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Mediterranean diet and health – a narrative review

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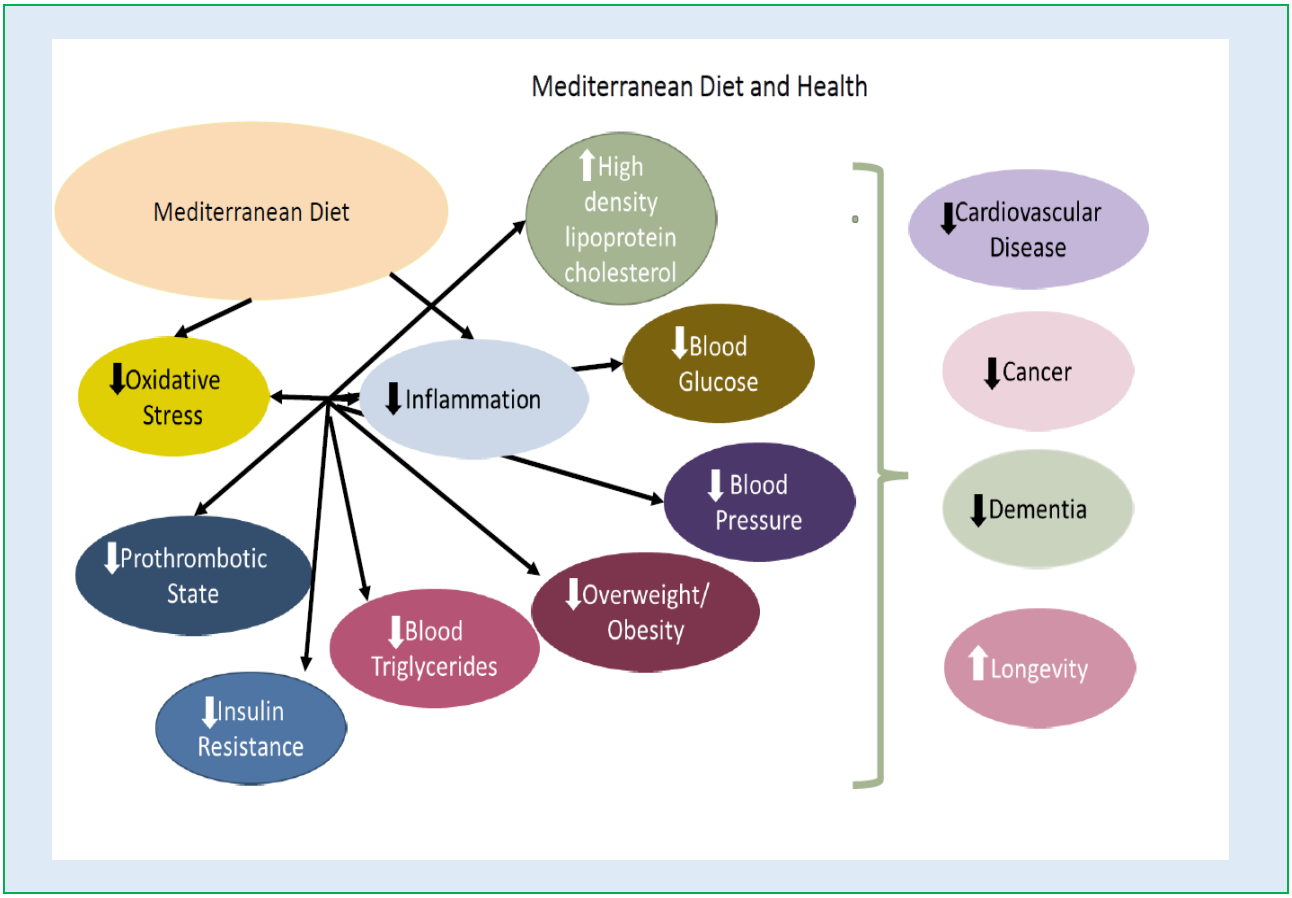
ABSTRACT

The Mediterranean Diet is a dietary pattern characterized by increased intake of olive oil, vegetables, fruits, cereals, nuts and pulses/legumes; as well as moderate intake of fish and other meat, dairy products and red wine. This dietary pattern has been associated with reduced risk for non-communicable diseases, including cardiovascular disease, type 2 diabetes mellitus, certain cancers, and dementia. The importance of modifying lifestyle risk factors to reduce these diseases is evidence by the increased obesity rates and aging of the global population. To examine associations between adherence to the Mediterranean Diet and non-communicable disease risk. There is evidence supporting a role for the Mediterranean Diet in primary and secondary non-communicable disease prevention; Furthermore, the Mediterranean Diet has been associated with reduced all-cause mortality.

Conclusions: The Mediterranean Diet is associated with demonstrable and measurable health benefits, including non-communicable disease prevention and reduced mortality risk. The Mediterranean Diet is frequently consumed by individuals in Blue Zones.

Keywords: Mediterranean diet; olive oil; non-communicable disease risk



INTRODUCTION In the 1950s and 1960s, American physiologist Ancel Keys and his Italian colleague, Flaminio Fidanza wrote about the lower rates of cardiovascular disease in the region around Italy and Greece [1]. They attributed this to what they called "the Mediterranean diet," characterized by increased olive oil and reduced meat consumption [2]. Indeed, the Seven Countries Study identified an inverse association between the Mediterranean diet pattern and coronary heart disease (CHD) [3].

Today, guidelines for the Mediterranean diet emphasize the intake of cold pressed olive oil, vegetables, fruits, cereals, nuts and pulses/legumes, moderate intakes of fish and other meat, dairy products (mainly fermented) and red wine, and reduced intake of saturated fats and added sugar [4]. Nevertheless, an Italian Mediterranean Diet Pyramid provides the following recommendations [5]: Each meal should include 1-2 servings of fruit (150 g), 1-2 servings of vegetables (200 g), and two servings of cereals (pasta, rice, spelt – 80 g) bread (50 g).The following foods should be consumed daily: 2 servings of milk or yogurt (125 g), one portion of breakfast products (40 g), 2-3 servings of olive oil (10 g), 1.5-2L water, and one portion (for women) or two servings (for men) of wine (125 g). The following foods should/can be consumed weekly: 1-2 servings of potatoes (200 g), 2-3 servings of pulses (50 g dry), one portion of red meat (100 g), 1-2 servings of chicken/poultry (100 g), 2-3 servings of fish (150 g), two servings of egg (50 g), 1-2 servings of processed meat (50 g), two servings of cheese (50 g matured cheese or 100 g soft cheese), three servings of dried fruit (15 g) and one serving of sweets (100 g).

Other recommendations have been offered [6, 7], mainly differing in the frequency poultry, meat and eggs should be consumed. Additionally, the various versions of the recommendations differ in their tone, from quite proscriptive and particular to more general. Regardless of the specifics, the Mediterranean diet pattern can clearly be tailored to reflect the individual food preferences and nutritional needs of consumers.

Due to its health claims associated with specific foods emphasized in the Mediterranean diet, this pattern can be considered to meet the definition of functional foods. Specifically, a functional food is defined as a food containing biologically active compounds for which there is evidence supporting their use to reduce disease risk and promote health and wellness [8]. Health benefits appear to be conferred through reduction of oxidative stress and attenuation of chronic disease [9].

Over time, the Mediterranean diet has been associated with numerous health benefits, including reductions in chronic disease mortality, especially cardiovascular disease (CVD), and certain cancers [10]. More recently, this diet pattern has been associated with reductions in dementia risk and other endpoints. The objective of the present review is to assess these associations as presented in the most recent literature using WHO, CDC, NIH (PubMed) and Google Scholar sources; and to consider mechanisms through which they may be explained.

Mediterranean diet and cvd prevention: CVDs can be described as disturbances of the heart and blood vessels and include CHD, stroke, peripheral artery disease (PAD), and so on [11]. Globally, CVD remains the leading cause of death, most of which are attributable to myocardial infarction (MI) or stroke [12]. The World Health Organization estimates that almost 18 million people die annually from CVD [13].

CVD risk is associated with all four of the major behavioral chronic disease risk factors: unhealthy diet, physical inactivity, tobacco use and harmful use of alcohol [14]. These risk factors are associated with elevations in cardiometabolic risk factors well established as intermediate risk factors for CVD: blood pressure, serum glucose, markers of inflammation, and serum lipids [15]. An unhealthy diet, physical inactivity, and harmful use of alcohol are also associated with overweight, obesity, and the development of type 2 diabetes, which also increases CVD risk [16].

Alterations in modifiable risk factors, including smoking cessation, increased physical activity, moderate alcohol consumption, and improved diet quality, have been associated with reduced CVD risk [17]. The Mediterranean diet is a pattern that has been shown to reduce CVD risk, as well as total mortality risk [18].

The association between the Mediterranean diet and any CVD endpoint consistently shows that this dietary pattern is associated with reduced total CVD risk [19]. In a meta-analysis of prospective studies, the Mediterranean diet has been associated with a reduction of total CVD risk of almost 20% [20]. The pooled findings of yet another meta-analysis detected an even larger inverse association between consuming a Mediterranean diet and total CVD risk of almost 30% [21]. In a meta-analysis including both clinical trials and prospective observational studies, both CVD risk and risk of death were significantly reduced in individuals who consumed a Mediterranean diet [22].

The efficacy of the Mediterranean diet in reducing CVD and mortality risk may be explained by its influence on intermediate CVD risk factors. For example, the Mediterranean diet has been shown to produce a small but significant reduction in both systolic and diastolic blood pressure compared to a control diet. But when compared to other intervention diets, such as a low-fat diet, blood pressure was not significantly reduced [23]. Another study found that the Mediterranean diet reduced diastolic but not systolic blood pressure, suggesting that it performed less impressively than other intervention diets, including the Dietary Approaches to Stop Hypertension (DASH) diet and various combinations of calorie and sodium restriction [24]. In the Prevención con Dieta Mediterránea (Prevention with Mediterranean Diet, PREDIMED) study, which randomized overweight or obese adults with metabolic syndrome to an intensive

lifestyle intervention featuring physical activity and a calorie-reduced Mediterranean diet pattern or a control group, the group consuming the Mediterranean diet had significant reductions in fasting glucose, HbA1c, circulating leptin, total and LDL cholesterol, and triglycerides together with a significant increase in HDL. Furthermore, markers of inflammation including IL-18 and monocyte chemoattractant protein (MCP) 1 underwent a greater reduction in the Mediterranean diet group; however, other markers of inflammation including C-reactive protein, IL-6, IL-8 and TNF-alpha, did not [25]. Because the Mediterranean diet was consumed in the framework of a total lifestyle intervention, it is not possible to attribute these beneficial, CVD risk-lowering changes to the Mediterranean diet alone. The Mediterranean diet has also been shown to reduce both the incidence and progression of type 2 diabetes, a condition very strongly associated with increased CVD risk [26].

At the population level, studies support a role for the Mediterranean diet in the reduction of incident CVD events. The reduction in intermediate endpoints is somewhat more variable, especially regarding blood pressure reduction. But, the reduction of other intermediate endpoints, including cardiometabolic markers and some measures of inflammation is reliably reduced by this diet pattern.

Mediterranean diet and cancer prevention: According to the World Health Organization, approximately 10 million people died of cancer in 2020 [27]. The National Cancer Institute has estimated that the most common incident cancers in 2020 were, in descending order: breast, lung, prostate, colorectal, melanoma of the skin, and bladder [28]. It has been predicted that incident cancers will increase by more than 60% and cancer mortality by more than 72% by the year 2040. According to the WHO International Agency for Research on Cancer Global Cancer Observatory, cancer incidence rates are generally greater in developed nations, which have older, better educated, and more affluent populations [29].

Cancer may arise when cell function is disturbed by intracellular genetic and epigenetic alterations leading to abnormalities at the molecular level, ultimately culminating in genetic disruption. It is generally accepted that cancer evolves through an interaction between environmental and genetic risk factors; nevertheless, approximately 80-90% of cancers can be attributed to environmental risk factors (carcinogens). Some of these are ascribed to lifestyle choices. As per all chronic diseases, the human lifestyle behaviors associated with cancer incidence and mortality include tobacco use, sedentary lifestyle, harmful alcohol use, and an unhealthy diet [30]. While more than 20% of incident cancers can be attributed to smoking, approximately, it has been estimated that improving the diet can prevent 30-50% of cancers [31].

The Mediterranean diet pattern has been associated with reductions in some of the most common cancers. For example, in a European hospital-based case-control study, investigators enrolled more than 6000 participants and compared Mediterranean diet adherence measured using the Mediterranean Diet Score between cases and controls. Odds of breast cancer were reduced from 14-18% in higher vs. the lowest Mediterranean Diet Score category in both pre- and post-menopausal women [32].

While less intuitive, an inverse association between the Mediterranean diet pattern and lung cancer risk has been reported in a nine-study meta-analysis. The analysis indicated that for every three-point increase in the Mediterranean Diet Score from 0, the lung cancer risk was decreased by 9%. [33].

A large meta-analysis including more than 3 million participants and various study designs did not detect an association between the Mediterranean diet pattern and prostate cancer [34]. On the other hand, a narrative review identified an inverse association

between consuming a Mediterranean diet and the risk of prostate cancer mortality [35].

The prospective Netherlands Cohort Study (NLCS) examined the association between adherence to the Mediterranean diet and colorectal cancer risk. At 20.3 years of follow-up, an association between the Mediterranean Diet Score and colorectal cancer was not detected in this Dutch study population [36]. By contrast, the European Prospective Investigation into Cancer and Nutrition (EPIC), a prospective conducted in 10 European countries, examined associations between various diet patterns and cancer incidence and mortality. In a meta-analysis of EPIC cohort reports, investigators found that consuming a Mediterranean diet pattern reduced colorectal cancer risk. Furthermore, the study found that aspects of the Mediterranean diet also reduced colorectal cancer risk, including increased fruit and vegetable intake; increased fish coupled with reduced intake of red or processed meat; and increased milk and yogurt intake. Alcohol intake was associated with increased colorectal cancer risk [37]. A focused review of the impact of the Mediterranean diet on cancers of the digestive tract, including colorectal cancer, found that this dietary pattern was associated with reductions of cancer incidence at all gastrointestinal sites with the exception of the pancreas (38).

In a case-control study in Italy including more than 1000 participants, the Healthy Eating Index, a measure of diet quality, was associated with reduced cutaneous melanoma risk; however, the Mediterranean diet pattern was not significantly associated with this outcome [39]. Conversely, a prospective study with 15 years of follow-up in middle-aged French women identified that the Mediterranean diet pattern reduced skin cancer risk, including melanoma and basal cell carcinoma, but not squamous cell carcinoma [40].

While not all cancers are influenced by diet, some of the most common cancers are. Breast and lung cancers are robustly associated with the Mediterranean diet, while associations between this diet pattern and prostate, colorectal and cutaneous melanoma cannot be ruled out.

Mediterranean diet and dementia prevention: Dementia, the most common type of which is Alzheimer's disease, is a cognitive state characterized by difficulties with memory, thinking, and decision-making that impair daily activities [41]. While age is the single strongest predictor of dementia/Alzheimer's disease, it is not a normal part of the aging process. Other risk factors for dementia/Alzheimer's disease include family history, CVD, smoking, and brain trauma. The chronic disease risk factors are also risk factors for dementia: physical activity, smoking, unhealthy alcohol use, and an unhealthy diet [42].

A randomized clinical trial was conducted to determine if a Mediterranean diet could affect cognitive function. Included in the study were 447 participants in the PREDIMED study who were randomized to consume a Mediterranean diet supplemented with 1L/week of extra virgin olive oil; a Mediterranean diet supplemented with 30 g mixed nuts/day; or a reduced fat diet. A battery of cognitive measures was performed at a median follow-up of approximately four years. Participants randomized to the Mediterranean diet supplemented with olive oil or nuts scored better than controls on several of the cognitive tests, suggesting that the Mediterranean diet was associated with reduced cognitive decline in older adults [43]. A narrative review of dietary patterns and cognitive decline indicated that the Dietary Approaches to Stop Hypertension (DASH), the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND), and the Mediterranean diets were all associated with reduced cognitive decline, an observation attributed by the authors to the effects of olive oil [4].

In comparison to western-style diets, which are characterized by high intakes of saturated fat and processed foods, the Mediterranean diet is associated with reduced cognitive decline over time in older adults. While the suggested component of the diet pattern associated with this observation may be olive oil, it may also be increased fruit and vegetable intake and reduced processed food intake.

Possible mechanisms through which the mediterranean diet influences health outcomes: The components of the Mediterranean diet associated with morbidity and mortality risk reduction include olive oil and nuts; increased fruit and vegetable intake; and increased intake of whole grains and legumes [21], though reduced intake of red and processed meat [45] and reduced intake of added sugars and sweets [46] are also likely of benefit.

It has been suggested that the health benefits of olive oil consumption are attributable to its bioactive polyphenols, such as tyrosol, hydroxytyrosol, and secoiridoids [47]. Tyrosol down-regulates the MAPK-ERK pathway, inhibiting cell proliferation [48], while hydroxytyrosol has been shown to downregulate markers of inflammation, such as TNF-alpha, IL-1B, and COX2 [49]. In addition to anti-inflammatory effects, these compounds also confer antioxidant effects [50]. Secoiridoids, such as oleocanthal and oleacein, also downregulate markers of inflammation; specifically, oleocanthal has been shown to downregulate COX1 and COX2, while oleacein downregulates adhesion molecules VCAM1 and ICAM1 [51]. Viewed together, these compounds, which reflect inflammation and oxidative stress have a favorable effect on cardiometabolic health.

Frequent and varied consumption of fruits, vegetables, and legumes is also foundational to the Mediterranean diet. These nutrient-rich foods provide many bioactive compounds, vitamins, minerals, fiber, and phytochemicals [52]. Many of these phytochemicals confer an anti-inflammatory effect by modulating markers of inflammation, including cytokines and prostaglandins [53]. Additionally, fruits, vegetables, and legumes enrich the diet with fiber, which has been shown to reduce CVD risk as well as risk for certain cancers, most notably colorectal cancer [54].

Red wine also contains a variety of polyphenolic compounds, including catechin, epicatechin, quercetin, and anthocyanin, but perhaps the best known among them is resveratrol. An antioxidant, resveratrol, has been associated with changes in cardiometabolic measures [55]. Resveratrol also downregulates the inflammatory response by modifying eicosanoid synthesis, preventing the synthesis of proinflammatory molecules such as COX-2 and iNOS, and inhibiting NF (kappa)B [56].

CONCLUSIONS

The Mediterranean diet pattern has been associated with reduction in the risk of several chronic diseases, including CVD, cancer, and dementia. This diet pattern has been shown to reduce both incidence and mortality from these conditions. Additionally, components of the diet provide antioxidant and anti-inflammatory compounds, which act on established disease-associated pathways.

In observational studies, findings may be confounded by other lifestyle patterns. For example, people in blue zones - areas in which a large proportion of the population lives to 100 years or more [57] - who consume a Mediterranean diet also engage in active lifestyles characterized by walking, gardening, and housecleaning; additionally, they typically eat meals with others and feel connected to friends and family [58]. Nevertheless, meta-analyses, including randomized clinical trials, overwhelmingly support this pattern as a way to prevent chronic disease and mortality.

List of Abbreviations: CHD: Coronary heart disease; CVD: Cardiovascular disease; COX1: Cyclo-oxygenase 1; COX2: Cyclo-oxygenase 2; DASH: Dietary Approaches to Stop Hypertension; EPIC: The European Prospective Investigation into Cancer and Nutrition; HbA1c: Glycated hemoglobin; HDL: High density lipoprotein cholesterol; ICAM1: Intercellular adhesion molecule 1; IL-1B: Interleukin 1 beta; INF(kappa)B: Nuclear factor kappa-light-chain-enhancer of activated B cells; iNOS: inducible isoform nitric oxide synthase; MAPK-ERK: Mitogen-activated protein kinase- Extracellular signal-regulated kinase; MI: Myocardial Infarction; MIND: Mediterranean-DASH Intervention for Neurodegenerative Delay diet; NLCS: Netherlands Cohort Study; PAD: peripheral arterial disease; PREDIMED: Primary prevention of cardiovascular disease with a Mediterranean diet; TNF-alpha: Tumor necrosis factor alpha; VCAM1: Vascular Cell Adhesion Molecule 1; WHO: World Health Organization;.

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