panagiotakos et al [62], 3042 participants took part in order to evaluate the incidence of T2D in relation to both physical activity and dietary patterns. The study revealed that a 10- point increase in the MeDiet score was associated with 21% lower odds of acquiring diabetes. The study adds that commitment to the MeDiet together with light physical activity can reduce diabetes risk by 35%, compared to sedentary individuals.

One large case cohort, multicenter prospective study showed that individuals with a high MeDiet score were 12% less likely to develop diabetes than those with low MeDiet scores. Additionally, a two- point increase in the MeDiet score was associated with a 4% reduction in the risk of T2D. It should be noted that the association between the two variables was attenuated in obese participants, compared to the youngest ones.

Finally, two randomized controlled trials searched the relation between MeDiet and the incidence of T2D. Salas Salvado et al, [42] compared the effects of two MeDiets supplemented with olive oil or nuts, versus a low- fat diet on the incidence of T2D in 418 non diabetic participants at high cardiovascular risk. The study found that MeDiet with either olive oil or nuts reduces diabetes incidence by 52%, compared with the low-fat dietary pattern. Similarly, later in 2014 Salas Salvado et al, [65] found that a MeDiet supplemented with extra olive oil and without energy restriction, succeeded in limiting the incidence of T2D among high cardiovascular risk patients

3.2 Diabetes Treatment

Fifteen studies explored the relationship between MeDiet and glycaemic control.   Of them, five were cross- sectional studies [41, 35, 45, 51, 54], two were randomized cross- over intervention studies [36, 41], three were reviews [44] and five were randomized trials [66, 65, 43, 56, 59]. Most of these studies demonstrate the beneficial effect of the MeDiet in

T2D patient's glycemic control and insulin sensitivity.

Cross- sectional research results show the salutary effect of the MeDiet to both diabetic and non- diabetic participants. Evidence reveals that non- diabetic participants, consisted with the MeDiet, had lower insulin levels, blood glucose (4), and better fasting indices of glucose homoeostasis [54]. Additionally, in diabetic patients with greater attach to the MeDiet, was observed reduced HbA_{1c} and post- meal glucose concentrations [45].

Cross- over intervention studies of Ryan et al [36] and Itsiopoulos et al (9), included of non- diabetic and diabetic participants respectively. Both studies found that insulin sensitivity improved with the MeDiet. Furthermore, Itsiopoulos observed that consumption of the MeDiet fell HbA_{1c} from 7.1% to 6.8%, compared to the usual diet. Liver steatosis reduced with MeDiet, compared with low fat/high carbohydrate diet in participants with NAFLD [36].

Two randomized intervention trials carried out in non- Mediterranean countries, in order to evaluate the effect of the MeDiet on diabetes markers at diabetic population. The study of Lindeberg et al [56] failed to prove any significant correlation between these variables. Particularly, Lindeberg et al estimated the effect of the Paleolithic diet, based on fish, fruits, eggs, nuts, root vegetables and lean meat, compared to the MeDiet on glucose tolerance and postchallenge insulin response in glucose intolerant IHD patients. The study recommends that healthy diets, such as the MeDiet constitute the second best choice for the prevention and control of diabetes condition. On the other hand, Elhayany et al [43], compared two MeDiets, a low carbohydrate MeDiet (LCM) and the traditional MeDiet, to the 2003 American Diabetic Association diet (ADA) between overweight diabetic patients, and found that only the LCM had a significant impact on improving glycaemic control in this population group. Additionally, the recent report of Esposito et al [64] supports that a LCM can improve not only diabetes indices, but also can delay the need for medication use between overweight, diabetic individuals.

3.3 MeDiet and MetS

We identified five primary studies that assessed the association between the MeDiet and diabetes indices, as components of MetS [34, 38, 46, 57, 59] and four reviews [12, 47, 48, 52].

The sum of the reviews ended up that the MeDiet has an anti-inflammatory impact against diseases related to chronic inflammation, including abdominal obesity, MetS and T2D. Traits of MetS such as insulin resistance, hypertension and dyslipidemia are attenuated with the consumption of the MeDiet.

Regarding the impact of the MeDiet on the incidence of MetS, Tortosa et al prospectively found that the MeDiet reduces the odds of acquiring MetS together with all risk factors that are responsible for its development, except plasma glucose. Additionally, the prospective study of Rumawas et al [46] found that MetS prevalence was significantly reduced with MeDiet. Moreover, MetS traits were attenuated (less abdominal obesity, less insulin resistance, and less atherogenic dyslipidemia).

Moreover, the cross- sectional study of Viscogliosi et al [34] searched the incidence of MetS and the insulin resistance and fasting glucose levels among non diabetics. They observed that MeDiet protects against MetS and prediabetes, and improves glucose metabolism. Similarly, Gouveri et al [38] observed a reduced incidence of MetS and a subsequent benefit on T2D and CVD development with the commitment to the MeDiet. In contrary, Michalsen et al [59] examined the impact of MeDiet on patients with treated CAD

with regard to inflammation and metabolic risk factors. Commitment to the MeDiet had no effect on indices of inflammation and metabolic risk factors, including fasting insulin.

3.4 MeDiet and Cardiovascular Disease

Three randomized controlled trials [60, 61, 63] and one review [47], were identified in order to test the effectiveness of the MeDiet on cardiovascular risk factors. Champagne et al [47] carried out a review in 2009 ending up that individuals consuming the MeDiet pattern derive advantage against the development of MetS and CVD. Vincent- Baudry et al [31] conducted an intervention study of 212 overweight and obese participants with moderate CVD risk factors who classified into a MeDiet or a low- fat diet group. The study showed that both diets had a beneficial effect on CVD risk factors, including insulinemia, glycemia, and HOMA score. Particularly, a 9% reduction was observed in CVD risk with the low- fat diet and a 15% reduction with the MeDiet. Furthermore, in another randomized trial, 772 participants at high cardiovascular risk were classified into a MeDiet group with olive oil, a MeDiet group with nuts, or a low- fat group. Both MeDiets improved blood pressure, lipid profiles, reduced insulin resistance and decreased concentrations of inflammatory molecules, compared with the low- fat group. As a result, both MeDiets exert a beneficial effect on CVD risk factors [60]. Finally, Toobet et al [63], investigated the impact of the Mediterranean Lifestyle Program on CVD. He found that stress management, exercise, smoking cessation and the Mediterranean low- saturated fat diet, improved glycemic control, some coronary heart disease risk factors and the overall quality of life.

4   Labels of Figures and Tables

Total studies (n=129)

Studies excluded on the basis of the title or abstract due to the deliberation of only one of the two aspects (T2D and MeDiet) (n=41)

88 studies

Studies excluded due to the non specific dietary pattern(n=8), type 1 diabetes population (n=3), follow-up less than 3 months (n=3), restricted calorie/weight loss (n=8), components of MeDiet only (n=25), in different than English language (n=1)
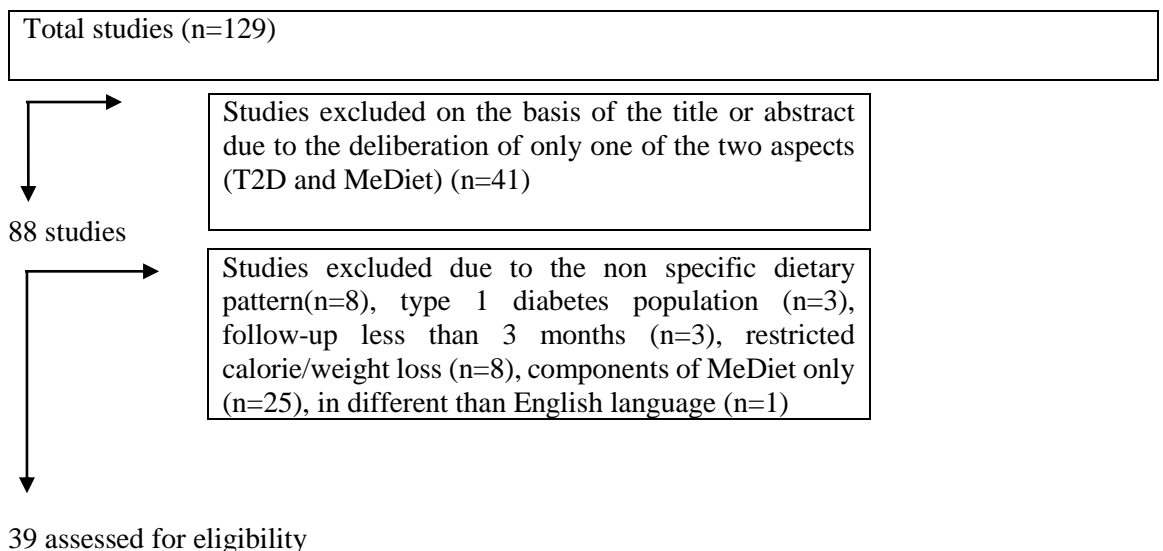
39 assessed for eligibility

Figure 1: Diagram flow of literature review

Table 1: Studies exploring the effect of the Mediterranean diet on type 2 diabetes mellitus incidence and treatment

Author/Year Publication	Country	Type of study	Population	Criteria for inclusion/excursion	Objective	Methodology	Follow up	Results	Conclusion
Salas-Salvado et al., 2014	Spain	Randomized trial	3541 patients, aged 55 to 80 years	Patients without T2D but at high cardiovascular risk were eligible for the study	To assess the efficacy of MeDiets for the primary prevention of diabetes	Participants were randomly assigned to 1 of 3 nutrition interventions: MeDiet with extra-virgin olive oil (EVOO),MeDiet supplemented with mixed nuts, or a control diet (advice on a low fat diet)	Median of 4.1 years	- 80, 92, and 101 new-onset cases of T2D occurred in the MeDiet with EVOO, MeDiet with mixed nuts, and control diet groups, respectively - Multivariate-adjusted hazard ratios were 0.6 for the MeDiet with EVOO, and 0.82 for the MeDiet with nuts compared with the control diet	A MeDiet enriched with EVOO but without energy restrictions reduced diabetes risk among persons with high cardiovascular risk
Lasa et al., 2014	Spain	Randomized controlled trial	191 participants (77 men and 114 women)	Participants with T2D were included	The aim of this work was to compare the effect of two Mediterranean diets versus a low-fat diet on several parameters and indices related to glycemic control in type 2 diabetic subjects	Participants were assigned to 1 of 3 nutrition interventions: two Mediterranean diets supplemented with virgin olive oil (n=67) or mixed nuts (n=74) and a low-fat diet (n=50). Insulin resistance was measured by HOMA-IR index, adiponectin/leptin and adiponectin/HOMA-R ratios	1 year	- Increased values of adiponectin/leptin ratio (P=0.043, P=0.001 and P<0.001 for low-fat, olive oil and nut diets, respectively) and adiponectin/HOMA-IR ratio (P=0.061, P=0.027 and P=0.069 for low-fat, olive oil and nut diets, respectively) - Decreased values of waist circumference (P=0.003, P=0.001 and P=0.001 for low-fat, olive oil and nut diets, respectively) were observed in the three groups - In both Mediterranean diet groups, but not in the low-fat diet group, the variation above was associated with a significant reduction in body weight (P=0.347, P=0.003 and P=0.021 for low-fat, olive oil and nut diets, respectively)	Mediterranean diets supplemented with virgin olive oil or nuts reduced total body weight and improved glucose metabolism to the same extent as the usually recommended low-fat diet
Esposito et al., 2014	Italy	Randomized trial	215 overweight, middle-aged men and women with newly diagnosed T2D	Participants with T2D were included	To assess the long-term effects of dietary interventions on glycemic control, need for diabetes medications, and remission	Participants were randomized to a low-carbohydrate MeDiet ($n = 108$) or a low-fat diet ($n = 107$). After	6.1 years	- The primary end point was reached in all participants after a total follow-up of 6.1 years in the low-fat	In patients with newly diagnosed type 2 diabetes, an LCMD resulted in a greater reduction of

of type 2 diabetes					4 years, participants who were still free of diabetes medications were further followed up until the need of a diabetic drug. Remission of diabetes (partial or complete) and changes in weight, glycemic control, and cardiovascular risk factors were also evaluated		group and 8.1 years in the low carbohydrate MeDiet group - Median survival time was 2.8 years and 4.8 years, respectively - Low carbohydrate MeDiet participants were more likely to experience any remission (partial or complete), with a prevalence of 14.7% during the first year and 5.0% during year 6 compared with 4.1% at year 1 and 0% at year 6 in the low-fat diet group	HbA$_{1c}$ levels, higher rate of diabetes remission, and delayed need for diabetes medication compared with a low-fat diet
Georgoulis et al., 2014	Greece	Review	-	-	To examine current scientific knowledge on the association between the MeDiet and diabetes mellitus	-	-	- According to epidemiological data, a greater adherence to the MeDiet, is inversely associated with T2D risk in the general population, in individuals at high cardiovascular risk and in patients with established CVD - International studies also demonstrate the beneficial role of the MeDiet in T2D management, with patients allocated to a MeDiet exhibited greater improvements in glycemic control and CVD risk factors, compared with those following a control diet - There is evidence that MeDiet may also have a beneficial role in the primary and secondary prevention of CVD and a favorable effect on liver and sexual function in diabetic patients	Mounting evidence suggests the beneficial effect of the MeDiet on T2D prevention and treatment

Esposito et al., 2014	Italy	Review	-	-	To review the impact of MeDiet on T2D	-	-	- Prospective studies report a lower risk of T2D in healthy people or at risk patients with the highest adherence to a MeDiet - MeDiet improved HbA$_{1c}$ levels from 0.1% to 0.6% - No trial reported worsening of glycaemic control with a MeDiet	Adopting a MeDiet may help prevent T2D. Moreover, lower carbohydrate MeDiet seems good for HbA$_{1c}$ reduction in persons with established diabetes
Dominguez et al.,2013	Spain	Cross sectional/prospective cohort study	20.155 individuals for cross-sectional analyses, & 9.109 individuals for longitudinal analysis, university graduates-former students, non-obese with mean age 38.4 years	Excluded participants: - with energy intake out of <800 or >8000kcal/day for men and <500 or >6000kcal/day for women - with cancer, CVD, and diabetes at baseline, - with missing information - without at least a 2-year follow up	To evaluate the macronutrient distribution, assessed with MDS or MEDAS scoring systems. To evaluate disease incidence or mortality, associated with adherence to MeDiet	Individuals completed a validated FFQ, together with other questionnaires that collected sociodemographic, lifestyle and clinical characteristics. Participants returned completed questionnaires every 2 years	Mean time: 6.2 years	- The macronutrient distribution, disease incidence and mortality had similar prediction for both scoring systems - Adherence to MeDiet was associated with reduced occurrence of diabetes, CVD or death - Most participants had intermediate values of adherence to MeDiet (3-5points on a 0-9 point scale: 62.9%) - Compliance with MeDiet increased with age	Adherence to MeDiet was associated with a decreased incidence of T2D, CVD, and all-cause mortality
Rossi et al., 2013	Italy	Prospective cohort study	22.295 participants	Excluded participants who: - did not respond or could not be traced during follow up - had diabetes, cancer and/ or stroke and/or CVD - had missing values of the covariates of interest	To investigate the association between MeDiet and GL with diabetes incidence	Participants completed a validated FFQ at enrolment. Adherence to MeDiet and dietary GL were calculated from MDS score	Mean time: 11.34 years	- Participants in the highest quartile of adherence to the MD (MDS > 5) exhibited a 12% (95% CI 0.78–0.99) reduced risk of T2DM, compared with those in the lowest quartile (MDS < 4) - Adherence with MeDiet increased with better educated participants - Older participants reported a diet with a lower GL, compared with younger ones - MeDiet reduced diabetes risk independently of GL levels	A low GL diet that also adequately adheres to the principles of the traditional MedDiet may reduce the incidence of T2D

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Author	Country	Study type	Participants	Exclusion/Inclusion	Aim	Methods	Follow-up	Results	Conclusions
								- Both MeDiet and GL/GI associated with a lower diabetes risk - A high MeDiet score both with a low GL offer protection of about 20% against diabetes	
Viscogliosi et al., 2013	Italy	Cross sectional	120 individuals with mean age 59.8± 10.2 years	Excluded participants: -who changed their dietary habits within the last year - with diabetes - with history of CHD, stroke, ischemic attack - with cardiovascular events and chronic diseases except blood hypertension, obesity, dyslipidemia, IFG - taking anti-inflammatory agents, statins or other lipid-lowering agents - current or former smokers - with daily consumption of more than 2 glasses of alcohol for women and more than 3 for men for a period of 6 consecutive months	To investigate whether the commitment with MeDiet affects the prevalence of MetS, impaires fasting glucose, insulin resistance and microinflamation	- Commitment with MeDiet was calculated with a validated 14-item questionnaire - venous blood sample for FBG, triglycerides, HDL-C, fasting insulin, CRP - face to face interview for medical patient/family history, lifestyle habits and home therapy	-	- The overall adherence to the MeDiet was low (most subjects succeeded 6-9 points on a 0-14 point scale) - No differences in mean age, physical activity, education and consumption of antiplatelet and β-blocker agents were found across categories of adherence - Participants with higher adherence to MeDiet were more likely to be women - Subjects with MetS were less likely to consume olive oil and vegetables - BMI and the overall MeDiet were strongly associated with the presence of MetS - IFG was independently predicted by age, BMI and overall MeDiet - Adherence to MeDiet may protect against MetS and prediabetes and exert a beneficial role on glucose metabolism	Inverse associations observed between adherence to MeDiet and the prevalence of MetS and prediabetes due to the effects of the entire dietary pattern
Abiemo et al., 2013	USA	Cross sectional/prospective cohort study	5390 multi-ethnic men and women aged 45-84 years, free of diabetes and CVD	Subjects with CVD or T2D excluded from the study	To investigate if conformity to the MeDiet is related cross-sectionally with lower insulin resistance and prospectively with reduced risk of T2D incidence	Five examinations during follow up which included questionnaire information from participants, physical measurements and tests, blood sample, CT, MRI, and	6 years	- The average MeDiet score was 5 on a 0-10- point scale - Participants with higher conformity to the MeDiet were more likely to be female, more educated, had higher	Greater consistency with MedDiet was associated with lower insulin levels among non-diabetics, and with lower blood glucose before adjustment for obesity, but not

						ultrasound scanning		- incomes, a smaller waist circumference and were non-smokers - Higher adherence to the MeDiet was associated with lower blood glucose and insulin levels before adjustments for obesity - The MeDiet was not related to the incidence of T2D	with a lower incidence of diabetes
Ryan et al., 2013	Australia	Randomized, cross-over intervention study	12 non-diabetic subjects (6 female/6 male) with biopsy proven NAFLD	Subjects included if: - There were evidence of steatosis on ultra-sonography and histology - presence of MetS - consumption of no more than 7/10 standard alcoholic drinks per week for women/men -.excluded those with T1/2D	To examine the effect of the MeDiet on steatosis and insulin sensitivity	MeDiet group compared to a LF/HCD group. All subjects undertook both diets. Insulin sensitivity was determined with a 3-h hyperinsulinemic-euglycemic clamp study, hepatic steatosis assessed with H-MRS	6 weeks intervention - 6 weeks wash out-6weeks intervention	- At baseline, the 12 subjects were obese, had elevated mean fasting serum concentrations of glucose, insulin, triglycerides, ALT and GGT - Insulin sensitivity at baseline was low (M=2.7±1.0 mg/kg/min^{-1}) - Mean weight loss was not different between the two diets - There was a significant relative reduction in hepatic steatosis after MeDiet compared with the LF/HCD - Insulin sensitivity improved with the MedDiet whereas after the LF/HCD there was no change	Even without weight loss, MeDiet reduces liver steatosis and improves insulin sensitivity in an insulin resistant population with NAFLD
Koning et al., 2011	USA	Prospective cohort study	41.615 male health professionals	Excluded participants with T2D, CVD(heart attack, stroke, angina, or coronary artery bypass graft), cancer, or implausible energy intake (<800 or >4200 kcal/day)	To compare associations of diet-quality scores, which were inversely associated with CVD, with incident T2D and to test for differences in absolute-risk reduction across various strata	The HEI 2005, the alternative HEI (aHEI), the recommended Food Score, the alternative MeDiet (aMedDiet) Score, and the DASH score were calculated from FFQs quintiles and continuous intervals. Questionnaires were mailed to participants every 2-4 years from 1986 to access lifestyle and health status. FFQs were completed	≤20 years	- Participants in the highest quintile of adherence to the MD (aMED > 6) exhibited a 25% (95% CI 0.66–0.86) decreased risk of T2DM, compared with those in the lowest quintile (aMED < 3 - Alternative HEI, aMedDiet, and DASH scores were significantly associated with reduced risk of T2D	Several diet-quality scores were associated with a lower risk of T2D and reflect a common pattern characterized by high intakes of plant-based foods, moderate alcohol, low intakes of red and processed meat, sodium, sugar-sweetened beverages and trans fat

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Author, Year	Country	Study type	Sample	Exclusion	Aim	Description	Person-years	Results	Conclusion
						every 4 years		- A 1-SD increase was associated with 9-13% reduced risk of T2D - DASH score was associated with lower risk independently of other scores - Risk reduction was greater among overweight or obese subjects, compared with normal-weight ones ($p < 0.01$)	
Gouveri et al., 2011	Greece	Retrospective	2074 adults, 900 men and 1.174 women (age, 46.6±14.9 years)	-	To investigate the association between MeDiet and MetS in a representative sample of the Athenian population in the early 1980s	A cross-sectional epidemiologic survey of CVD and their risk factors, was conducted in a representative sample of the adult Athenian population in the early 1980s. MetS was defined according to criteria of the National Cholesterol Education Program-Adult Treatment Panel III. MedDiet was assessed according to guidelines of the Division of Nutrition/epidemiology, Athens University Medical School	-	- 49.3% followed MeDiet with similar rates across age groups - MetS was diagnosed in 24.0% of those following Med Diet, compared with 27.9% of those not following it - Participants with CVD or T2D were less likely to follow Med Diet - MeDiet was associated with a 20% reduction in MetS, after adjustment for age, gender, smoking, light physical activity, serum levels of low-density lipoprotein cholesterol and γ-glutamyl transferase, diabetes mellitus, CVD, family history of hypertension, and/or hyperlipidemia	Adherence to MeDiet may attenuate the prevalence of MetS and, consequently, the increasing burden of diabetes mellitus and CVD, especially in urban populations
Romaguera et al., 2011	Denmark, France, Germany, Italy, the Netherlands, Spain, Sweden and the	Case-cohort prospective study	11.994 incident T2D case subjects and a stratified subcohort of 15.798 participants	Were excluded : - individuals without stored blood or with prevalent diabetes status at baseline , - participants within the lowest and highest 1% of the cohort distribution of the ratio of reported total energy intake: energy	To study the association between adherence to the MedDiet and risk of developing T2D, across European counties	A case-cohort study including 11.994 incident T2D case subjects and a stratified subcohort of 15.798 participants selected from a total cohort of 340.234 participants with 3.99 million person – years of follow-up from	4 million person-years	- Individuals with a high rMeDiet score range (11-18 points) were 12% less likely to develop diabetes than individuals with low rMeDiet scores (0-6 points) - The alcohol, meat, and olive oil	Adherence to MedDiet was associated with a small reduction in the risk of developing T2D

	U.K				requirement	eight European cohorts participating in EPIC study. The relative MedDiet score was used to assess adherence to MedDiet. Cox proportional hazards regression, modified for the case-cohort design, was used to estimate the association between rMedDiet and risk of T2D, adjusting for confounders			components of the rMeDiet accounted for the most of the observed association - Two-point increment in rMeDiet was associated with a 4% reduction in the risk of T2D - No association between rMeDiet and diabetes was observed among the youngest participants - The association between rMeDiet and diabetes was attenuated in obese participants	
Itsiopoulos et al., 2011	Australia	Randomized cross-over study	27 people, aged between 47 and 77 years, with confirmed T2D	Exclusion criteria were: presence of disabling stroke, cancer not in remission, renal failure, or liver disease	To examine the impact of a traditional Mediterranean-type cuisine on HbA1c and vascular risk in T2D	Participants were randomly assigned to consume either the intervention diet ad libitum or their usual diet for 12 weeks and then cross over to the alternate diet. Biochemical data and anthropometric characteristics were assessed at baseline, and at the end of both diet periods. Dietary adherence was monitored using plasma carotenoid and fatty acid analysis, complemented by diet diaries	24 weeks	- Compared with usual diet, on the ad libitum MedDiet HbA1c fell from 7.1% to 6.8% - There was a trend towards improved insulin sensitivity - Diet quality improved significantly	A traditional MedDiet improves glycemic control and diet quality in men and women with well controlled T2D, without adverse effects on weight
Diez- Espino et al., 2011	Spain	Cross- sectional study	385 participants, 53.4% women (mean age 69±6 years)	Included participants with T2D	To analyze the association between adherence of a MeDiet in patients with T2D and levels of HbA1c	Information on diet was collected with a validated 14 point scale of adherence to the MeDiet and blod samples were obtained to assess HbA1c	-	- Although there was a potential inverse non-significant association between adherence to MeDiet and HbA1c levels after adjusting for age and sex, it was not statistically significant - Multivariate analysis found similar findings	Although not enough evidence was found to support that MeDiet is associated with lower levels of HbA1c in patients with T2D, the results suggest an inverse trend
Salas- Salvado et al., 2011(10)	Spain	Randomized controlled trial	418 non diabetic subjects aged 55-80 years	Participants without prior CVD but having at least three cardiovascular risk factors: smoking,	To test the effects of two MedDiets supplemented with either extra virgin olive oil or mixed nuts, versus a low- fat control diet on incidence of	Participants were randomly assigned to education on a low- fat diet (control group) or to one of two	4.0 years	- Diabetes incidence was 10.1%, 11.0% and 17.9% in the MedDiet with olive oil group, the	MedDiets without calorie restriction seem to be effective in the prevention of diabetes in subjects

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				hypertension, dyslipidemia, overweight (BMI≥25kg/m^2), and family history of premature CVD, were included in the study. Excluded those with prevalent diabetes, with severe chronic illness, alcohol or drug abuse, BMI ≥40kg/m^2, and history of allergy or intolerance to olive oil or nuts	diabetes	MedDiets, supplemented with either free virgin olive oil (1lt/week) or nuts(30gr/day). Diets were ad libitum. The main outcome was diabetes incidence diagnosed by the 2009 American Diabetes Association criteria. Questionnaires about lifestyle variables, medical condition, medication use, conformity to MedDiet and leisure- physical activity time, administered annually		-	MedDiet with nuts group and the control group, respectively - When the two MedDiet groups were pooled and compared with the control group. Diabetes incidence was reduced by 52% - In all study arms, increased adherence to the MedDiet was inversely associated with diabetes incidence	at high cardiovascular risk
Elhayany et al., 2010	Israel	Prospective randomized intervention study	259 overweight, diabetic patients (mean age 55 years)	Inclusion criteria: age 30- 65 years, T2D diagnosed within 1-10 years, BMI 27-34 kg/m^2, last HbA1c measurement 7-10%, last plasma TG level 1.8- 4.5 mmol/l, last serum creatinine<123.2mmol/l, and no change in diabetes medication for at least 3 months before entering study Exclusion criteria: proliferative diabetic retinopathy, current insulin treatment, active oncologic or psychiatric disease and uncontrolled hypothyroidism or hyperthyroidism	To examine the effects of a low carbohydrate MedDiet (LCM), a traditional MedDiet (TM) and the 2003 American Diabetic Association diet (ADA), on CDV risk factors and diabetes control	Participants were randomly assigned to one of the three diets. The main outcome measures were glycemic control and biomarkers for cardiovascular risk. Adherence to MedDiet was evaluated from Food Frequency Questionnaire (FFQ) administered at 6 months	1 year	-	Weight, BMI and waist circumference were reduced in all dietary interventions with no significant difference between the groups - HbA1c, blood lipids and HOMA decreased in all groups, fasting insulin levels increased over time - The reduction in HbA1c was significantly greater in the LCM diet than in ADA diet - HDL cholesterol increased only on the LCM diet - The reduction in serum TG was greater in the LCM and TM than in the ADA diet	Dietary intervention was effective in improving most modifiable CDV risk factors on all dietary groups. Only the LCM diet improved HDL levels and was superior to both the ADA and TM in improving glycaemic control in overweight diabetic patients
Kastorini et al., 2010	Greece	Review	-	-	To investigate whether the protective role of MedDiet on T2D is a myth or fact	-		-	Many epidemiological studies show the beneficial effect of the MedDiet on T2D and glucose metabolism in general [2,4,5,23,12,24]	Results from epidemiological studies and clinical trials evaluating the role of the MedDiet, regarding the development and treatment of T2D, indicate the protective role of this pattern

| Esposito et al., 2009 | Italy | Cross-sectional study | 901 outpatients with T2D | Inclusion criteria: a diagnosis of T2D for at least 6 months but< 10 year, age 35-70 years. BMI ≥ 24.0kg/m², HbA_{1C} ≥6.5% and treatment with diet or oral glucose- lowering drugs Exclusion criteria: need for insulin use, concomitant chronic diseases, including kidney, liver and CVD diseases, resent acute illness or change in diet, treatment or lifestyle within the 3 months before the initial assessment | To Explore whether a MedDiet improves glycaemic control in diabetes | Subjects were asked to measure home blood glucose and fasting glucose level on three and two non-consecutive days respectively, during a period of 1 month. Subjects were invited to follow their usual treatment and eat their usual diet during the month. Blood sample was obtained. Diet history was collected twice (at entry and 1 month later). Nutrient intakes were assessed using FFQ. Adherence to MedDiet was measured with a 0-9 point scale questionnaire | - | - | - Diabetic patients with the highest scores (6-9) had lower BMI, waist circumferences, a lower prevalence of the MetS and lower HbA_{1c} and post- meal glucose levels than diabetic patients with the lowest scores (0-3).
 - Mean HbA_{ic} and 2-h post- meal glucose concentrations were significantly lower in diabetic patients with high adherence to MedDiet than those with low adherence | In T2D, greater adherence to MedDiet is associated with lower HbA_{ic} and postprandial glucose levels |
| Rumawas et al., 2009 | USA | Prospective | 2730 participants without T2D (median age: 54y) for the analyses of MetS traits and 1918 participants free of MetS to assess the incidence of MetS | Excluded participants with diabetes and missing or invalid FFQ data, those who did not attend the follow-up and those who were missing covariates. Participants with prevalent MetS at baseline were also excluded | To examine the prospective association between the MedDiet and metabolic syndrome | Adherence to MedDiet was measured with MSDPS. Dietary intake was assessed by using the Harvard semiquantitative FFQ. The association between MSDPS and MetS traits homeostasis model assessment- insulin resistance, fasting glucose, waist circumference, triglyceride, HDL, cholesterol and systolic and diastolic blood pressure was examined | Mean time: 7 years | - | - Participants in the highest quintile category were older, more likely to be women, multivitamin users, and ERT users, more likely to have a greater change in BMI over follow-up, and less likely to be current smokers
 - A higher MSDPS was associated with lower homeostasis model assessment- insulin resistance, waist circumference, fasting plasma glucose, and triglycerides and higher HDL cholesterol after adjustment for the corresponding baseline values and for several confounding factors associated with T2D risk
 - Participants in the highest quintile category of the MSDPS had a lower incidence of MetS | Consuming a diet consistent with the principles of the MedDiet was favorably associated with avoiding MetS traits- specifically with less abdominal obesity, less insulin resistance, and less atherogenic dyslipidemia. The study also showed that a diet consistent with a MedDiet was associated with a lower incidence of MetS |

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Study	Country	Type			Aim					Results	Conclusion
										than those in the lowest quintile category	
Babio et al., 2009	Spain	Review	-	-	To analyze the effect of diet on MetS and its components	Review of the available literature in relation to MedDiet and MetS			-	Several components of MedDiet patterns have been inversely related with BMI. They are considered to be modulators of insulin resistance, can exert beneficial effects on blood pressure, improve atherogenic dyslipidemia or attenuate the inflammatory burden associated with MetS	MedDiet could serve as an anti-inflammatory dietary pattern, which could help to fight diseases related to chronic inflammation, including MedS
Champagne et al., 2009	USA	Review	-	-	To review the usefulness of a Mediterranean- based diet in individuals with T2D	This article reviews data available on the MedDiet related to its use in a diabetic population	-	-	-	Mediterranean diet may be used in dietary interventions for the treatment of overweight and obesity, conditions associated with the development of T2D	The review of the literature points to using the MedDiet as a viable option for people with T2D. Advisors should stress not only adherence to a fairly MedDiet but also a lifestyle that includes sufficient physical activity
									-	MedDiet has been found to be inversely related to the MetS, often a feature of diabetic individuals	
									-	Consuming MedDiet, there was a positive response of insulin, blood glucose, blood lipids, and other metabolic factors predicting CVD risk and outcomes	
Giugliano et al., 2008	Italy	Review	-	-	To present evidence illustrating the relationship between MedDiets and metabolic diseases, including obesity, T2D, and the MetS, and to briefly discuss potential mechanisms by which these diets can help in disease prevention and treatment	-	-	-	Mounting evidence indicates a favorable effect of MedDiet on obesity and T2D	Mounting evidence suggests that MedDiets could serve as an anti-inflammatory dietary pattern, which could help fighting diseases that are related to chronic inflammation, including visceral obesity, T2D and the MetS
									-	MedDiet is attenuating the inflammatory burden associated with T2D	
									-	A lower prevalence of the MetS is associated with dietary patterns rich in fruits, vegetables, whole grains, dairy products, and unsaturated fats	
									-	Both epidemiological and interventional	

									studies have revealed a protective effect of the MedDiet against mild chronic inflammation and its metabolic complications
Sanchez- Tainta et al., 2008	Spain	Cross- sectional	3204 asymptomatic, high cardiovascular risk individuals	Eligible participants were community-dwelling men, 55-80 years old, and women, 60-80 years old, who have diabetes or who meet at least three or more other CVD risk factors. Exclusion criteria were: previous history of CVD, any severe chronic illness, drug or alcohol addiction, and history of allergy or intolerance to olive oil or nuts	To estimate the association between adherence to a MedDiet and the prevalence of hypertension, dyslipidemia, diabetes and obesity, or their clustering in a large sample of asymptomatic high- risk patients	Trained personnel made weight, height, blood pressure, diabetes testing, hypertension, and hypercholesterolemia measurements. A 14-item questionnaire specifically designed to assess adherence to the traditional MedDiet and a 137-item FFQ were administered	-	-	- Adherence to MedDiet was inversely associated with individual risk factors and, above all, with the clustering of them - The multivariate adjusted odds ratio to present simultaneously the 4 risk factors for those above the median value of the MedDiet score was 0.67 - The multivariate odd ratios for successive categories of adherence to MedDiet were 1, 1.03, 0.85, 0.7 and 0.54	Following the MedDiet was inversely associated with the clustering of hypertension, diabetes, obesity, and hypercholesterolemia among high- risk patients
Brunner et al., 2008	UK	Prospective analysis	7731 participants with mean age of 50y	Excluded participants who were members of outlying dietary clusters, and energy misreporters	To analyze the prospective relation of dietary patterns with incident chronic disease and mortality	Dietary patterns were identified in order to study their relations to incident major coronary events and diabetes as well as mortality. Follow –up carried out by means of screening contacts every 5y. Usual dietary intake was assessed by using a 127- item FFQ. Coronary death or nonfatal myocardial infarction and incident diabetes were verified by record tracing and oral- glucose-tolerance tests	15 years	-	- 4 dietary patterns were identified at baseline: unhealthy(white bread, processed meat, fries, and full-cream milk), sweet(white bread, biscuits, cakes, processed meat, and high fat dairy products), Mediterranean-like(fruit, vegetables, rice, pasta, and wine), and healthy (fruit, vegetables, whole-meal bread, low-fat dairy, and little alcohol - Compared with the unhealthy pattern, the healthy pattern reduced the risk of	The healthy eating pattern reduced risks of diabetes and major coronary events. Such dietary patterns offer considerable health benefits to individuals

									Results	Conclusion
								-	coronary death or nonfatal myocardial infarction and diabetes	
								-	Dietary pattern was not associated with all-cause mortality	
Martinez-Gonzalez et al., 2008	Spain	Prospective cohort study	13.380 Spanish university graduates without diabetes at baseline	Excluded participants who had diabetes at baseline and those who reported a baseline history of CVD	To assess the relation between adherence to a MedDiet and the incidence of diabetes among initially healthy participants	Dietary habits assessed at baseline with a 137-item FFQ with a 9 point index. Adherence to MedDiet was appraised according to the score created by Trichopoulou et al. Every 2 years, follow-up questionnaires on diet, lifestyle, risk factors, and medical conditions, were send to participants. New cases of diabetes confirmed through medical reports and an additional detailed questionnaire posted to those who self reported a new diagnosis of diabetes by a doctor during follow-up	A median of 4.4years	- - -	Participants with high adherence to the MD (MDS > 6) exhibited a 83% (95% CI 0.04–0.72) reduced risk of T2DM, compared with those with low adherence (MDS < 3) · The incidence rate ratios adjusted for sex and age were 0.41 for those with moderate adherence (score 3-6) and 0.17 for those with the highest adherence (score 7-9) compared with those with low adherence (score < 3) · A 2-unit increase in the MDS score was associated with a 35% (95% CI 0.44–0.95) reduced risk of T2DM	Adherence to a MedDiet is associated with a reduced risk of diabetes
Tzima et al., 2007	Greece	Cross-sectional study	1762 participants with excess body weight, meaning overweight(BM I: 25- 29.9kg/m²) and obese (BMI> 30kg/m²), 20-89 years old	Included people without any clinical history of CVD, or any other atherosclerotic disease, as well as chronic viral infections. Participants did not have cold or flu, acute respiratory infection, dental problems or any type of surgery during past weeks. All people living in institutions were excluded from the study	To investigate if overweight and obese adults ''close'' to MedDiet present better insulin, lipids profile and better pressure levels, compared to individuals close to a more Westernized diet	Adherence to MedDiet was assessed through a FFQ. Blood pressure, fasting glucose, insulin and blood lipids were measured. Insulin sensitivity was also assessed by the HOMA approach	-	- -	Individuals with excess bodyweight in the highest tertile of diet score, were more insulin sensitive than those in the lowest tertile, had 13% lower levels of total cholesterol and 3mmHg decrease of systolic blood pressure levels when adjusted for age, sex and BMI · Multivariate analysis after taking into account several confounders demonstrated that insulin sensitivity, total cholesterol and systolic blood pressure were	Overweight and obese people, attached to the MedDiet, had a limited profit against cardiovascular risk factors.

								independently but only modestly correlated with MedDiet in people with excess bodyweight	
Esposito et al., 2007	Italy	Review	-	-	To review the association between MedDiet and MetS	-	-	-	Dietary patterns close to MedDiet, rich in fruit and vegetables, and high in monounsaturated fats are negatively associated with features of the MetS(abdominal obesity, insulin resistance, hypertension, dyslipidemia)	The favorable benefit/ hazard ratio makes MedDiets particularly promising to reduce the cardiovascular burden associated with the MetS
Schroder et al., 2007	Spain	Review	-	-	To discuss potential mechanisms by which the MedDiet prevents besity and diabetes	-	-	-	High fiber diets, such as MedDiet, increase satiety and reduce hunger	Several mechanistic links offer potential explanations of the MedDiet's protective effect on obesity and T2D
								-	Olive oil consumption was not associated with increased weight gain but with lower insulin resistance	
								-	The average density of the MedDiet is remarkably lower than that reported for the US	
								-	Diets preventing weight gain, such as the MedDiet, exert a protective effect on the development of T2D	
								-	MedDiet protects individuals from oxidative stress, that is responsible for pathogens of T2D	
								-	Polyphenol- rich foods seems to exert a protective effect on the development of T2D	
								-	High adherence to the MedDiet is associated with a high consumption of magnesium and reduced risk of T2D	

								- Moderate alcohol drinking, such as in the MedDiet, was associated with a 30% risk reduction of T2D - Dietary fiber, in particular cereal fiber, exert a protective effect on insulin sensitivity and the risk of T2D	
Panagiotakos et al., 2007	Greece	Cross-sectional	3042 participants	Subjects with history of CVD or any other atherosclerotic disease, with chronic viral infections, those who had a cold or flu, acute respiratory infection, dental problems or any type of surgery during the past weeks were excluded. Subjects with type 1 diabetes were also excluded	To investigate the associations between adherence to MedDiet and fasting indices of glucose homeostasis	T2D and IFG were defined according to the established ADA criteria. Insulin resistance was evaluated by HOMA-IR. Dietary habits were assessed through a validated FFG and a diet score (range 0-55) was developed (higher values means greater adherence to the MedDiet	-	- The overall prevalence of T2D was 7.9% in men and 6.0% in women - Mean diet score was 26.3± 6.8 in normoglycemic, 25.7±6.4 in IFG, and 22.2±5.8 in diabetic subjects - In normoglycemic subjects in the upper tertile of the diet score, was observed 7% lower glucose, 5% lower insulin and 15% lower HOMA-IR compared to subjects in the lower tertile - In diabetic/IFG subjectsinf the upper tertile of the diet score, was observed 15% lower glucose, 15% lower insulin and 27% lower HOMA-IR levels compared to those in the lower tertile - After multiple regression analysis, was observed, only in normoglycemic subjects an inverse relationship between diet score and fasting plasma glucose, insulin and HOMA-IR levels	Adherence to MedDiet was related to better fasting indices of glucose homoeostasis in normoglycemic people, but not in diabetic or pre-diabetic
Panagiotakos et al., 2007	Cyprus	Cross-sectional	150 subjects, aged 65 to 100 years	People with clinical history of CVD and those living in institutionswere excluded from the	To investigate the association of MedDiet on clinical status elderly people	A diet score that assess the inherent characteristics of the MedDiet was developed (range 0-	-	- Mean diet score had no differences between men and women	Adherence to the MedDiet is associated with reduced odds of having

Author, year	Country	Study type	Population	Inclusion criteria	Aim	Methods / Intervention	Duration	Results	Conclusion
		study				55). Lifestyle habits were evaluated and clinical characteristics were measured. Adoption of the MedDiet was evaluated against the presence of hypertension, diabetes, hypercholesterolemia and obesity		- The level of adherence to MedDiet was 64% - More than 9 out of 10 of the participants reported that they followed the reported dietary habits for at least 30- 40 years of their life - MedDiet score was inversely correlated with BMI, total cholesterol, triglycerides, glucose, and systolic blood pressure levels - Taking into account age, sex, smoking habits and physical activity status, was observed that 10-unit increase in the diet score was associated with 17% lower odds of having one additional risk factor - Stratified the analysis by gender, the reduction in the odds was 21% in women and 14% in men - A 10- unit increase in the diet score was associated with a 6% lower odds of having hypertension, 9% lower odds of having hypercholesterolemia, 6% lower odds of having diabetes and 12% lower odds of being obese	hypercholesterolemia, hypertension, diabetes and obesity among elderly people
Lindeberg et al., 2007	Sweden	Randomized controlled intervention trial (type 1)	29 male IHD patients with waist circumference >94cm and increased blood glucose or known diabetes	Included patients with an ongoing acute coronary syndrome, a history of myocardial infarction diagnosed by creatine kinase MB isoenzyme or troponin elevation, percutaneous coronary intervention or coronary artery bypass surgery or angiographically diagnosed coronary stenosis ≥ 30%.	To examine the effect of the Paleolithic diet model, compared to the Mediterannean- like diet on glucose tolerance and postchallenge insulin response in glucose- intolerant IHD patients	Participants were randomized to receive a Paleolithic diet, based on lean meat, fish fruits, vegetables, root vegetables, eggs and nuts, or a Mediterranean- like diet based on whole grains, low- fat dairy products, vegetables, fruits, fish, oils and margarines. Outcome variables were changes	3 months	- There was a 26% decrease of AUC glucose $_{1-120}$ in the Paleolithic group and a 7% decrease in the MedDiet group - The larger improvement in the Paleolithic group was independent of change in waist circumference - In the study population as a	A Paleolithic diet may improve glucose tolerance, independently of decreased waist circumference. Subjects who followed the MedDiet did not significantly improve their glucose tolerance despite decreases in weight and waist

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				Exclusion criteria were BMI < 20kg/m^2 , serum creatinine>130µmol/l, poor general condition, dementia, unwillingness/inability to prepare food at home, participation in another medical trial, chronic inflammatory bowel disease, type 1 diabetes and treatment with hypoglycaemic agents, warfarin or oral steroids. Other drugs were not restricted and treatment with statins and beta blockers was usually initiated and/or changed during the trial.		in weight, waist circumference and plasma glucose AUC and plasma insulin AUC in OGTTs			whole, there was no relationship between change in AUC Glucose$_{0-120}$ and changes in weght or waist circumference	circumference. Healthy diets based on wholegrain cereals and low-fat dairy products are only the second best choice in the prevention and treatment of T2D
Tortosa et al., 2007	Spain	Prospective cohort study	2.563 participants initially free of MetS or risk factors	Participants were excluded if at baseline they had implausible values for total energy intake, had BMI>30kg/m^2 or reported risk factors (diabetes, hypertension, hypercholesterolemia, or hypertriglyceridemia), or met the criteria for MetS	To assess the relationship between adherence to the MedDiet and the subsequent development of MetS	Baseline assessment of participants consists of a self- administered questionnaire, gathering information on lifestyle factors and including a 136- item FFQ. Biennially mailed follow-up questionnaires were used to collect information about diet, lifestyle and medical conditions. MetS was defined according to the International Diabetes Federation criteria	A median of 74 months	-	Adherence to the MedDiet was higher among women, older subjects, ex-smokers, and more physically active participants - Participants with higher baseline adherence to the MedDiet exhibited lower levels of all risk factors except plasma glucose - HDL levels were higher among participants who better adhered to the MedDiet - Subjects with the highest adherence to the MedDiet had lower cumulative incidence of MetS than those with the lowest adherence	MedDiet inversely associated with the incidence of MetS
Mozzaffarian et al., 2007	Italy	Prospective	8291 patients with a myocardial infarction within the previous 3 months, who were free of diabetes	Excluded individuals with prevalent diabetes at enrolment, those with missing information about diet or weight at baseline, or about glucose at baseline or during follow- up	To estimate the incidence of new- onset diabetes and IFG in patients with recent myocardial infarction and investigate whether dietary habits might alter this risk	Incidence of new- onset diabetes and IFG were assessed at follow- up at 0.5, 1.0, 1.5, 2.5, and 3.5 years. Data for BMI, other risk factors, dietary habits and medications were updated during follow- up. A MedDiet score was assigned	Mean time: 3.2 years	-	Participants in the highest quintile of adherence to the MD (MD score > 10) exhibited a 35% lower risk of T2DM (95% CI 0.49–0.85), compared with those in the lowest quintile (MD score < 6)	Myocardial infarction could be a prediabetes risk equivalent. Smoking cessation, prevention of weight gain and consumption of typical Mediterranean foods might lower this risk

Author, year	Country	Study design	Participants	Exclusion criteria	Aim	Methods	Duration	Results	Conclusion
						according to consumption of cooked and raw vegetables, fruit, fish, and olive oil. Associations of demographic, clinical, and lifestyle risk-factors with incidence of diabetes and IFG were assessed with multivariable Cox proportional hazards		- The average age was 59 years, and 13% of participants were women - Patients were on average overweight (mean BMI: 26.3kg/m²)and 13% were obese - Greater intake of MedDiet was associated with older age, being female, slightly greater BMI, hypertension, previous acute myocardial infarction and former rather current smoking - Independent risk factors for new-onset diabetes or IFG included older age, hypertension, use of beta- blockers, lipid-lowering medications(protective) and diuretic use - Independent lifestyle risk factors included higher BMI, greater BMI gain during follow-up, current smoking, a lower MedDiet score and wine consumption of more than 1l/day	
Michalsen et al., 2006	Germany	Randomized, controlled trial	101 patients(59.4±8.6 years, 23%female) with established and treated CAD	Excluded individuals with an ACS or CABG within the previous 3 months, diabetes mellitus type1, manifest cardiac arrhythmias, heart failure, life- threatening comorbidity and BMI> 33kg/m²	To investigate the effect of MedDiet on markers of inflammation and metabolic risk factors in patients with treated CAD	Participants were assigned to a MedDiet group with 1- year program of 100h of education, or to a written advise - only group. Before and after intervention, serum hs-CRP , fibrinogen, fasting insulin, homocysteine, serum lipids and plasma fatty acids were measured	1 year	- The MedDiet group individuals, increased the intakes of fish, fruits/vegetables and moderately of canola/olive oil and increased plasma concentrations of long- chain n-3 polyunsaturated fatty acids - Median hs-CRP and mean fibrinogen, homocysteine, fasting insulin, triglycerides and serum cholesterols remained unchanged in both groups	Adoption of a MedDiet by patients with medically treated CAD has no effect on markers of inflammation and metabolic risk factors

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Estruch et al., 2006	Spain	Randomized trial	772 asymptomatic persons 55 to 80 years old at high cardiovascular risk	Eligible participants were community-dwelling men, 55 to 80 years old and women, 60 to 80 years old, who fulfilled at least 1 of 2 criteria: T2D or 3 or more CHD risk factors(current smoking, hypertension, LDL cholesterol level ≥4.14mmol/L, HDL cholesterol level ≤1.04mmol/L. Exclusion criteria were history of CVD, any severe chronic illness, drug alcohol addiction, history of allergy or intolerance to olive oil or nuts, or low predicted likelihood of changing dietary habits according to the stages-of- change model	To compare the short term effects of 2 MedDiets versus those of a low- fat diet on intermediate markers of cardiovascular risk	Participants were assigned to one of two MedDiets (with virgin oil or with mixed nuts) or to a low- fat diet. Those allocated to MedDiets received nutritional education. A 14- item questionnaire assessed the degree of adherence to the MedDiet. FFQ and a 47-item questionnaire about education, lifestyle, history of illness, and medication use, were used. Anthropometric and blood pressure measurements were performed, and samples of fasting blood and spot urine were obtained	3 months	-	Compared with the low- fat diet, the 2 MedDiets decreased systolic(-5.9mm/Hg and -7.1mm/Hg respectively for MedDiet with olive oil and MmedDiet with nuts) and diastolic blood pressure, blood glucose levels(-0.39mmol/L and – 0.30mmol/L respectively for MedDiet with olive oil and MedDiet with nuts), and cholesterol- HDL cholesterol ratio (-0.38 and -0.26, respectively for MedDiet with olive oil and MedDiet with nuts) and increased HDL cholesterol levels - Fasting insulin levels and HOMA scores were also lower in participants without diabetes in the 2 MedDiet groups - Total cholesterol and triglyceride levels decreased only in the MedDiet with nuts - The MedDiet with olive oil reduced C- reactive protein levels by 0.54mg/L compared with the low- fat diet	Participants who improved their baseline MedDiet, showed lower blood pressure, improved lipid profiles, decreased insulin resistance and reduced concentrations of inflammatory molecules compared with those allocated to a low- fat diet. MedDiets have beneficial effects on cardiovascular risk factors
Vincent-Baudry et al., 2005	France	Intervention study	212 subjects with moderate risk factors for CVD	Participants met at last one of the following criteria: fasting plasma cholesterol concentration of 6.5-7.7mmol/L, triacylglycerol concentration of 2.1-4.6 mmol/L, glycemia(glucose concentration of 6.1-6.9 mmol/L), systolic and diastolic blood pressure between 140-	To investigate the effects of a MedDiet or a low-fat diet on cardiovascular risk factors	After the 3- month dietary intervention, changes in many risk factors were evaluated. Dietary questionnaires and plasma nutritional markers were used to test compiance	3 months	-	The mean age of the subjects was 50.8±10.8 and 51.6±10.3 in the MedDiet group and the low-fat group respectively - 35% of the subjects were overweight and 38% were obese - Changes in dietary habits were observed in both groups	Both diets significantly reduced CVD risk factors

				180 and 90-105mmHg, respectively, BMI>27, smoking, sedentary or family history of CVD. Subjects treated with hypolipemic or hypoglycemic drugs were excluded			- BMI, total and triacylglycerol- rich lipoprotein (TRL) cholesterol, triacylglycerols, TRL triacylglycerols, apolipoproteins A-I andB, insulinemia, glycemia and the HOMA score were significantly lower after 3 months - There was a 9% reduction in CVD risk with the low-fat diet and a 15% reduction with the MedDiet	
Panagiotakos et al., 2005	Greece	Cross-sectional	3042 subjects with no evidence of CVD or any other chronic disease	Participants with type 1 diabetes, history of CVD or any other atherosclerotic disease were excluded.	To evaluate the prevalence of T2D in a Greek adult population, in relation to physical activity and dietary habits	Diabetes was defined according to the established ADA criteria. Dietary habits were assessed through a validated FFQ and a diet score measured the adherence to the MedDiet. Weekly energy expenditure was assessed by considering frequency, duration and intensity of sports-related physical activity	-	- The projection prevalence of diabetes was 7.6% in men and 5.9% in women - Diabetic people were less likely to smoke, less physically active and less educated than the participants without diabetes - Diabetic people were less devoted to the MedDiet compared with participants without diabetes - The prevalence of diabetes in a person with no physical activity was 4.6% and in low physical active people was 4.2%. The relative risk reduction was 9.5% - Increasing age, smoking habits, family history of diabetes, elevated systolic blood pressure and triglycerides levels were significantly associated with the presence of diabetes - 24% of men and 30% of women were unaware of their condition	Light physical activity and greater adherence to the MedDiet was associated with significantly lower odds of having diabetes

							- A 10-unit increase in the diet score was associated with 21% lower odds of diabetes - Individuals taking light physical activity were at 35% lower odds ratio of diabetes compared to sedentary individuals	
Toobert et al., 2003	USA	Randomized controlled trial	279 postmenopausal women with T2D	Inclusion criteria were female sex, diagnosis of T2D for at least 6 months, postmenopausal, living independently, having a telephone, able to read English, not developmentally disabled and living within 30 miles of the intervention site. Exclusion criteria were being >75 years of age or planning to move from the area within the study's time span	To test the effectiveness of the Mediterranean Lifestyle Program(MLP)(Mediterranean low-saturated fat diet, stress management training, exercise, group support and smoking cessation), in reducing cardiovascular risk factors in postmenopausal women with T2D	Participants were randomized to either usual care control or treatment (MLP) conditions. MLP participants took part in an initial 3-day retreat followed by 6 months of weekly meetings to learn and practice program components. Biological end points were changes in $HbAc_{1c}$, lipid profiles, BMI, blood pressure, plasma fatty acids, and flexibility. Impact on quality of life was assessed	6 months	- HbA_{1c} decreased from 7.43 to 7.07mg/dl for the MLP women, HbA_{1c} remained at 7.4mg/dl for the control subjects, this would translate into a 14% reduction in risk of diabetes complications - A drop of 0.37 in BMI observed in the MLP women and an increase of 0.20 in BMI for the control group - Quality of life improved significantly for the MLP women	Postmenopausal women with T2D can make comprehensive lifestyle changes that may lead to clinically significant improvements in glycemic control, some coronary heart disease risk factors and quality of life

5   Discussion

The MeDiet has been widely reported to be a model of healthy eating for its contribution to a favourable health status, better biochemical profile and a better quality of life. In the present review, the role of the MeDiet in T2D prevention and treatment, as well as its potential protective mechanisms against the MetS and CVD, were briefly presented [28, 29]. According to epidemiological data, a greater adherence to the MeDiet, as assessed by various MeDiet indices, is inversely associated with T2DM risk in the general population, in individuals at high cardiovascular risk and in patients with established CVD. Interventional studies also demonstrate the beneficial role of the MeDiet in T2D management, with patients allocated to a MeDiet exhibiting greater improvements in glycemic control and CVD risk factors, compared with those following a control diet [12, 22, 25, 26].

Although this review provides useful information, all studied outcomes must be interpreted with caution because of some weaknesses. The wide variety of available MeDiet scores makes it difficult to compare the results of studies, in which different scores are used. This observation, along with the fact that diet varies significantly across populations, suggest that an analysis of this type cannot provide universally applicable results [67]. In addition, MeDiet indices may not precisely describe the overall MeDiet, since most available scores focus on selected aspects of the diet and involve some level of arbitrary decision in the type and number of components to be included as well as their scoring system [68]. Secondly, the availability of few controlled trials designed to evaluate the metabolic and cardiovascular outcomes of the MeDiet specifically in MeDiet, as well as the fact that most clinical studies focused on surrogate markers for early CVD risk assessment, signify major limitations of the present review. Moreover, some major randomized controlled trials, which showed that intensive lifestyle interventions can reduce the incidence of T2D in individuals at high risk for T2D in the general population, did not decrease the risk of CVD and CVD-associated mortality [69,70].

Although some relevant differences among the studies are present and further long-term intervention trials are crucial in evidencing the long-term efficacy in the T2D prevention and treatment, strategies aiming to promote adherence to MeDiet dietary pattern are of considerable public health interest [71,72].

6   Conclusion

In conclusion, this review seems to be clinically relevant in terms of public health, particularly for reducing the risk of premature death in the general population, and is strictly concordant with current guidelines and recommendations from all the major scientific associations that strongly encourage a Mediterranean-like dietary pattern for primary and secondary prevention of major chronic diseases [26]. Indisputably, the development and implementation of national policies for the prevention of T2D and its complications with optimum efficiency and minimum cost is the only way to reduce the personal and socio-economic burden of the disease and its complications.

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