Review Article

# Effectiveness of Mediterranean Diet on Prevention and Management of Prediabetes and Type 2 Diabetes

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## ABSTRACT

In recent years, growing evidence linking nutrition to chronic degenerative diseases has prompted researchers to identify optimal dietary patterns for health maintenance. Among various diets, the Mediterranean Diet (MD) has emerged as the most extensively studied and promising approach. This review synthesizes current literature on the MD's effectiveness for type 2 diabetes (T2DM) and prediabetes, drawing from PubMed, Scopus, ProQuest, Google Scholar, Cochrane, and Embase databases (2011-2024) using keywords including 'Mediterranean Diet,' 'MD,' 'Type 2 Diabetes,' and 'Prediabetes.' The MD emphasizes plant-based foods, particularly minimally processed whole grains and olive oil, with studies showing higher olive oil consumption correlates with reduced diabetes incidence. Research demonstrates significant improvements in glycaemic control, including reduced fasting plasma glucose and HbA1c levels, with high MD adherence associated with an 18% lower T2DM risk compared to low adherence. While limitations exist in dietary adherence across populations, the MD remains a practical, evidence-based strategy for diabetes prevention and management, with compelling epidemiological evidence supporting its role in metabolic health improvement for both T2DM and prediabetes.

## Keywords

Mediterranean Diet; Type 2 Diabetes; Diabetes; Prediabetes.

## INTRODUCTION

Recently, a growing body of evidence regarding the correlation between nutrition and chronic degenerative diseases has prompted researchers to explore the most appropriate dietary patterns for maintaining optimal health[1]. It is well-established that nutrition plays a pivotal role in modulating risk factors at both individual and population levels, serving as a critical component in primary and secondary prevention strategies. Various diets have garnered attention, but the one that has generated the most interest is the Mediterranean Diet (MD). This was majorly shown among diabetic patients. In 2019, the global prevalence of diabetes was approximated at 9.3%, affecting 463 million individuals[2]. Around 7.5% (374 million) of the global population was estimated to have impaired glucose tolerance. It is predicted that this figure will rise to 8.0% (454 million) by 2030 and 8.6% (548 million) by 2045[2]. An average follow-up period of 4.9 years showed that adherence to the MD was associated with a reduced incidence of cardiovascular disease.

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A follow-up period of 10.5 years showed 40% lower risk of cardiovascular events in individuals who strictly adhered to the MD compared to those with lower adherence[3] . Moreover, the gradual increase in the adherence level to the MD was associated with a 26% lower risk of coronary artery disease development. Adopting a MD can potentially prevent other health conditions including approximately 25% of colorectal cancers, 15–20% of breast cancers, and 10–15% of prostate, endometrial, and pancreatic tumors[4]. A cause-and-effect relationship between the MD and cancer risk was found in the Lyon Diet Heart Study indicating that after 4 years, a substantial 61% reduction in cancer cases among participants who adhered to the MD compared to the control group[5].

A 6-year randomized controlled trial involving 3,232 participants demonstrated a 53% reduction in metabolic syndrome risk among study subjects [6]. Furthermore, recent studies carried out in Spain demonstrated a significant inverse association between the MD and the risk of obesity[7]. During a 4-year study involving 13,380 participants, it was discovered that individuals who closely adhered to the MD (with a score of > 6) had a reduced risk of developing diabetes[8] . Additionally, there was a 35% reduction in the risk of diabetes with each 2-point rise in adherence to the diet. Recent intervention studies have also confirmed the potential benefits of the MD in managing diabetes, including a randomized controlled trial involving newly diagnosed diabetes patients[8]. More recently, intervention studies have reinforced the potential benefits of the MD in managing diabetes. A randomized controlled trial on patients newly diagnosed with diabetes. Those assigned to the MD experienced favourable modifications to their glycaemic status, improved control of cardiovascular risk factors, and a delay in the need for hypoglycaemic therapy compared to a low-fat, low-carbohydrate diet[9]. Higher adherence to the MD was associated with a 12% reduction in diabetes onset[10]. Therefore, the aim of the present review article is to summarize the available literature on the effectiveness of MD on T2DM or prediabetes management.

## Literature strategy

This review summarizes interventional and observational studies (no comments or editorials) that evaluated the effectiveness of MD in treating T2DM or prediabetes in individuals of any age. The research databases included PubMed, Scopus, ProQuest, Google Scholar, Cochrane, and Embase databases, using keywords such as 'MD,' OR, 'MD,' OR 'Type 2 Diabetes', OR 'T2DM', OR 'Diabetes,' OR 'Prediabetes,' OR 'DM'. The studies included in this review were conducted between 2011 and 2024.

## The Mediterranean Diet: Definition and Components

The origins of the MD can be found in Ancel Keys' adoption of the term in the 1960s following epidemiological research. According to the study, those who live close to the Mediterranean Sea—particularly in Italy and Greece—have lower rates of cancer and cardiovascular illness than people who live in other regions[11]. The core of the MD revolves around plant-based foods, with a focus on incorporating whole grain bread with little or no processing, grains, legumes, nuts, and seeds as a food staple, and fresh fruit as a snack; nuts, honey, and olive oil-based sweets that are only eaten on special occasions; nuts, and seeds as the main sources of fat; cold-pressed extra-virgin olive oil (EVOO); moderate to low intake of dairy products, primarily unprocessed yogurt, and cheese; a moderate amount of red meat (about once a week), moderate amounts of fish, poultry, and eggs, and moderate amounts of wine, usually with meals.[12] Furthermore, A regular exercise regimen is another aspect of the Mediterranean lifestyle.[12].

## Diagnosing Prediabetes and T2DM

Prediabetes is the condition of elevated blood glucose levels that do not yet meet the diagnostic criteria for type 2 diabetes. This is defined by American Diabetes Association (ADA), the International Expert Committee, and the World Health Organization (WHO). This is assessed by fasting glucose concentrations and two-hour plasma glucose concentrations during an OGTT, as well as HbA1c levels. The two primary diagnostic criteria for prediabetes are impaired fasting glucose (IFG), where fasting blood glucose levels range between 100 and 125 mg/dL, and impaired glucose tolerance (IGT), where glucose levels two hours after consuming a glucose-rich solution fall between 140 and 199 mg/dL.[13] Diagnostic thresholds for HbA1c differ between organizations: ADA defines prediabetes as 39–46 mmol/

mol (5.7–6.4%), while the WHO criteria use 42–46 mmol/mol (6.0–6.4%). Pre-diabetes prevalence varies according to the population studied. As a result of the differences in cut-off values compared with the WHO criteria, older people tend to have a higher prevalence of pre-diabetes when using the ADA criteria, which has a higher prevalence than the WHO criteria. The recent inclusion of HbA1c as a criterion for T2DM has led to some discussion, mainly because this results in a higher prevalence of pre-diabetes and T2DM.[14] The global prevalence of IGT in 2021 was 9.1% (464 million) and is projected to increase to 10.0% (638 million) in 2045. The global prevalence of IFG in 2021 was 5.8% (298 million) and is projected to increase to 6.5% (414 million) in 2045. [15] The global burden of prediabetes is substantial and developing. The enhancement of prediabetes surveillance is necessary for the effective implementation of diabetes prevention policies and interventions. Early detection of prediabetes will help in taking the preventative measures to help stop or slow the development of type 2 diabetes, and even progression to cardiovascular illnesses, and death from all causes[16]. In the Chinese Da Qing Diabetes Prevention Study, the cumulative incidence of diabetes among control-group participants with prediabetes reached 95.9% during 30 years of follow-up [17]. Hypertension, obesity, low HDL-cholesterol levels and alcohol consumption are modifiable risk factors independently related to the development of prediabetes[18]. Prediabetes and type 2 diabetes risk is significantly affected by an individual's genetics and family history. Additionally, an increased waist circumference and age further increase the risk[19]. Prediabetes risk can also be raised by lifestyle choices such as eating a diet heavy in added sugars, refined carbs, and saturated fats[20]. Furthermore, one controllable risk factor for prediabetes is a lack of regular physical activity. Prediabetes is more common in some racial and ethnic groups, including Asian Americans, African Americans, and Hispanics[21].

## The Association between Mediterranean Diet and Prediabetes

The primary treatment for prediabetes is lifestyle change, however this can be challenging to maintain in daily life. Research shows that lifestyle interventions not only improve glucose tolerance but also significantly improve quality of life compared with usual diabetes care.[22] During the 6-year active trial and the post-trial period of the Da Qing study, a significant decrease in diabetes was observed due to lifestyle adjustment.[23] Among the many benefits of a lifestyle approach are its potential cost-effectiveness and flexibility to different environments across the globe. Clinical trials, such as the PREDIMED study, demonstrate the effectiveness of the MD in improving glycaemic control and insulin sensitivity, along with triglycerides and HDL cholesterol levels.[24] According to the ATTICA trial, a moderate adherence to the MD could decrease the 10-year threat of diabetes by over 70%, while a high adherence can reduce it by more than 85%[25].

## Mediterranean Diet and risk Reduction of T2DM

Among several dietary approaches, the MD has emerged as a promising dietary strategy for T2DM risk reduction[26]. This is due to its potential to improve overall health and well-being due to its wide range of macro and micronutrients and unique blend of bioactive compounds in its primary elements[27]. In elderly with high cardiovascular risk, a low-fat diet elevated the likelihood of developing diabetes by 52%, whereas an MD enriched with almonds or EVOO reduced the risk by the equivalent amount, according to the PREDIMED RCT trial[28]. This positive effect was mostly ascribed to the dietary pattern's overall composition rather than to weight loss, increased physical activity, or calorie restriction[28]. A cohort study showed that higher consumption of olive oil was linked to a lower incidence of diabetes during a 22-year follow-up. An inverse relationship was shown between the development of the disease and the substitution of other fat-rich foods for olive oil[29].

## Contribution of the Mediterranean Diet to Glycaemic Control

A number of recent studies have consistently demonstrated that individuals with type 2 diabetes may have better blood sugar control while following a MD. Additionally, MD showed that it is capable in lowering the increases in glucose levels that occur after meals, which eventually help control blood sugar levels. One study studied individuals diagnosed with T2DM or prediabetes, who maintained a Mediterranean-inspired diet for 16 weeks[30]. The results showed significant reductions in fasting plasma glucose levels and

improvements in HbA1c, bringing glycaemic control closer to normal levels. Based on this perspective, individuals with type 2 diabetes may improve their blood sugar control and body composition by following a Mediterranean-style diet. When compared to groups following a low-fat diet or no specific dietary intervention, the MD seems to reduce HbA1c levels by around 0.32% to 0.53%[31]. Conversely, two meta-analyses did not find any advantage in reducing HbA1c levels in comparison with vegan diet[32]. Yet, in a separate clinical study, individuals recently diagnosed with diabetes experienced enhanced glycaemic control when they adhered to a MD with calorie restriction, as opposed to those who adhered to a low-fat diet.[31] Moreover, in both normoglycemic and diabetic subjects, a MD was associated with reduced insulin levels, fasting glucose homeostasis, and an improved insulin resistance index (HOMA).[33] PRIMED study declared that after three months of intervention, among individuals at high cardiovascular risk, the groups consuming diets enriched with oil and nuts experienced a decrease in fasting blood sugar levels compared to the control group, even without any weight loss. Therefore, Effective glycaemic management through following a MD may lower the short-, medium-, and long-term risks of complications from diabetes.[34] According to these studies, the definition of a MD varies, notably incorporating olive oil as the primary fat source. Nevertheless, all findings suggest a decrease in HbA1c levels when adopting a MD versus the control diet. Thus, there are more similarities than differences between various interpretations of the MD[35,36] .

## The Mediterranean Diet's Impact on T2DM and CVD Risk Factors

People with type 2 diabetes (T2DM) often have cardiovascular risk factors as well. Therefore, an important step in managing T2DM is to reduce heart-related complications. This is possible as healthy fats are important component of the MD including olive oil and omega-3 fatty acids from fish have been shown to improve the cardiovascular health[37]. According to an RCT trial, patients with a high risk of CVD had a 40% lower risk of type 2 diabetes (T2DM) while following a MD enhanced with extra virgin olive oil (EVOO), as compared to the control group.[28] Additional results from the PREDIMED study indicated a negative correlation between obesity and high phenol consumption, along with a reduction in new cases of type 2 diabetes among the elderly with the highest phenol intake[38]. Furthermore, a review of numerous studies published explores the motivations and challenges of applying the MD for individuals with cardiovascular diseases and T2DM[39]. The motivation stems from the diet's potential health benefits and distinctive characteristics[40]. Despite the numerous benefits of MD, there are some limitations of it. This includes the lack of the universal definition and scoring system of this diet as well as the challenge of the influences of nutritional transition. However, the MD will continue to be a practical and promising approach to prevent and manage cardiovascular diseases and type 2 diabetes.

## Weight Management in T2DM through Mediterranean Diet

Strong evidence showed that obesity is associated with shorter life expectancy, infertility and reproduction complications[41] as well as higher risk of several preventable chronic diseases, including T2DM[42]. The significance of the MD in aiding weight management was highly highlighted, which consequently helps improve insulin sensitivity and glycaemic control[32]. A meta-analysis with 1178 diabetic patients, showed that the MD substantially decreased the diabetes and obesity biomarkers including haemoglobin A1c, fasting insulin, fasting plasma glucose, body weight, and BMI[31]. Likewise, there was an elevation of HDL cholesterol and a decrease in the amounts of triglycerides and total cholesterol[31]. Another meta-analysis with interventions lasting more than six months including low-carb, low-glycaemic index (GI), vegetarian, vegan, high-fibre, MD, and high-protein diets were compared to high-GI, low-fat, and low-protein diets in Type 2 diabetes patients. Out of all the dietary patterns, only the MD showed significant weight loss results[43]. Additionally, individuals who were randomized to the MD lost 4 to 10 kg of body weight, and their LDL cholesterol levels did not significantly change.[43] However, their triglyceride levels significantly improved, and their glycaemic control improved[43]. A multifactorial intervention, including education and technological support, is utilized to enhance compliance with the MD among patients diagnosed with T2DM[26]. The results demonstrate a significant improvement in following

the MD and the overall quality of diet, both at 3 and 12 months. This study indicates that such interventions effectively promote the uptake of the MD among patients with T2DM and support weight loss efforts[27].

## Understanding the Therapeutic Mechanisms of the Mediterranean Diet in Managing Prediabetes and T2DM

Figure 1 presents the overview of the MD effects on Type 2 diabetes and prediabetes. It was shown that individuals with prediabetes who consistently followed a MD that is rich in EVOO showed improvements in endothelial function compared to individuals following a low-fat diet[44]. The MD was also associated with better insulin sensitivity, that is crucial in the onset and progress of prediabetes and T2DM[45]. Olive oil being a good source of mono- and polyunsaturated fats showed improvements in insulin sensitivity through modulating cellular membrane composition and function[46]. In addition to this, polyphenols which are present in fruits and vegetables, were shown to possibly contribute to insulin signalling pathways[47]. Moreover, the high intake of MD components such as whole grains, fruits, and vegetables, provides the body with good amounts of fibre that helps in controlling the blood glucose levels[48]. This is done by slowing the absorption of glucose, consequently promoting better glycaemic control[45]. Since chronic inflammation and oxidative stress are major contributors to the development of insulin resistance and prediabetes, the MD helps in alleviating this inflammatory process through the diverse anti-inflammatory and antioxidants foods[49]. Antioxidants, such as flavonoids and carotenoids, are potential for eliminating the free radicals and protecting cells from damage, contributing to improved metabolic health[47,50]. The incretin hormone glucagon-like peptide-1 (GLP-1) treats T2DM through enhancing insulin production and secretion, along with slowing stomach emptying and inhibiting glucagon secretion[51]. Improvement in endothelial function was also shown with GLP-1, through enhancing endothelial antioxidant defences and decreasing oxidative stress production[52]. Furthermore, GLP-1 may influence the central nervous system's satiety signals, reducing appetite and food intake, thereby ensuring that energy intake does not surpass energy expenditure[53]. Several theories suggest that hyperglycaemia primarily induces oxidative stress,

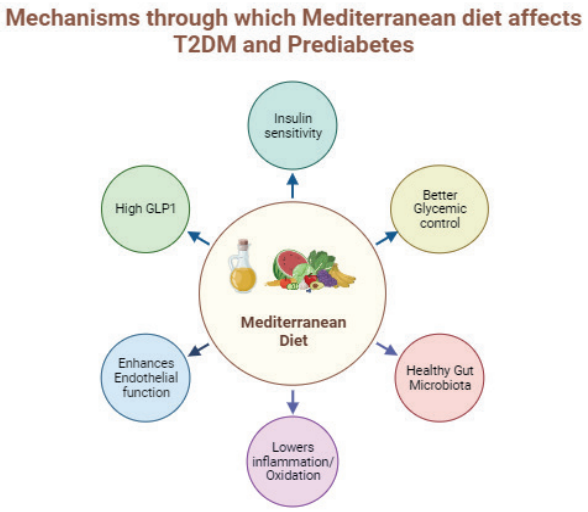


**Figure 1:** Overview of the MD effects on Type 2 diabetes and prediabetes.

which then leads to GLP-1 resistance. Consequently, this resistance contributes to the gradual decline in β-cell function[54]. The GLP-1 activity is enhanced by the MD[55]. Specifically, evidence suggests that PUFA from EVOO may bind to and activate receptors such as GPR120, potentially enhancing GLP-1 secretion from intestinal L-cells. Elevated GLP-1 levels may reduce postprandial hyperglycaemia by enhancing insulin secretion from pancreatic β-cells, which in turn promotes glucose uptake by skeletal muscles[56]. Human microbiota function and composition are significantly influenced by the type and quantity of food consumed[57]. Health outcomes for the host are determined by the intricate relationships between bacteria and nutrients[58]. There is evidence that the MD positively affects gut microbiota. Obese individuals who adhered to this diet for a year experienced specific changes in their gut flora, which helped prevent the development of Type 2 diabetes[59]. The MD is rich in complex carbohydrates and dietary fibre. Short-chain fatty acids (SCFA) are produced as a result of the fermentation of the dietary fibres by the gut microbiota. Acetate, butyrate, and propionate, or SCFA, perform various important functions for the body's host. SCFAs help regulate lipid and glucose metabolism related to Type 2 diabetes by activating SCFA receptors in adipose tissue, the liver, brain, and pancreas[60]. Furthermore, SCFA could increase GLP-1 and GLP-2 secretion, which improves

satiety, proliferation of pancreatic β-cell, and insulin sensitivity[61]. Thus, because of its higher dietary fibre content, the MD can stimulate the gut microbiota to produce SCFA.

## Long-Term Adherence: The Mediterranean Diet in T2DM Management

The adherence level to any dietary intervention can be affected by different factors, such as food preferences, socioeconomic status and cultural background. It can also be affected by beliefs and thoughts, attitudes, and awareness of the diet's health benefits. The palatability of Mediterranean food, characterized by rich flavours and diverse food options, may enhance long-term adherence compared to more restrictive diets. It was shown that individuals with strong adherence exhibited an 18% lower likelihood of developing T2DM compared to low adherence, while individuals with moderate adherence exhibited an 11% reduction in risk[62]. Interventions and strategies that raise the awareness which highlight the cultural importance of the diet may improve dietary habits. Moreover, support provision from family and people is essential in influencing the individual's dietary choices. The communal nature of the MD components, makes it easier to be shared with family and friends, promoting a supportive environment contributing to sustained adherence. Utilizing social support mechanisms within community-based interventions can enhance the effectiveness of promoting the MD. Dietary patterns also have a significant impact on the environment in all parts of the world.

While the amount of evidence is still insufficient, the scientific literature that is currently accessible indicates that adopting MD pattern can have a lesser environmental impact than the mass consumption cultures currently have[63].

## The effect of the Mediterranean Diet on the gut microbiome and its impact on T2DM and prediabetes

Diet has a major contribution to the development and maintenance of healthy gut microbiota (eubiosis). Therefore, the health is determined by the diversity of gut microbiota. It was indicated in the majority of the research that adoption of the MD was associated with increased gut microbial diversification[64]. In the gut, the MD is linked to the presence of the genus Prevotella and higher levels of Faecalibacterium prausnitzii, if compared to the Western diet that is recognized with high levels of Bacteroides[64,65]. Among individuals with metabolic, the MD was associated with reduction in dysbiosis and a rise in the Bifidobacterium genera[64,66]. Moreover, one study found no discernible changes in gut microbiota after six months on either a Western-style diet or an MD[64,67].

The MD provides around 14 g of dietary fibre per 1000 Kcal, making it a diet rich in fiber[64]. In addition, "Microbiota-accessible carbohydrates" (MACs), are complex carbohydrates present fibre-rich food sources like fruits, vegetables, legumes, and wholegrains, which are highly incorporated in the MD. MACs were shown to change the gut microbiota and promote the growth of species that generate butyrate and other short-chain fatty acids (SCFAs). These SCFAs may aid in improving cardiometabolic health and lowering cancer rates, in which both of them are linked to MD[64,68]. A compelling evidence was shown in a mouse model in which MACs showed a positive effect in suppressing Clostridium difficile infection[69]. Consuming complex carbohydrates encourages the proliferation of health-promoting Bifidobacterium species, such as Bifidobacterium longum, Bifidobacterium breve, and Bacteroides thetaiotaomicron, within the fibre-rich MD[70,71]. Complex carbohydrates' fermentable (soluble) portion is linked to an increase in butyrate-producing bacteria including Clostridium leptum and Eubacterium rectale[70,72]. The MD provides a plenty of polyphenols, secondary metabolites with anti-inflammatory and antioxidant properties, in addition to the dietary fiber[64]. Polyphenols in olive oil were shown to have a bactericidal impact on Helicobacter pylori strains, suggesting that they may be used as a chemo preventive agent to prevent stomach ulcers[64]. Another study compared the MD (with 40 g per day of EVOO) with a control diet in overweight and obese participants showed the potential of the MD in the modification of the composition of gut microbiota, including lactic acid bacteria[64,73]. Oily fish, a major source of polyunsaturated fatty acids (PUFA) believed to enhance cardiovascular health[64]. In diabetic rats, administration of flaxseed oil, a source of polyunsaturated fatty acids (α-linoleic acid), decreased the amount of Firmicutes and Blautia. According to that, it was predicted that PUFA enhances the inflammation by manipulation of gut microbiota,

given the link between Firmicutes and Blautia with inflammatory cytokines like TNF-α[64,74]. Furthermore, it seems that ω-3 PUFAs strengthen the intestinal epithelial barrier and lessen its permeability in colitis[64].

## CONCLUSION

Investigating the correlation between the MD and prediabetes/T2DM shows promising potential for metabolic health. Compelling evidence from epidemiological studies demonstrates the diet's impact on the risk of chronic diseases, including T2DM, with emerging evidence supporting its specific effect on prediabetes. Studying and understanding the underlying mechanisms will help design effective interventions and strategies, while promoting the Mediterranean diet as a viable approach for diabetes management and prevention. Future research should explore the interrelationships between different factors and mechanisms. This will guide dietary recommendations, improving public health outcomes. By pursuing further research, fostering collaborations, and implementing personalized care, the benefits of the Mediterranean diet could improve metabolic health, prevent T2DM onset, and halt its progression from prediabetes—ultimately promoting healthier populations the future.

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## REFERENCES

1. Sofi F, Macchi C, Abbate R, Gensini GF, Casini A. MD and health. *Biofactors* 2013; **39**(4): 335-42.
2. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. *Diabetes research and clinical practice* 2019; **157**: 107843.
3. Buckland G, González CA, Agudo A, et al. Adherence to the MD and risk of coronary heart disease in the Spanish EPIC Cohort Study. *American journal of epidemiology* 2009; **170**(12): 1518-29.
4. Trichopoulou A, Lagiou P, Kuper H, Trichopoulos D. Cancer and MDary traditions. *Cancer Epidemiology Biomarkers & Prevention* 2000; **9**(9): 869-73.
5. de Lorgeril M, Salen P, Martin J-L, Monjaud I, Boucher P, Mamelle N. MDary pattern in a randomized trial: prolonged survival and possible reduced cancer rate. *Archives of Internal Medicine* 1998; **158**(11): 1181-7.
6. Kesse-Guyot E, Ahluwalia N, Lassale C, Hercberg S, Fezeu L, Lairon D. Adherence to MD reduces the risk of metabolic syndrome: a 6-year prospective study. *Nutrition, Metabolism and Cardiovascular Diseases* 2013; **23**(7): 677-83.
7. Schroder H, Marrugat J, Vila J, Covas MI, Elosua R. Adherence to the traditional MD is inversely associated with body mass index and obesity in a Spanish population. *The Journal of nutrition* 2004; **134**(12): 3355-61.
8. Martínez-González MÁ, De la Fuente-Arrillaga C, Nunez-Cordoba J, et al. Adherence to MD and risk of developing diabetes: prospective cohort study. *Bmj* 2008; **336**(7657): 1348-51.
9. Esposito K, Maiorino MI, Ciotola M, et al. Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes: a randomized trial. *Annals of internal medicine* 2009; **151**(5): 306-14.
10. Consortium I. MD and type 2 diabetes risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study: the InterAct project. *Diabetes care* 2011; **34**(9): 1913-8.
11. Keys A, Mienotti A, Karvonen MJ, et al. The diet and 15-year death rate in the seven countries study. *American journal of epidemiology* 1986; **124**(6): 903-15.
12. Ingrassia M, Altamore L, Columba P, et al. MD, Sustainability,

and Tourism—A Study of the Market's Demand and Knowledge. *Foods* 2023; **12**(13): 2463.

13. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. *Diabetes Care* 2020; **43**(Suppl 1): S14-s31.
14. Barry E, Roberts S, Oke J, Vijayaraghavan S, Normansell R, Greenhalgh T. Efficacy and effectiveness of screen and treat policies in prevention of type 2 diabetes: systematic review and meta-analysis of screening tests and interventions. *BMJ* 2017; **356**: i6538.
15. Rooney MR, Fang M, Ogurtsova K, et al. Global Prevalence of Prediabetes. *Diabetes Care* 2023; **46**(7): 1388-94.
16. Cai X, Zhang Y, Li M, et al. Association between prediabetes and risk of all cause mortality and cardiovascular disease: updated meta-analysis. *BMJ* 2020; **370**: m2297.
17. Gong Q, Zhang P, Wang J, et al. Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30-year results of the Da Qing Diabetes Prevention Outcome Study. *Lancet Diabetes Endocrinol* 2019; **7**(6): 452-61.
18. Díaz-Redondo A, Giráldez-García C, Carrillo L, et al. Modifiable risk factors associated with prediabetes in men and women: a cross-sectional analysis of the cohort study in primary health care on the evolution of patients with prediabetes (PREDAPS-Study). *BMC Fam Pract* 2015; **16**: 5.
19. Auad R, Kakaje A, Alourfi Z. Prediabetes in Syria and Its Associated Factors: A Single-Center Cross-Sectional Study. *Diabetes Ther* 2022; **13**(9): 1573-83.
20. Abshirini M, Mahaki B, Bagheri F, et al. Dietary Fat Quality and Pre-diabetes: A Case-control Study. *Int J Prev Med* 2020; **11**: 160.
21. Formagini T, Brooks JV, Roberts A, et al. Prediabetes prevalence and awareness by race, ethnicity, and educational attainment among U.S. adults. *Front Public Health* 2023; **11**: 1277657.
22. Jiang Q, Li J-T, Sun P, Wang L-L, Sun L-Z, Pang S-G. Effects of lifestyle interventions on glucose regulation and diabetes risk in adults with impaired glucose tolerance or prediabetes: a meta-analysis. *Archives of endocrinology and metabolism* 2022; **66**: 157-67.
23. Zhang M, Zucatti KP, Teixeira PP, et al. Cancer Outcomes Among Prediabetes and Type 2 Diabetes Populations With Dietary and Physical Activity–based Lifestyle Interventions. *The Journal of Clinical Endocrinology & Metabolism* 2023; **108**(8): 2124-33.
24. Salas-Salvadó J, Díaz-López A, Ruiz-Canela M, et al. Effect of a lifestyle intervention program with energy-restricted MD and exercise on weight loss and cardiovascular risk factors: one-year results of the PREDIMED-Plus trial. *Diabetes Care* 2019; **42**(5): 777-88.
25. Filippatos TD, Panagiotakos DB, Georgousopoulou EN, et al. MD and 10-year (2002-2012) incidence of diabetes and cardiovascular disease in participants with prediabetes: the ATTICA study. *The review of diabetic studies: RDS* 2016; **13**(4): 226.
26. Alonso-Domínguez R, García-Ortiz L, Patino-Alonso MC, Sánchez-Aguadero N, Gómez-Marcos MA, Recio-Rodríguez JI. Effectiveness of a multifactorial intervention in increasing adherence to the MD among patients with diabetes mellitus type 2: a controlled and randomized study (EMID study). *Nutrients* 2019; **11**(1): 162.
27. Kaur KK. MD Still Holds a Place in Obesity Treatment Despite the Considerable Effectiveness of the Very Low-Calorie Ketogenic Diet: A Short Communication. 2023.
28. Salas-Salvadó J, Bulló M, Estruch R, et al. Prevention of diabetes with MDs: a subgroup analysis of a randomized trial. *Annals of internal medicine* 2014; **160**(1): 1-10.
29. Guasch-Ferré M, Hruby A, Salas-Salvadó J, et al. Olive oil consumption and risk of type 2 diabetes in US women. *The American journal of clinical nutrition* 2015; **102**(2): 479-86.
30. Derrick SA, Nguyen ST, Marthens JR, Dambacher LL, Sikalidis AK, Reaves SK. A Mediterranean-Style Diet Improves the Parameters for the Management and Prevention of Type 2 Diabetes Mellitus. *Medicina* 2023; **59**(10): 1882.
31. Huo R, Du T, Xu Y, et al. Effects of Mediterranean-style diet on glycemic control, weight loss and cardiovascular risk factors among type 2 diabetes individuals: a meta-analysis. *European journal of clinical nutrition* 2015; **69**(11): 1200-8.
32. Schwingshackl L, Missbach B, König J, Hoffmann G. Adherence to a MD and risk of diabetes: a systematic review and meta-analysis. *Public health nutrition* 2015; **18**(7): 1292-9.
33. Kouvari M, Boutari C, Chrysohoou C, et al. MD is inversely associated with steatosis and fibrosis and decreases ten-year diabetes and cardiovascular risk in NAFLD subjects: Results from the ATTICA prospective cohort study. *Clinical Nutrition* 2021; **40**(5): 3314-24.
34. McEvoy JW, Whelton Seamus P, Blumenthal RS. 38—Dyslipidemia. *Hypertension: a companion to Braunwald's heart disease* 2017: 353-60.
35. Esposito K, Maiorino MI, Bellastella G, Chiodini P, Panagiotakos D, Giugliano D. A journey into a MD and type 2 diabetes: a systematic review with meta-analyses. *BMJ open* 2015; **5**(8): e008222.
36. Zheng X, Zhang W, Wan X, et al. The effects of MD on cardiovascular risk factors, glycemic control and weight loss in patients with type 2 diabetes: a meta-analysis. *BMC Nutr* 2024; **10**(1): 59.

37. Itsiopoulos C, Brazionis L, Kaimakamis M, et al. Can the MD lower HbA1c in type 2 diabetes? Results from a randomized cross-over study. *Nutrition, Metabolism and Cardiovascular Diseases* 2011; **21**(9): 740-7.
38. Guo X, Tresserra-Rimbau A, Estruch R, et al. Polyphenol levels are inversely correlated with body weight and obesity in an elderly population after 5 years of follow up (the randomised PREDIMED study). *Nutrients* 2017; **9**(5): 452.
39. Toi PL, Anothaisintawee T, Chaikledkaew U, Briones JR, Reutrakul S, Thakkinstian A. Preventive role of diet interventions and dietary factors in type 2 diabetes mellitus: an umbrella review. *Nutrients* 2020; **12**(9): 2722.
40. Milenkovic T, Bozhinovska N, Macut D, et al. MD and type 2 diabetes mellitus: a perpetual inspiration for the scientific world. A review. *Nutrients* 2021; **13**(4): 1307.
41. Ahmad R, Haque M. Obesity inflicted reproductive complications and infertility in men. *Bangladesh Journal of Medical Science* 2023; **22**(1): 7.
42. Ma F, Zhang Q, Shi J, Li S, Wu L, Zhang H. Risk factors for cognitive dysfunction and glycemic management in older adults with type 2 diabetes mellitus: a retrospective study. *BMC Endocrine Disorders* 2023; **23**(1): 220.
43. Ajala O, English P, Pinkney J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. *The American journal of clinical nutrition* 2013; **97**(3): 505-16.
44. Torres-Peña JD, Garcia-Rios A, Delgado-Casado N, et al. MD improves endothelial function in patients with diabetes and prediabetes: A report from the CORDIOPREV study. *Atherosclerosis* 2018; **269**: 50-6.
45. Mirabelli M, Chiefari E, Arcidiacono B, et al. MD Nutrients to Turn the Tide against Insulin Resistance and Related Diseases. *Nutrients* 2020; **12**(4).
46. González-Becerra K, Ramos-Lopez O, Barrón-Cabrera E, et al. Fatty acids, epigenetic mechanisms and chronic diseases: a systematic review. *Lipids Health Dis* 2019; **18**(1): 178.
47. Fraga CG, Croft KD, Kennedy DO, Tomás-Barberán FA. The effects of polyphenols and other bioactives on human health. *Food Funct* 2019; **10**(2): 514-28.
48. D'Alessandro A, Lampignano L, De Pergola G. MD Pyramid: A Proposal for Italian People. A Systematic Review of Prospective Studies to Derive Serving Sizes. *Nutrients* 2019; **11**(6).
49. Martínez-González MA, Salas-Salvadó J, Estruch R, Corella D, Fitó M, Ros E. Benefits of the MD: Insights From the PREDIMED Study. *Progress in Cardiovascular Diseases* 2015; **58**(1): 50-60.
50. Fedorova T, Semenenko N, Tazina S, Mamonov A, Sotnikova T. Metabolic syndrome and chronic heart failure: a modern aspect of the problem. *Bangladesh Journal of Medical Science* 2022; **21**(1).
51. Viggers R, Rasmussen NHh, Vestergaard P. Effects of Incretin Therapy on Skeletal Health in Type 2 Diabetes—A Systematic Review. *JBMR plus* 2023: e10817.
52. Matata B, Elahi M. Oxidative Stress and Leukocytes Activation The Two Keystones of Ischemia/Reperfusion Injury during Myocardial Infarction, Valve Disease, and Atrial Fibrillation. *Blood Oxidant Ties: The Evolving Concepts in Myocardial Injury and Cardiovascular Disease* 2023: 25.
53. Rai C, Priyadarshini P. Whey protein hydrolysates improve high-fat-diet-induced obesity by modulating the brain–peripheral axis of GLP-1 through inhibition of DPP-4 function in mice. *European Journal of Nutrition* 2023: 1-19.
54. Kong F, Wu T, Dai J, et al. Glucagon-like peptide 1 (GLP-1) receptor agonists in experimental Alzheimer's disease models: a systematic review and meta-analysis of preclinical studies. *Frontiers in Pharmacology* 2023; **14**.
55. Bouzas C, Pastor R, Garcia S, et al. Comparative effects of glucagon-like peptide-1 receptors agonists, 4-dipeptidyl peptidase inhibitors, and metformin on metabolic syndrome. *Biomedicine & Pharmacotherapy* 2023; **161**: 114561.
56. Di Mauro A. A Mediterranean-pattern Meal Increases GLP-1 and Oxyntomodulin more than an energy-matched High Fiber Plant-based meal in Type-2 Diabetes patients: A Crossover, Randomized, Controlled Inpatient Physiology Study. 2019.
57. Berding K, Bastiaanssen TF, Moloney GM, et al. Feed your microbes to deal with stress: a psychobiotic diet impacts microbial stability and perceived stress in a healthy adult population. *Molecular psychiatry* 2023; **28**(2): 601-10.
58. Huda MN, Salvador AC, Barrington WT, et al. Gut microbiota and host genetics modulate the effect of diverse diet patterns on metabolic health. *Frontiers in Nutrition* 2022; **9**: 896348.
59. Deledda A, Palmas V, Heidrich V, et al. Dynamics of Gut Microbiota and Clinical Variables after Ketogenic and MDs in Drug-Naïve Patients with Type 2 Diabetes Mellitus and Obesity. *Metabolites* 2022; **12**(11): 1092.
60. Ban Q, Chi W, Tan Y, et al. Melatonin improved glucose homeostasis is associated with the reprogrammed gut microbiota and reduced fecal levels of short-chain fatty acids in db/db mice. *Food Science & Nutrition* 2023; **11**(4): 2012-26.
61. Sharma VK, Singh TG, Dhiman S, Garg N. Mechanisms of beneficial effects of probiotics in diabetes mellitus. Probiotic Research in Therapeutics: Volume 5: Metabolic Diseases and Gut Bacteria: Springer; 2022: 97-124.
62. Kotzakioulafi E, Bakaloudi DR, Chrysoula L, et al. High Versus Low Adherence to the MD for Prevention of Diabetes Mellitus

Type 2: A Systematic Review and Meta-Analysis. *Metabolites* 2023; **13**(7): 779.

63. Grosso G, Fresán U, Bes-Rastrollo M, Marventano S, Galvano F. Environmental Impact of Dietary Choices: Role of the Mediterranean and Other Dietary Patterns in an Italian Cohort. *Int J Environ Res Public Health* 2020; **17**(5).
64. Merra G, Noce A, Marrone G, et al. Influence of MD on human gut microbiota. *Nutrients* 2020; **13**(1): 7.
65. Jin Q, Black A, Kales SN, Vattem D, Ruiz-Canela M, Sotos-Prieto M. Metabolomics and microbiomes as potential tools to evaluate the effects of the MD. *Nutrients* 2019; **11**(1): 207.
66. Haro C, Garcia-Carpintero S, Alcala-Diaz JF, et al. The gut microbial community in metabolic syndrome patients is modified by diet. *The Journal of nutritional biochemistry* 2016; **27**: 27-31.
67. Djuric Z, Bassis CM, Plegue MA, et al. Colonic mucosal bacteria are associated with inter-individual variability in serum carotenoid concentrations. *Journal of the Academy of Nutrition and Dietetics* 2018; **118**(4): 606-16. e3.
68. Nicholson JK, Holmes E, Kinross J, et al. Host-gut microbiota metabolic interactions. *Science* 2012; **336**(6086): 1262-7.
69. Hryckowian AJ, Van Treuren W, Smits SA, et al. Microbiota-accessible carbohydrates suppress Clostridium difficile infection in a murine model. *Nature microbiology* 2018; **3**(6): 662-9.
70. Barber TM, Kabisch S, Pfeiffer AF, Weickert MO. The health benefits of dietary fibre. *Nutrients* 2020; **12**(10): 3209.
71. Pokusaeva K, Fitzgerald GF, van Sinderen D. Carbohydrate metabolism in Bifidobacteria. *Genes & nutrition* 2011; **6**: 285-306.
72. Simoes CD, Maukonen J, Kaprio J, Rissanen A, Pietiläinen KH, Saarela M. Habitual dietary intake is associated with stool microbiota composition in monozygotic twins. *The Journal of nutrition* 2013; **143**(4): 417-23.
73. Luisi MLE, Lucarini L, Biffi B, et al. Effect of MD enriched in high quality extra virgin olive oil on oxidative stress, inflammation and gut microbiota in obese and normal weight adult subjects. *Frontiers in pharmacology* 2019; **10**: 1366.
74. Zhu L, Sha L, Li K, et al. Dietary flaxseed oil rich in omega-3 suppresses severity of type 2 diabetes mellitus via anti-inflammation and modulating gut microbiota in rats. *Lipids in health and disease* 2020; **19**: 1-16.