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Research Article – Biology

The effects of the mediterranean diet on chronic diseases: cardiovascular diseases, oxidative stress, dyslipidemia, diabetes mellitus, blood pressure, cancer, neurodegenerative disease and obesity

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Abstract

Poor dietary habits lead to the emergence of chronic diseases such as coronary heart disease, stroke, hypertension, diabetes mellitus, dyslipidemia, cancer, dementia, obesity and oxidative stress involved through the aggression of cells by free radicals, Knowing that these diseases cause a global burden both individually and economically, Several studies focus on the relationship between diet and chronic disease. Studies suggest that the Mediterranean diet, (MD) traditional eating habits and lifestyle specific to the Mediterranean region, reduce the incidence of chronic diseases and improve longevity. The MD is known to be one of the healthiest diets, this diet is based on herbs, spices, vegetables, fruits, olive oils, cereals (preferably whole grains), legumes and nuts, fish and shellfish, white meat, so the main source of dietary fat from MD is olive oil. Moderate consumption of eggs and dairy products, and reduced consumption of red meats, processed meats and foods rich in sugars and fats. MD has a beneficial fatty acid profile with a higher content of monounsaturated fatty acids (MSFA) and a higher MSFA / saturated fatty acid (SFA) ratio than non-Mediterranean diets. High consumption of dietary fiber. a low glycemic index, anti-inflammatory effects, and antioxidant compounds, can work together to produce favorable effects on health status. MD is rich in vitamins and minerals, such as: vitamin B (B1, B2, niacin, B6, folate and B12) and antioxidant vitamins (vitamins E and C), and polyphenol, flavonoids, phytosterols, n-fatty acids 3 (alpha linoleic acid), resveratrol, quercetin, oleic acid, carotenoids and lutein. The purpose of this review is to provide an update on the current state of science regarding the relationship between the traditional Mediterranean diet and lifestyle related chronic diseases, and discuss the mechanisms involved and opportunities. In this area of research, to clarify and increase the confidence of the role of nutrition in the etiology of chronic diseases.

Key words: Mediterranean diet, Chronic diseases, Cardiovascular diseases, Oxidative stress, Dyslipidemia, Diabetes mellitus, Blood pressure, Cancer, Neurodegenerative disease, Dementia and Obesity

I. Introduction

Currently, more than one in three adults (about 92.1 million) with at least one type of cardiovascular disease in the USA. [1], and cardiovascular disease (CVD) kills an estimated 17.7 million people each year, or 31% of all deaths worldwide [2]. WHO predicts that diabetes will be the seventh leading cause of death in 2030 [3] [4]. The type 2 diabetes pandemic is a huge public health problem, with 380 million cases worldwide by 2025 [5] [6] The number of people with diabetes rose from 108 million in 1980 to 422 million in 2014 [7]. The global prevalence of diabetes among adults over 18 has increased from 4.7% in 1980 to 8.5% in 2014 [7]. In 2015, 1.6 million deaths from diabetes [7], drug therapy often fails over time [8], and some drugs have cardiovascular risks [9] [10] a major cause of blindness, insufficiency kidney, heart attack, stroke and lower limb amputation [11].

About 47 million people have dementia and there are nearly 10 million new cases each year.

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[12] evidence suggesting that more than 115 million people will be affected by 2050 [13]. Dementia is a syndrome characterized by progressive global deterioration of cognitive abilities in multiple domains: memory, learning, orientation, behavior, language, comprehension and judgment, and ability to perform daily activities. Although there are several types of dementia, the most common is Alzheimer's disease (AD) [14] [15] [16] Dementia is one of the leading causes of disability and dependence worldwide. Dementia has a physical, psychological, economic and social impact on caregivers, families and society [17]. The burden of dementia, both from the disease itself and financially, is great on individuals, families, and public health services, and the efficacy of current pharmacological treatments is inconsistent [27] [28]. High cholesterol increases the risk of heart disease and stroke. Overall, one third of ischemic heart disease is attributable to high cholesterol levels. The rise in total cholesterol is a major cause of the burden of disease in developed and developing countries, as a risk factor for ischemic heart disease and stroke. In Ireland, a 30% reduction in the death rate from heart disease was attributed to a 4.6% reduction in the average population for total cholesterol. In Finland, 50% of the decline in mortality from ischemic heart disease has been explained by the reduction of blood cholesterol levels in the population [18].

Obesity, a chronic disorder whose prevalence is increasing in adults, adolescents and children, is now considered a global epidemic and a real problem for health facilities [19] [20]. In many populations, the prevalence of overweight and obesity has increased rapidly over the last 20 years. In the United States, more than 35% of adults and nearly 17% of young people were classified obese in 2009-2010 [21] and the risk of being overweight or obese was estimated at 50% and 25% respectively [22]. high health costs worldwide [23] Global obesity has almost tripled since 1975. In 2016, over 1.9 billion adults aged 18 and over were overweight. Of these, more than 650 million were obese.39% of adults 18 years and older were overweight in 2016 and 13% were obese. The majority of the world's population lives in countries where overweight and obesity kill more people than underweight. [24]. The global burden of cancer will double over the next two decades, [25] raising the prospect of a huge public health problem and, consequently, medical care. [25] [26]. The mortality attributed to chronic diseases is increasing especially among the elderly population. In parallel with bad eating habits, in addition that the population adopts more sedentary lifestyles. All of these factors contributed to the increase in chronic noncommunicable diseases [57]. Over the past three decades, various dietary strategies have been developed to promote dietary fitness and reduce the burden of chronic disease. Compared to Western eating habits,MDfavors local and seasonal food production to a greater extent. The studies have helped to find the link between MD and the risk reduction of chronic diseases such as cancer, cardiovascular disease, diabetes, dyslipidemia and neurodegenerative diseases [57].

I-1. Objectives of the review

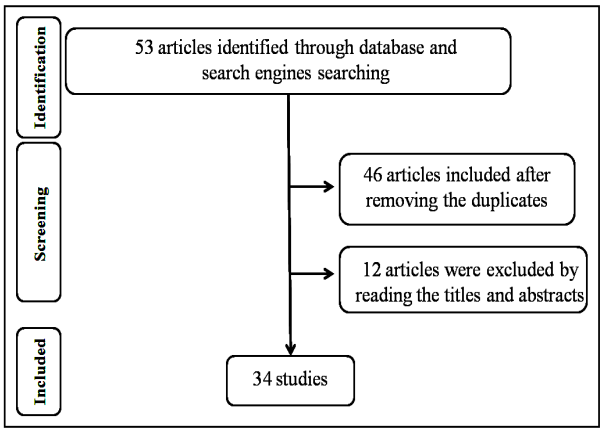
This review highlights some of the opportunities and challenges for adopting a traditional Mediterranean diet, and serves to provide an update on the current state of science regarding the relationship between the traditional Mediterranean diet and lifestyle in relation to chronic diseases, and discuss the mechanisms involved and opportunities in this area of research, to clarify and increase confidence in the role of nutrition in the etiology of chronic diseases, and thus promote aging in good health.

II. Materials and methods

II-1. Strategy of research

This review is based on bibliographic research that has been done on various databases and search engines: PubMed, Sciencedirect, Google Scholar, Cochrane Library, ClinicalTrials.gov and Psychinfo. The research was reduced to studies published in English, additional publications were identified from the references of the articles searched, and those published studies from January 1, 2008 to October 23, 2017, and which focused on Mediterranean diet and its relationship to the prevention and treatment of chronic diseases, such as: cardiovascular diseases, dyslipidemia, diabetes mellitus, hypertension,

obesity and oxidative stress and neurodegenerative diseases. Epidemiological and clinical studies were included. The main search terms with various combinations were used: "Mediterranean Diet", "Micronutrients", "Macronutrients", "Lifestyle", "Chronic Diseases", "Diabetes Mellitus", "Glucose Intolerance", "Prevention" »,« Treatment »,« Blood pressure »,« Dyslipidemia »,« Cardiovascular diseases »,« Oxidative stress »,« Neurodegenerative diseases »,« Dementia »,« Hypertension »,« Metabolic syndrome »,« Obesity »,« Clinical trials »,« Cohort »,« Cases / Witnesses ». There were 53 studies after the exclusion of duplicate studies (7 studies) and the exclusion of studies after reading the title and summary (12 studies). 34 studies were selected dealing with the Mediterranean diet and its relation to chronic diseases.



III. Results

III-1. The Mediterranean diet

MR seems to provide a balanced diet, suitable for all age groups and significantly reduces the risk of chronic disease [63]. Several studies [64] [65] have proven the cardio protective and neuro-protective roles of MD and its protective roles against metabolic disorders, certain cancers, and other age-related degenerative diseases. Several publications have highlighted the correlation between MD and longevity [66] [67]. Sofi et al. [68] [69] [70] [71] [72] have shown that greater adherence to MD is associated with a significant

Table 1: MDM compounds and their effects on health

The compound	Nutrient	Mechanism involved	Effect on health
Polyphenol [225] [226]	Vegetables and fruits, Olive oil	Antioxidant effect, and reduction of inflammation	Protector against type 2 diabetes, Protector against cardiovascular disease, Reduced risk of lung cancer,
Flavonoids [226] [227]	The fat of the seeds	Antiproliferative	Breast cancer prevention
Phytosterols [225] [228]	Soy, Vegetables	Reduces serum cholesterol, Reduces oxidative stress and inflammation	Risk reduction of cardiovascular diseases, Prevention of obesity
N-3 fatty acids (alpha linoleic acid) [225] [226]	Pisces, Flax seed, Soya oil, Walnut, Green leafy vegetables	Anti-angiogenesis, Reduces oxidative stress, Reduces aggregation of thrombocytes, Anti-lipidémiant, Antiplatelet, Anti-inflammatory, Antiarrhythmic	Stroke prevention, Protector of the cardiovascular system, Prevention of sudden deaths, Reduced risk of colon and rectal cancer,
Resveratrol [228] [226]	The fat of the seeds	Reduces aggregation of thrombocytes, Reduces serum cholesterol	Protector of the cardiovascular system
Quercetin [226]	Grape seed	Vasodilatation, Anti-aggregating effect	Anti-coagulation, Reduced risk of hypertension
Oleic acid [228] [226]	Olive oil	Inhibits HER2 which plays a role in the etiology of metastasis, Protects against, atherosclerosis	Antihypertensive effect, Reduced risk of cardiovascular disease, Reduced risk of breast cancer
Carotenoids [226]	Red, yellow and orange fruits, Vegetables, Tomato	Antioxidant	Reduced risk of lung cancer
Lutein [225] [253]	Green vegetables, Grains	Antioxidant	Reduced risk of diabetes, Reduced risk of cancer

improvement in health status, as evidenced by a significant reduction in overall mortality (9). %), mortality due to cardiovascular diseases (9%), 6%) and the incidence of Parkinson's disease and Alzheimer's disease (13%) [69] [70] [71] [72] [73]: Several studies have shown that adherence to traditional MD is associated with a significant reduction in cancer incidence, based on an examination of the different components of MD [73]. [74] thus benefits of MD related to the protective role of phenolic components, reducing daily oxidative stress, and the effects of MD in the modulation of inflammation [75].

III-1-1. Polyunsaturated fatty acids: Omega-3:

The Mediterranean diet containing several nutrients such as fish, which are rich in polyunsaturated fatty acids, omega-3, which are recommended by American Heart Association (AHA) as a cardio-protective [77] especially for patients with cardiovascular disease [76]. Thus the beneficial effects of fish include the improvement of lipid profiles [78] and the reduction of blood pressure [79] [80] through the reduction of inflammation, oxidation, and coagulation [81] [82].

III-1-2. Unsaturated fatty acids (such as olive oil):

One of the most important aspects of the Mediterranean diet is the high concentration of unsaturated fatty acids in its fiber and protein sources, coupled with a lack of saturated fat [83] [84] as well, AHA and the European Society of Cardiology (ESC) strongly support the substitution of mono- and polyunsaturated fats in place of saturated fats and trans-fatty acids [85] [77].

Extra virgin olive oil containing potent antioxidant properties, including simple and complex phenols, which are present in its phenolic compounds, mainly include: hydroxytyrosol and oleuropein which are potent antioxidants [86].

III-1-3. Fruits and vegetables

The dietary use of fruits and vegetables is considered as cornerstone of the Mediterranean diet. In fact, the European Society of Cardiology encourages the daily consumption of several servings of fruits and vegetables [77], the AHA strongly recommends the addition of a variety of phytochemicals, including fruits and vegetables in large quantities [87].

III-1-4. Fiber-rich whole grain foods

Many data suggest beneficial effects of whole grains on cardiovascular disease, morbidity and mortality, as well as AHA guidelines indicate that diets high in fiber, such as whole grains, oats and barley, reduce morbidity and mortality related to cardiovascular disease lipid-lowering, and recommends a total dietary fiber intake of 25 to 30 g per day [88]. Consumption of whole grains increases the consumption of foods high in dietary fiber to promote health [77].

Randomized control trials show significant improvements in CRP levels, cholesterol profile, and beneficial effects on body mass index and waist circumference in the randomized group consuming low calorie whole grains versus those consuming grain [89] Thus, observational studies show that the benefits go up to the improvement of glucose metabolism [90] [91] weight reduction [92], and reinforcement of antioxidant capacities [93].

III-1-5. Nuts and legumes

Replacing the consumption of carbohydrates and saturated fats with nuts, peanuts, almonds, reduces the level of blood fats and the risk of cardiovascular disease by 30% to 45% [94] [95] In addition, the increased consumption of nuts leads to a significant reduction in LDL cholesterol, inflammatory proteins and oxidative mediators [96] thus soy consumption has beneficial effects on endothelial functions [97].

III-2. Chronic diseases

The Mediterranean diet is considered a protective factor against many chronic diseases. By reducing the important risk factors and comorbidities of cardiovascular diseases, such as high blood pressure, dyslipidemia and diabetes, the cardio-protective effect provided by the Mediterranean diet could be an important route for the protective effect of the diet. the Mediterranean on cognition and dementia [98][99][101][102] RM has also been associated with a low risk of cardio-metabolic syndrome [100].

III-2-1. Cardiovascular diseases

Adherence to the traditional Mediterranean diet has always been beneficial for cardiovascular risk. [103] [104] and is considered the most likely

dietary model for providing protection against coronary heart disease. [105]. A key feature of this diet is its low trans fat content. [85] [77]. Extra virgin olive oil, the main source of fat in the RM, along with plant foods and nuts, makes this dietary diet beneficial to health as these fresh foods undergo minimal treatment. They are therefore rich in fiber, antioxidant polyphenols and essential trace elements and macronutrients. Recently, primary prevention trials have shown dietary intervention to promote adherence to traditional DM significantly reducing the risk of cardiovascular disease [106].

III-2-2. Cognitive Function and Dementia

The neuroprotective effect can be used to improve preventative measures and to critically change the way people at high risk of dementia are managed. The interactions between nutrition and the aging brain are numerous and complex, but there are 3 main features that may play a pivotal role [107]: Reduced blood flow [108], thought to be related to atherosclerosis and arterial plaque formation [108]; Mitochondrial dysfunction, resulting from the accumulation of reactive oxygen species in the brain; and inflammation, which is generally considered a natural process of aging [109]. A distinct feature of Alzheimar Disease is the accumulation of β-amyloid and the formation of neurofibrillary tangles composed of highly phosphorylated forms of microtubule-associated tau protein [107], so that β-amyloids increase the production of reactive oxygen species, which exacerbates the formation of tau entanglements as a compensatory mechanism for oxidative stress [107].

Among other benefits, adherence to MD has been associated with a lower risk of various chronic diseases [110] [111], and its protective properties are seen as a combination of high monounsaturated fatty acid consumption and polyphenols of olive oil and polyunsaturated fatty acids of fish; and antioxidants from fruits, vegetables [112].

Long-term observational studies show that MD as a diet reduces biomarkers of oxidative stress and positively affects cognition. Taking unsaturated fatty acids (both monounsaturated fatty acids and polyunsaturated fatty acids) has been associated with improved cognitive performance and decreased risk of age-related cognitive decline [113]. consumption of micronutrients such as vitamins C, E, B12 and folate [60] [61] flavonoids [62] and carotenes [61] have been associated with a decreased risk of cognitive decline and Alzheimar Disease in human observational studies. RM could reduce oxidative stress [114] and inflammation [115] associated with an increased risk of cognitive decline [116] In addition, a growing body of evidence, mainly from prospective studies, suggests that MD slows down the decline age-related cognitive and progression of dementia. A meta-analysis, also published in 2013, assessed the effects of Parkinson's disease on stroke, cognitive impairment and depression and included a total of 22 studies, including 8 on cognitive impairment [119]. High and moderate adhesion to the mediterranean diet has been shown to be associated with a reduced risk of cognitive impairment [119].

Despite the fact that the causes of dementia are multifactorial, there is growing evidence that modifiable risk factors such as cardio-metabolic diseases and lifestyle play an important role; Thus, nutrition is a key role [120] [121] [117] [118]. The typical mechanisms of aging of brain cells show signs of atrophy, most of which are related to 3 main mechanisms, as explained (above) in setting up, namely, the decline in supply flow blood and, mitochondrial dysfunction (caused by oxidative stress), increasing inflammation of the patient's brain [107]. There are several mechanisms that could explain the positive effects of MD on cognitive function. The first is the reduction of vascular risk factors and thus improving the blood circulation to the brain, so MD adherence favorably increases HDL cholesterol and reduces LDL cholesterol vascular risk [111] which is strongly correlated with cognitive dysfunction [122].

Second, MD can protect cognition through its effect on oxidative stress. MD is known to be a rich source of antioxidants such as vitamin E, vitamin C, folate, and polyphenols [123]. Epidemiological studies suggest that vitamin E is used for protection against cognitive disorders [124] and nutrients, such as folate [125]. Third, the effect MD on cognitive function can be mediated by the lowering of inflammation in the brain. MD

with the ability to reduce inflammatory biomarkers such as C-reactive protein (CRP) in neuritic plaques and nfts in the brain and serum [126] [127]. Thus diet, such as fruits, vegetables, cereals, and unsaturated fatty acids in the Mediterranean diet, is associated with a lower risk of cognitive decline [128] [129].

III-2-3. Type 2 diabetes

Diabetes prevention studies focusing on lifestyle [136] have shown strong reductions in the risk of type 2 diabetes [137] [138] in favor of this beneficial effect, the American Diabetes Association recommends that patients with newly diagnosed type 2 diabetes are being treated with lifestyle-related pharmacotherapy [139] and also recommends low-carbohydrate or low-fat diets for weight loss in overweight or obesity associated with type 2 diabetes [140] because drug therapy alone often fails over time [141], and some drugs are at risk for cardiovascular disease and other serious complications [142] [143]. For these reasons, the combination of pharmacotherapy and lifestyle changes is proving to be the most effective.

Regarding lifestyle, taking the example of the Mediterranean diet characterized by its low carbohydrate content and high proportion of monounsaturated fatty acids provide cardiovascular benefits and increase insulin sensitivity [144] [145] in addition to changes in fashion of life promote weight loss and increase activity levels, which facilitates the management of diabetes [139]. A study published by United Kingdom Prospective Diabetes Study (UKPDS) evaluating the effect of the Mediterranean diet on body weight in 190 overweight women who were followed for 2 years in a Mediterranean diet, lost weight in a significant way [146] also prospective studies have shown that Mediterranean dietary habits are associated with reduced risk of type 2 diabetes, in healthy participants [147]. Trials have shown that Mediterranean diets protect against insulin resistance and metabolic syndrome, thus, a mechanism through which Mediterranean diets can improve glycemic control may be through improved insulin sensitivity mediated increased levels of circulating adiponectin [144] [148] [174].

III-2-4. The arterial pressure

According to the medical diagnosis based on the guidelines of the National Mixed Committee [152] hypertension is defined as an increase in blood pressure; systolic beyond 140 mmHg or diastolic blood pressure greater than 90 mmHg [152]. High blood pressure is a major risk factor for cardiovascular disease and is independent of other factors [31]. Therefore, from the point of view of public health, it is urgent to find ways to fight this disease.

The Mediterranean diet is of the utmost importance in the prevention and treatment of hypertension [149] and the reduction of its complications such as cardiovascular disease and stroke. In fact, several publications reporting results of clinical studies that confirm the protective role of the Mediterranean diet vis-à-vis systolic blood pressure both systolic and diastolic [150]. Thus a study by Beitz R, et al. showed a systolic blood pressure drop of 3.0 mmHg in women who consumed a high amount of fruit, vegetables or vitamin C [153]. also, a prospective cohort study has shown that consumption of fruits and vegetables is inversely associated with blood pressure in the population of the Mediterranean basin with a high intake of vegetable fats [154].

III-2-5. Obesity

Obesity predisposes to a number of conditions, including cardiovascular diseases [155] [156], type 2 diabetes [157] [158], metabolic syndrome [159], non-alcoholic fatty liver disease [160], certain types of cancer [161] [162], obstructive sleep apnea [163], osteoarthritis [164] and asthma [165] and increases the risk of premature death [166], resulting in health costs raised all over the world [23]. Factors predisposing to obesity include excessive food intake, lack of physical activity, and genetic susceptibility [167]. However, obesity is a heterogeneous condition and thus intra-abdominal adipose tissue accumulation has a greater impact on the development of cardio-metabolic risk factors and significant lipid profile effects [168]. The increased availability of free fatty acids, the release of pro-inflammatory cytokines and adipokines from adipose tissue, hepatic insulin resistance, inflammation, and the resulting dyslipidemia are among the many metabolic disorders associated with this affection,

also hormonal status and drug treatments may also play an important role [169]. Low-calorie diet is still the main and essential step in the treatment of obesity, associated with increased physical activity and lifestyle changes [170].

RM is the most common tool for weight reduction in obese individuals [171]. Even moderate weight loss of about 10% or less has been shown to contribute to several health benefits including improved metabolic parameters, reduced blood pressure, and increased longevity [172] [173]. evidence that calorie restriction improves insulin sensitivity and reduces systemic inflammation [174] [175]. Several studies have shown the benefits of the Mediterranean diet for weight loss in obese patients, by evaluating physical and biochemical markers after at least 6 months after adherence to theMD[176] [177] [178]. Mediterranean diet has been shown to be associated with greater improvement in insulin sensitivity parameters [176].

Adipose tissue is an endocrine organ with a large and biologically active secretome [180] [181] and fat tissue in obese individuals is characterized by increased expression and / or secretion of several pro-inflammatory cytokines. as well as adipokine to promote inflammation, atherogenesis and insulin resistance, while the biosynthesis of anti-inflammatory, anti-atherogenic and insulin-sensitizing adipokines such as adiponectin decreases [182] [183] Several studies have shown an increase in circulating levels of leptin and an increase in adiposity associated with leptin resistance and that this condition may contribute to the onset and / or maintenance of obesity [184].] [185] One study shows decreased circulating levels of Epidermal Growth Factor (EGF) after introduction of the Mediterranean diet in obese subjects in parallel with an improvement in insulin sensitivity. [190]. During fasting, salivary and plasma EGF increases physiologically [191] to inhibit gastric acid secretion and preserve the esophageal and gastrointestinal system (as a sign of intestinal adaptation to food). Increased EGF may result in insulin-like biological activities in tissues expressing high numbers of EGFR receptors (EGFR), such as fat and skeletal muscle [192]. By binding to EGFR, a receptor belonging to the family of tyrosine kinase receptors, such as the insulin receptor [201], EGF can amplify downstream signaling of insulin by PI3-kinase recruitment. additional, leading to EGF-induced translocation of GLUT4 on plasma membranes and stimulation of glucose uptake into target tissues [192]. These molecular mechanisms are important in insulin resistance states, including obesity, in which the increase in EGF due to dietary restriction can trigger insulin-like compensatory mechanisms, so insulin regulates expression of EGF [193]. This explains the parallel decrease in insulin and EGF in patients with more constant weight loss, in which insulin sensitivity has been improved or restored [193].

Lactate Dehydrogenase (LDH) is an intracellular enzyme that is released into the bloodstream when tissues are destroyed or injured. Therefore, LDH is an important clinical marker of tissue or cell integrity. In obese patients, adipose tissue is dysfunctional [194] [195] has a reduced ability to store and retain non-esterified fatty acids (NEFA), resulting in increased circulating levels of AGNE, thereby promoting the development of lipotoxicity in peripheral tissues [196].

III-2-6. Cancer

Tobacco control, reduction of excessive alcohol consumption, vaccination against human papillomavirus and reduced exposure to ultraviolet light are obvious strategies for reducing cancer incidence rates [197] [198]. As citing the World Cancer Research Fund (WCRF) such examples; Aflatoxins with liver cancer, red meat and / or processed meat with colorectal cancer, alcohol with cancers of the gastrointestinal tract, and, for smokers, β-carotene increases the risk of lung cancer [199] [200].

Guidelines proposed by WCRF and recommendations on nutrition and physical activity for cancer prevention [202] [203]. have been consistent with those aimed at preventing other chronic diseases, such as diabetes and heart disease [203] [204] [205], which raises the prospect of a huge public health problem and, therefore, medical care. [204] [205]. Both the aging of the population and changes in the distribution of risk factors contribute to the increased burden of cancer [25] [26] nutrition and

physical activity are also among the most important determinants cancer risk in humans, through their contributions to obesity, which is a risk factor for many malignancies [199] [206].

III-2-7. Oxidative stress

MR reduces oxidative stress [114] and C-reactive protein and interleukins involved in the mechanisms of oxidative stress leading to chronic pathophysiology [132] [133]. The neuroprotective effects of the Mediterranean diet are related to its ability to reduce inflammation and oxidative stress, which are also related to the pathophysiology of degenerative diseases [134] [135] adherence to RM, with higher consumption of fruit and vegetable rich in phytochemicals, demonstrates an increase in endogenous and exogenous antioxidant levels, enhancing immunity and protecting the selected sample against oxidative stress and maintaining a healthy state. Thus vegetable consumption has been closely associated with a low risk of degenerative diseases [241] [242]. Eating habits can play a key role in regulating the redox state of human plasma improving defense against oxidation. [245] [246, 247, 249]. The Mediterranean diet is associated with a significant reduction in several risk factors, including cardiovascular risk [250, 251, 252].

III-2-8. Cholesterol and oxidative stress

The bioavailable quantity of bioactive molecules in subjects with high consumption of fruits and vegetables promotes their protective and preventive action against lipid oxidation and therefore against oxidative stress [233]. Also, the influence of the rate Plasma cholesterol on the atherosclerotic process and the effects of diet-induced cholesterol influence the progression and development of cardiovascular disease [235]. Several researchers have also suggested that diets have a significant effect on the mechanisms of progression of atherosclerosis and thrombosis [236, 237].

Numerous studies have demonstrated the inhibitory activity of several compounds present in fruits and vegetables on the oxidation of LDL in vitro [238, 239]. Thus, interesting results seem to highlight the circulating levels of carotenoids (lutein, zeaxanthin, cryptoxanthin, lycopene, a and b-carotene), vitamin A and vitamin E have reached the highest values in subjects with a higher great adherence to the Mediterranean diet [238, 239]. Several studies show that vitamin A reduces the production of pro-inflammatory cytokines such as TNF-a and IL-12 and promotes the activation of lymphocyte subpopulations through the secretion of specific cytokines (eg IL-10). , [240], thus the phytochemical components of fruits and vegetables consist of different phytochemicals beneficial to the systemic circulation, thus absorbed antioxidants reach the large intestine and contribute to the protection against gastrointestinal diseases induced by oxidation [243, 244].

III-2-9. Dietary recommendations

The guidelines and recommendations published in several reports to maintain body weight within the normal range [199, 218]. The equivalent of 60 minutes of exercise per day to be physically active; consume a plant-based diet comprising a variety of fruits and vegetables; choose unprocessed cereals and grains over processed products; limit the intake of red meat and salt; avoid or limit alcohol consumption, to meet nutritional needs without the use of food supplements [218] avoid energy-rich foods, sugary drinks, fast foods and processed meat, and genetically modified foods modified to increase certain types of cancer (such as colorectal cancer) by modification in the nucleic acids thus causing changes in enzymatic activity [219, 220, 223, 224].

IV. Discussion

Adopting a healthy lifestyle is the cornerstone of chronic disease prevention and treatment, and healthy eating is a major lifestyle change. Various studies show that dietary treatment is most effective for reducing the average body weight of people suffering from overweight or obesity, and a statistically significant reduction in BMI, and thus showing beneficial effects on health [172, 173, 179].

The traditional MD is a plant-based diet, where vegetables, fruits, cereals (preferably whole grains), legumes and nuts, fish and shellfish, white meat is consumed in large quantities and frequently. The main source of dietary fat in MD is olive oil and adequate daily water intake must be ensured. The Mediterranean diet also includes a moderate consumption of eggs and dairy products,

on the contrary, the consumption of red meats, processed meats and foods rich in sugars and fats is reduced in quantity and frequency. Seasonality, biodiversity, the use of traditional and local food products are also important elements of this trend. In addition, the Mediterranean diet also includes qualitative cultural and living elements, such as conviviality, culinary activities, physical activity and adequate rest [40]. Thus MD is known as one of the healthiest diets [39].

The critical importance of food and nutrition in cancer prevention is widely recognized, due to an impressive amount of data from epidemiological, clinical and laboratory research [199]. So, the issues of diet and cancer and the problems of diet, nutrition and cancer come from different types of research, including animal and mechanical studies, ecological studies in humans (correlation studies at the level of population, useful for generating hypotheses), observational analytical epidemiology studies (ie, case-control and cohort studies) and dietary intervention trials. In laboratory studies using cell cultures and experimental animal models, nutrients and other bioactive food components have been shown to affect key biological processes involved in the regulation of cell growth and carcinogenesis. Foods are naturally complex and provide many bioactive substances that can act individually and / or synergistically to influence processes such as cell differentiation and apoptosis, as well as the hormonal regulation of cellular functions. Hypocaloric diet is still the main and essential step in the treatment of obesity, associated with increased physical activity and lifestyle changes [170] Also, the dose-response relationship: For example, squamous cell carcinoma of the esophagus is very different from esophageal adenocarcinoma: the former is more strongly related to smoking and alcohol consumption in Western populations [207] [208], or human papillomavirus (HPV) infection in other populations, such as those in China [209] [210]; the latter is more closely associated with obesity and / or reflux disease [211]. In addition, the dietary factors associated with these two cancers have some overlap, but are also quite distinct [212] [213]. Similarly, an analysis of the NIH-AARP study on diet and health [214] pointed out that the high risk of endometrial cancer in obese compared to non-obese women was higher for subtypes. Type I tumors (endometrioid). With respect to nutrients, increased consumption of phytoestrogens was associated with a reduced risk of mucinous ovarian cancer, but no other subtypes of ovarian cancer, in the Australian ovarian cancer [215]. For example, in the large-scale long-term pooling of prospective studies on diet and cancer [212, 213], a protective effect of fruit and vegetable consumption on esophageal breast cancer (ER) Negative but not breast cancer has been consistently demonstrated in 20 studies [216, 217]. Several factors and their interactions, namely tobacco, dietary protein, and alcohol [221] increase the risk of cancer of various types of cancer [221] and exposures experienced by a person during his life including: metabolism, hormones, body composition, physical activity, gut microbiome, inflammation, oxidative stress, aging, diet, and alcohol, and broader psychosocial and environmental [222].

Bacteria can either promote or suppress cell growth and metastasis through bacterial toxins induced by the secretion of bacterial proteins leading to changes in gene expression, altering the tumor (inflammation, immune functions , or by altering host metabolism [229], and by promoting the production of endogenous factors that cause carcinogenesis (such as bile acids and steroid hormones) [230], and since diet influences both the type and the number of intestinal microorganisms [230] [231] the microbiome in the development of cancer, including host genome interactions with microbiota [232]. Thus, one of the main intermediate step in the the link between diet and cancer remain in research, and require technologies in the prevention and development of cancer to provide u ideas and data relevant to the relationship between food intake and cancer risk and progression.

The total antioxidant capacity of biological samples can also be evaluated in clinical studies that measure the end products of degradation of endogenous compounds such as lipids or DNA. Changes from baseline levels of these products could then be attributed to changes in the antioxidant capacity of the diet, so the antioxidant capacity of the biological samples can be controlled by a variety of tests, which do not

necessarily reflect the physiological mechanisms in humans vivo [248].

Several studies describe insulin and leptin resistance in obese subjects. The relationships between these two hormones are complex and poorly understood, and there is evidence that they are associated with body fat through different mechanisms [186, 187]. Other studies with comparable or even larger samples had similar results and found a statistically significant decrease in leptin levels and not adiponectin in weight loss [188] [189]. Several nutrients characterize MD and protect against various chronic diseases, such as olive oil, and prospective studies have shown that olive oil significantly improves cognitive function [130, 131].

V. Conclusion

The traditional Mediterranean diet has a protective effect against cardiovascular diseases, oxidative stress, dyslipidemia, diabetes mellitus, blood pressure, cancer, neurodegenerative diseases and obesity, this protective effect of the Mediterranean diet is provided by antioxidants, anti-inflammatories and bioactive components of foods characteristic of the Mediterranean basin, reducing the risk of development of chronic diseases.

References

[1] Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. Circulation. 2017;135:e1–e458.

[2]www.who.int/entity/cardiovascular_diseases/world-heart-day-2017/en

[3] Projections of global mortality and burden of disease from 2002 to 2030. Mathers CD, Loncar D. PLoS Med, 2006, 3(11):e442.

[4]www.who.int/entity/mediacentre/factsheets/fs312/en

[5] Hossain P, Kawar B, El Nahas M. Obesity and diabetes in the developingworld—a growing challenge. N Engl J Med. 2007;356:213-5.

[6] International Diabetes Federation. Diabetes Atlas. 3rd ed. Brussels: International Diabetes Federation; 2006.

[7] Projections of global mortality and burden of disease from 2002 to 2030. Mathers CD, Loncar D. PLoS Med, 2006, 3(11):e442.

[8] Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control withdiet, sulfonylurea, metformin, or insulin in patients with type 2 diabetesmellitus: progressive requirement for multiple therapies (UKPDS 49). UKProspective Diabetes Study (UKPDS) Group. JAMA. 1999;281:2005-12.

[9] Goldfine AB. Assessing the cardiovascular safety of diabetes therapies. N EnglJ Med. 2008;359:1092-5.

[10] Havas S. The ACCORD Trial and control of blood glucose level in type 2diabetes mellitus: time to challenge conventional wisdom. Arch Intern Med.2009;169:150-4.

[11]www.who.int/entity/mediacentre/factsheets/fs312/en

[12]www.who.int/entity/mediacentre/factsheets/fs362/en

[13] Alzheimer's SocietyAlzheimer's Society online information—Aboutdementia—What is dementia? Leading the fight against Dementia [Internet].2014 [cited 2016 Mar 30]. Available from:http://www.alzheimers.org.uk/site/scripts/documents.php? categoryID=200360.

[14] Gill SS, Seitz D. Lifestyles and cognitive health. What older individualscan do to optimize cognitive outcomes. JAMA 2015;314:774–5.

[15] Alzheimer's SocietyAlzheimer's Society online information—Aboutdementia—What is dementia? Leading the fight against Dementia [Internet].2014 [cited 2016 Mar 30]. Available from:http://www.alzheimers.org.uk/site/scripts/documents.php?categoryID=200360.

[16] www.who.int/entity/mediacentre/factsheets/fs362/en

[17]www.who.int/entity/mediacentre/factsheets/fs362/en

[18]http://www.who.int/gho/ncd/risk_factors/cholesterol_text/en

[19] World Health Organization, "Obesity: preventing and managingthe global epidemic,"

WHO Technical Report 894, WorldHealth Organization, Geneva. Switzerland, 2000.

[20] C. L. Ogden, M. M. Lamb, M. D. Carroll, and K. M. Flegal,"Prevalence of Obesity in the United States, 2009-2010," NCHSData Brief, vol. 82, pp. 1–8, 2012.

[21] C. L. Ogden, M. D. Carroll, L. R. Curtin,M.M. Lamb, and K.M. Flegal, "Prevalence of high body mass index in US childrenand adolescents, 2007-2008," Journal of the American MedicalAssociation, vol. 303, no. 3, pp. 242–249, 2010.

[22] R. S. Vasan, M. J. Pencina, M. Cobain, M. S. Freiberg, and R.B. D'Agostino, "Estimated risks for developing obesity in theFraminghamHeart Study," Annals of Internal Medicine, vol. 143,no. 7, pp. 473–I12, 2005.

[23] D. Withrow and D. A. Alter, "The economic burden of obesityworldwide: a systematic review of the direct costs of obesity,"Obesity Reviews, vol. 12, no. 2, pp. 131–141, 2011.

[24]http://www.who.int/mediacentre/factsheets/fs311/en

[25] Vineis, P. & Wild, C. P. Global cancer patterns: causesand prevention. Lancet 383, 549–557 (2014).

[26] Siegel, R., Ma, J., Zou, Z. & Jemal, A. Cancer statistics,2014. CA Cancer J. Clin. 64, 9–29 (2014).

[27] Tricco AC, Soobiah C, Berliner S, Ho JM, Ng CH, Ashoor HM, ChenMH, Hemmelgarn BSS. Efficacy and safety of cognitive enhancers for patients with mild cognitive impairment: a systematic review andmeta-analysis. CMAJ 2013;185:1393–401.

[28] Tan CC, Yu JT, Wang HF, Tan MS, Meng XF, Wang C, Jiang T, Zhu XC,Tan L. Efficacy and safety of donepezil, galantamine, rivastigmine, andmemantine for the treatment of Alzheimer's disease: a systematic reviewand meta-analysis. J Alzheimers Dis 2014;41:615–31.

[29] C.K. Chow, K.K. Teo, S. Rangarajan, S. Islam, R. Gupta, A. Avezum, et al. Prevalence, awareness, treatment, and control of hypertension in rural and urban communities in high-, middle-, and low-income countries. JAMA, 310 (2013), pp. 959-968.

[30] S.S. Lim, T. Vos, A.D. Flaxman, G. Danaei, K. Shibuya, H. Adair-Rohani, M. Amann, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010 Lancet, 380 (2012), pp. 2224-2260.

[31] Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, JonesDW, Materson BJ, Oparil S, Wright JT Jr, et al: The Seventh Report of theJoint National Committee on Prevention, Detection, Evaluation, andTreatment of High Blood Pressure: the JNC 7 report. JAMA 2003,289(19):2560–2572.

[32] Lawes CM, Vander Hoorn S, Rodgers A: Global burden of blood-pressure-relateddisease, 2001. Lancet 2008, 371(9623):1513–1518.

[33] Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ: Global andregional burden of disease and risk factors, 2001: systematic analysis ofpopulation health data. Lancet 2006, 367(9524):1747–1757.

[34] Chow CK, Teo KK, Rangarajan S, Islam S, Gupta R, Avezum A, et al. Prevalence,awareness, treatment, and control of hypertension in rural and urbancommunities in high-, middle-, and low-income countries. JAMA2013;310:959–68.

[35] World Health Organization. Global status report on noncommunicablediseases 2010. Geneva: World Health Organization; 2011.

[36] P.W. Wilson. Established risk factors and coronary artery disease: the Framingham Study Am J Hypertens, 7 (1994), pp. 7S-12S.

[37] J.A. Staessen, R. Fagard, L. Thijs, H. Celis, G.G. Arabidze, W.H. Birkenhäger, et al. Randomized double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators Lancet, 350 (1997), pp. 757-764.

[38] J. Coresh, G.L. Wei, G. McQuillan, F.L. Brancati, A.S. Levey, C. Jones, et al. Prevalence of high blood pressure and elevated serum

creatinine level in the United States: findings from the third National Health and Nutrition Examination Survey (1988–1994). Arch Intern Med, 161 (2001), pp. 1207-1216.

[39] Willett, W.C.; Sacks, F.; Trichopoulou, A.; Drescher, G.; Ferro-Luzzi, A.; Helsing, E.;Trichopoulos, D. Mediterranean diet pyramid: A cultural model for healthy eating. Am. J.Clin. Nutr. 1995, 61, 1402–1406.

[40] Bach-Faig, A.; Berry, E.M.; Lairon, D.; Reguant, J.; Trichopoulou, A.; Dernini, S.; Medina, F.X.;Battino, M.; Belahsen, R.; Miranda, G.; et al. Mediterranean diet foundation expert group.Mediterranean diet pyramid today. Science and cultural updates. Public Health Nutr. 2011, 14,2274–2784.

[41] Bos, M.B.; de Vries, J.H.; Feskens, E.J.; van Dijk, S.J.; Hoelen, D.W.; Siebelink, E.; Heijligenberg, R.;de Groot, L.C. Effect of a high monounsaturated fatty acids diet and a Mediterranean diet on serumlipids and insulin sensitivity in adults with mild abdominal obesity. Nutr. Metab. Cardiovasc. Dis.2010, 20, 591–598.

[42] Serra-Majem, L.; Bes-Rastrollo, M.; Román-Viñas, B.; Pfrimer, K.; Sánchez-Villegas, A.;Martínez-González, M.A. Dietary patterns and nutritional adequacy in a Mediterranean country.Br. J. Nutr. 2009, 101, 21–28.

[43] Estruch, R.; Martínez-González, M.A.; Corella, D.; Basora-Gallisá, J.; Ruiz-Gutiérrez, V.;Covas, M.I.; Fiol, M.; Gómez-Gracia, E.; López-Sabater, M.C.; Escoda, R.; et al. Effects of dietary fibre intake on risk factors for cardiovascular disease in subjects at high risk. J. Epidemiol.Community Health 2009, 63, 582–588.

[44] Rodríguez-Rejón, A.I.; Castro-Quezada, I.; Ruano-Rodríguez, C.; Ruiz-López, M.D.;Sánchez-Villegas, A.; Toledo, E.; Artacho, R.; Estruch, R.; Salas-Salvadó, J.; Covas, M.I.; et al.Effect of a Mediterranean diet intervention on dietary glycemic index and dietary glycemic load:The PREDIMED study. J. Nutr. Educ. Behav., submitted for publication, 2013.

[45] : Estruch, R.; Martínez-González, M.A.; Corella, D.; Salas-Salvadó, J.; Ruiz-Gutiérrez, V.;Covas, M.I.; Fiol, M.; Gómez-Gracia, E.; López-Sabater, M.C.; Vinyoles, E.; et al. Effects of aMediterranean-style diet on cardiovascular risk factors: A randomized trial. Ann. Intern. Med.2006, 145, 1–11.

[46] Visioli, F.; Galli, C. The role of antioxidants in the Mediterranean diet. Lipids 2001, 36, 49–52.

[47] Pitsavos, C.; Panagiotakos, D.B.; Tzima, N.; Chrysohoou, C.; Economou, M.; Zampelas, A.;Stefanadis, C. Adherence to the Mediterranean diet is associated with total antioxidant capacity inhealthy adults: The ATTICA study. Am. J. Clin. Nutr. 2005, 82, 694–699.

[48] Sofi, F.; Abbate, R.; Gensini, G.F.; Casini, A. Accruing evidence on benefits of adherence to theMediterranean diet on health: An updated systematic review and meta-analysis. Am. J. Clin. Nutr.2010, 92, 1189–1196.

[49] Mitrou, P.N.; Kipnis, V.; Thiébaut, A.C.; Reedy, J.; Subar, A.F.; Wirfält, E.; Flood, A.; Mouw, T.;Hollenbeck, A.R.; Leitzmann, M.F.; et al. Mediterranean dietary pattern and prediction ofall-cause mortality in a US population: Results from the NIH-AARP Diet and Health Study.Arch. Intern. Med. 2007, 167, 2461–2468.

[50] Estruch, R.; Ros, E.; Salas-Salvadó, J.; Covas, M.I.; Corella, D.; Arós, F.; Gómez-Gracia, E.;Ruiz-Gutiérrez, V.; Fiol, M.; Lapetra, J.; et al. Primary prevention of cardiovascular disease with aMediterranean diet. N. Engl. J. Med. 2013, 368, 1279–1290.

[51] : Salas-Salvadó, J.; Bulló, M.; Estruch, R.; Ros, E.; Covas, M.I.; Ibarrola-Jurado, N.; Corella, D.;Arós, F.; Gomez-Gracia, E.; Ruiz-Gutiérrez, V.; et al. Prevention of diabetes with Mediterranean diets a subgroup analysis of a randomized trial. Ann. Intern. Med. 2013, 160, 1–10.

[52] Couto, E.; Boffetta, P.; Lagiou, P.; Ferrari, P.; Buckland, G.; Overvad, K.; Dahm, C.C.; Tjønneland, A.;Olsen, A.; Clavel-Chapelon, F.; et al. Mediterranean dietary pattern and cancer risk in the EPICcohort. Br. J. Cancer 2011, 104, 1493–1499.

[53] Sofi, F.; Abbate, R.; Gensini, G.F.; Casini, A. Accruing evidence on benefits of adherence to theMediterranean diet on health: An updated systematic review and meta-analysis. Am. J. Clin. Nutr.2010, 92, 1189–1196.

[54] Sofi, F.; Macchi, C.; Abbate, R.; Gensini, G.F.; Casini, A. Mediterranean diet and health.Biofactors 2013, 39, 335–342.

[55] Serra-Majem, L.; Ribas, L.; Ngo, J.; Aranceta, J.; Garaulet, M.; Carazo, E.; Mataix, J.;Pérez-Rodrigo, C.; Quemada, M.; Tojo, R.; et al. Risk of inadequate intake of vitamins A, B1, B6,C, E, folate, iron and calcium in the Spanish population aged 4 to 18. Int. J. Vitam. Nutr. Res. 2001,71, 325–331.

[56] Serra-Majem, L.; Ribas, L.; Pérez-Rodrigo, C.; García-Closas, R.; Peña-Quintana, L.; Aranceta, J.Factors associated to nutrient intake among children and adolescents: Results from the EnKidstudy. Ann. Nutr. Metab. 2002, 46, 31–38.

[57] Romagnolo DF, Selmin OI. Mediterranean Diet and Lifestyle ina Modern World Context. In: Mediterranean Diet. DietaryGuidelines and Impact on Health and Disease. AG Switzerland:Springer International Publishing; 2016:15Y26.

[58] Willett WC, Sacks F, Trichopoulou A,et al. Mediterranean diet pyramid: a culturalmodel for healthy eating. Am J ClinNutr 1995;61:Suppl:1402S-1406S.

[59] Bach-Faig A, Berry EM, Lairon D, Reguant J, Trichopoulou A, DerniniS, Medina FX, Battino M, Belahsen R, Miranda G, et al. Mediterraneandiet pyramid today. Science and cultural updates. Public Health Nutr2011;14 12A:2274–84.

[60] Engelhart MJ, Geerlings MI, Ruitenberg A, van Swieten JC, Hofman A,Witteman JCM, Breteler MMB. Dietary intake of antioxidants and riskof Alzheimer disease. JAMA 2002;287:3223–9.

[61] Li FJ, Shen L, Ji HF. Dietary intakes of vitamin E, vitamin C, and betacaroteneand risk of Alzheimer's disease: a meta-analysis. J AlzheimersDis 2012;31:253–8.

[62] Letenneur L, Proust-Lima C, Le Gouge A, Dartigues JF, Barberger-Gateau P. Flavonoid intake and cognitive decline over a 10-year period.Am J Epidemiol 2007;165:1364–71.

[63] WHO/FAO: Diet, nutrition and the prevention of chronic diseases. Tech.Rep. no. 916, Geneva, Switzerland 2003.

[64] Esposito K, Giugliano D: Diet and inflammation: a link to metabolic andcardiovascular diseases. European Heart Journal 2006, 27(1):15-20.

[65] di Giuseppe R, Bonanni A, Olivieri M, Di Castelnuovo A, Donati MB, deGaetano G, Cerletti C, Iacoviello L: Adherence to Mediterranean diet and anthropometric and metabolic parameters in an observational study inthe 'Alto Molise' region: the MOLI-SAL project. Nutr Metab Cardiovasc Dis2008, 18(6):415-21.

[66] Trichopoulou A, Vasilopoulou E: Mediterranean diet and longevity. Br JNutr 2000, 84(2):S205-S209. [67] Pérez-López FR, Chedraui P, Haya J, Cuadros JL: Effects of theMediterranean diet on longevity and age-related morbid conditions.Maturitas 2009, 64:67-79.

[68] Sofi F, Cesari F, Abbate R, Gensini GF, Casini A: Adherence toMediterranean diet and health status: meta-analysis. BMJ 2008,337:1344.

[69] Van de Rest, O., Berendsen, A. A., Haveman-Nies, A. & de Groot, L. C. Dietary patterns, cognitive decline, and dementia: asystematic review. Adv Nutr. 6, 154–168 (2015).

[70] Lourida, I. et al. Mediterranean diet, cognitive function, and dementia: a systematic review. Epidemiology. 24, 479–489 (2013).

[71] Singh, B. et al. Association of Mediterranean diet with mild cognitive impairment and Alzheimer's disease: a systematic review andmeta-analysis. J Alzheimers Dis. 39, 271–282 (2014).

[72] Psaltopoulou, T. et al. Mediterranean diet, stroke, cognitive impairment, and depression: A meta-analysis. Ann Neurol. 74, 580–591(2013).

[73] Benetou V, Trichopoulou A, Orfanos P, Naska A, Lagiou P, Boffetta P,Trichopoulos D: Conformity to traditional Mediterranean diet and cancer incidence: the Greek EPIC cohort. Br J Cancer 2008, 99:191-195.

[74] Bogani P, Galli C, Villa M, Visioli F: Postprandial anti-inflammatory andantioxidant effects of extra virgin olive oil. Atherosclerosis 2007,190(1):181-186.

[75] Giugliano D, Ceriello A, Esposito K: The effects of diet on inflammation.Emphasis on the metabolic syndrome. J Am Coll Card 2006, 48(4):677-685.

[76] Kris-Etherton P, Harris WS, Appel LJ, American Heart Association; Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation. 2002; 106(21):2747–57.

[77] Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R, Dallongeville J, De Backer G, Ebrahim S, Gjelsvik B, Herrmann-Lingen C, Hoes A, Humphries S, Knapton M, Perk J, Priori SG, Pyorala K, Reiner Z, Ruilope L, Sans-Menendez S, Scholte op Reimer W, Weissberg P, Wood D, Yarnell J, Zamorano JL, Walma E, Fitzgerald T, Cooney MT, Dudina A, European Society of Cardiology (ESC) Committee for Practice Guidelines (CPG). European guidelines on cardiovascular disease prevention in clinical practice: executive summary: Fourth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by representatives of nine societies and by invited experts). Eur Heart J. 2007; 28(19):2375–414. [PubMed: 17726041]

[78] Balk E, Lichtenstein AH, Chung M, Kupelnick B, Chew P, Lau J. Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: a systematic review. Atherosclerosis. 2006; 189(1):19–30.

[79] Appel L, Miller ER 3rd, Seidler AJ, Whelton PK. Does supplementation of diet with 'fish oil' reduce blood pressure? A meta-analysis of controlled clinical trials. Arch Intern Med. 1993; 153(12):1429–38.

[80] Morris M, Sacks F, Rosner B. Does fish oil lower blood pressure? A meta-analysis of controlled trials. Circulation. 1993; 88(2):523–33.

[81] Calder P. n-3 Fatty acids and cardiovascular disease: evidence explained and mechanisms explored. Clin Sci (Lond). 2004; 107(1):1–11. [PubMed: 15132735]

[82] Harris W, Miller M, Tighe AP, Davidson MH, Schaefer EJ. Omega-3 fatty acids and coronary heart disease risk: Clinical and mechanistic perspectives. Atherosclerosis. 2008; 197:12–24.

[83] Howard B, Van Horn L, Hsia J, Manson JE, Stefanick ML, Wassertheil-Smoller S, Kuller LH, LaCroix AZ, Langer RD, Lasser NL, Lewis CE, Limacher MC, Margolis KL, Mysiw WJ, Ockene JK, Parker LM, Perri MG, Phillips L, Prentice RL, Robbins J, Rossouw JE, Sarto GE, Schatz IJ, Snetselaar LG, Stevens VJ, Tinker LF, Trevisan M, Vitolins MZ, Anderson GL, Assaf AR, Bassford T, Beresford SA, Black HR, Brunner RL, Brzyski RG, Caan B, Chlebowski RT, Gass M, Granek I, Greenland P, Hays J, Heber D, Heiss G, Hendrix SL, Hubbell FA, Johnson KC, Kotchen JM. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA. 2006; 295(6):655–66.

[84] Hu F, Stampfer MJ, Manson JE, Rimm E, Colditz GA, Rosner BA, Hennekens CH, Willett WC. Dietary fat intake and the risk of coronary heart disease in women. N Engl J Med. 1997; 337(21):1491–9.

[85] Lichtenstein A, Appel LJ, Brands M, Carnethon M, Daniels S, Franch HA, Franklin B, Kris-Etherton P, Harris WS, Howard B, Karanja N, Lefevre M, Rudel L, Sacks F, Van Horn L, Winston M, Wylie-Rosett J, American Heart Association Nutrition Committee. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. Circulation. 2006; 114(1):82–96.

[86] Fuhrman B, Aviram M. Flavonoids protect LDL from oxidation and attenuate atherosclerosis. Curr Opin Lipidol. 2001; 12(1):41–8.

[87] Howard B, Kritchevsky D. Phytochemicals and cardiovascular disease. A statement for healthcare professionals from the American Heart Association. Circulation. 1997; 95(11):2591–3.

[88] Van Horn L. Fiber, lipids, and coronary heart disease. A statement for healthcare professionals from the Nutrition Committee, American Heart Association. Circulation. 1997; 95(12):2701–4.

[89] Katcher H, Legro RS, Kunselman AR, Gillies PJ, Demers LM, Bagshaw DM, Kris-Etherton PM. The effects of a whole grain-enriched hypocaloric

diet on cardiovascular disease risk factors in men and women with metabolic syndrome. Am J Clin Nutr. 2008; 87(1):79–90.

[90] Jenkins D, Wesson V, Wolever TM, Jenkins AL, Kalmusky J, Guidici S, Csima A, Josse RG, Wong GS. Wholemeal versus wholegrain breads: proportion of whole or cracked grain and the glycaemic response. BMJ. 1988; 297(6654):958–60.

[91] Tarini J, Wolever TM. The fermentable fibre inulin increases postprandial serum short-chain fatty acids and reduces free-fatty acids and ghrelin in healthy subjects. Appl Physiol Nutr Metab. 2010; 35(1):9–16.

[92] Good C, Holschuh N, Albertson AM, Eldridge AL. Whole grain consumption and body mass index in adult women: an analysis of NHANES 1999-2000 and the USDA pyramid servings database. J Am Coll Nutr. 2008; 27(1):80–7.

[93] Adom K, Liu RH. Antioxidant activity of grains. J Agric Food Chem. 2002; 50(21):6182–7.

[94] Hu F, Manson JE, Willett WC. Types of dietary fat and risk of coronary heart disease: a critical review. J Am Coll Nutr. 2001; 20(1):5–19.

[95] Hu F, Stampfer MJ. Nut consumption and risk of coronary heart disease: a review of epidemiologic evidence. Curr Atheroscler Rep. 1999; 1(3):204–9.

[96] Banel D, Hu FB. Effects of walnut consumption on blood lipids and other cardiovascular risk factors: a meta-analysis and systematic review. Am J Clin Nutr. 2009; 90(1):56–63.

[97] Li S, Liu XX, Bai YY, Wang XJ, Sun K, Chen JZ, Hui RT. Effect of oral isoflavone supplementation on vascular endothelial function in postmenopausal women: a meta-analysis of randomized placebo-controlled trials. Am J Clin Nutr. 2010; 91(2):480–6.]

[98] Izadi, V. et al. Adherence to the DASH and Mediterranean diets is associated with decreased risk for gestational diabetes mellitus.Nutrition pii: S0899-9007(16)00132-5, doi: 10.1016/j.nut.2016.03.006 [Epub ahead of print] (2016).

[99] Salas-Salvadó, J. et al. Protective Effects of the Mediterranean Diet on Type 2 Diabetes and Metabolic Syndrome. J Nutr pii: jn218487.[Epub ahead of print] (2016).

[100] García-Fernández E, Rico-Cabanas L, Rosgaard N, Estruch R, Bach-Faig A. Mediterranean diet and cardiodiabesity: a review. Nutrients2014;6:3474–500.)

[101] Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry CP, YaffeK. Obesity in middle age and future risk of dementia: a 27 year longitudinalpopulation based study. BMJ 2005;330:1360.

[102] Grosso G, Pajak A, Mistretta A, Marventano S, Raciti T, Buscemi S,Drago F, Scalfi L, Galvano F. Protective role of the Mediterraneandiet on several cardiovascular risk factors: evidence from Sicily, southernItaly. Nutr Metab Cardiovasc Dis 2014;24:370–7.

[103] Sofi F, Abbate R, Gensini GF, CasiniA. Accruing evidence on benefits of adherenceto the Mediterranean diet onhealth: an updated systematic review andmeta-analysis. Am J Clin Nutr 2010;92:1189-96.

[104] Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterraneandiet, traditional risk factors, andthe rate of cardiovascular complicationsafter myocardial infarction: final reportof the Lyon Diet Heart Study. Circulation1999;99:779-85.

[105] Mente A, de Koning L, Shannon HS,Anand SS. A systematic review of the evidencesupporting a causal link betweendietary factors and coronary heart disease.Arch Intern Med 2009;169:659-69.

[106] Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, Gomez-GraciaE, Ruiz-Gutierrez V, Fiol M, Lapetra J, et al: Primary prevention ofcardiovascular disease with a Mediterranean diet. Am J Clin Nutr 2013,368(14):1279–1290.

[107] Yankner BA, Lu T, Loerch P. The aging brain. Annu Rev Pathol 2008;3:41–66.

[108] Riddle DR, Sonntag WE, Lichtenwalner RJ. Microvascular plasticity inaging. Ageing Res Rev 2003;2:149–68.

[109] Wallace DC. Mitochondrial genetics: a paradigm for aging and degenerativediseases? Science 1992;256:628–32.

[110] Schwingshackl L, Hoffmann G. Adherence to Mediterranean diet andrisk of cancer: a systematic review and meta-analysis of observational studies. Int J Cancer 2014;135:1884–97.

[111] Keys A, Menotti A, Aravanis C, Blackburn H, Djordevic BS, Buzina R,Dontas AS, Fidanza F, Karvonen MJ, Kimura N. The seven countries study: 2,289 deaths in 15 years. Prev Med 1984;13:141–54.

[112] Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to aMediterranean diet and survival in a Greek population. N Engl J Med2003;348:2599–608.

[113] Solfrizzi V, Colacicco AM, D'Introno A, Capurso C, Torres F, Rizzo C,Capurso A, Panza F. Dietary intake of unsaturated fatty acids and agerelatedcognitive decline: a 8.5-year follow-up of the Italian LongitudinalStudy on Aging. Neurobiol Aging 2006;27:1694–704.

[114] Dai J, Jones DP, Goldberg J, Ziegler TR, Bostick RM, Wilson PW,Manatunga AK, Shallenberger L, Jones L, Vaccarino V. Associationbetween adherence to the Mediterranean diet and oxidative stress.Am J Clin Nutr 2008;88:1364–70.

[115] Chrysohoou C, Panagiotakos DB, Pitsavos C, Das UN, Stefanadis C.Adherence to the Mediterranean diet attenuates inflammation and coagulationprocess in healthy adults: the ATTICA study. J Am Coll Cardiol2004;44:152–8.

[116] Grimm A, Friedland K, Eckert A. Mitochondrial dysfunction: the missinglink between aging and sporadic Alzheimer's disease. Biogerontology2016;17:281–96.

[117] Féart C, Samieri C, Allès B, Barberger-Gateau P. Potential benefits ofadherence to the Mediterranean diet on cognitive health. Proc NutrSoc 2013;72:140–52.

[118] Panza F, Solfrizzi V, Colacicco AM, D'Introno A, Capurso C, Torres F,Del Parigi A, Capurso S, Capurso A. Mediterranean diet and cognitivedecline. Public Health Nutr 2004;7:959–63.

[119] Psaltopoulou T, Sergentanis TN, Panagiotakos DB, Sergentanis IN,Kosti R, Scarmeas N. Mediterranean diet, stroke, cognitive impairment,and depression: a meta-analysis. Ann Neurol 2013;74:580–91.

[120] Srisuwan P. Primary prevention of dementia: focus on modifiable riskfactors. J Med Assoc Thai 2013;96:251–8.

[121] Gill SS, Seitz D. Lifestyles and cognitive health. What older individualscan do to optimize cognitive outcomes. JAMA 2015;314:774–5.

[122] Stampfer MJ. Cardiovascular disease and Alzheimer's disease: commonlinks. J Intern Med 2006;260:211–23.

[123] Panagiotakos DB, Pitsavos C, Stefanadis C. Dietary patterns: a Mediterraneandiet score and its relation to clinical and biological markers ofcardiovascular disease risk. Nutr Metab Cardiovasc Dis 2006;16:559–68.

[124] Gemma C, Vila J, Bachstetter A, Bickford PC. Chapter 15 oxidativestress and the aging brain: from theory to prevention. Prevention. In:Riddle DR, editor. Brain Aging: Models, methods, and mechanisms.Boca Raton (FL): CRC Press/Taylor & Francis 2007;(15)1–19.

[125] Blazer DG, Yaffe K, Karlawish J. Cognitive aging: A report from the instituteof medicine. JAMA 2015;313:2121–2.

[126] Scarmeas N, Stern Y, Tang M-X, Mayeux R, Luchsinger JA. Mediterraneandiet and risk for Alzheimer's disease. Ann Neurol 2006;59:912–21.

[127] Gu Y, Luchsinger JA, Stern Y, Scarmeas N. Mediterranean diet, inflammatoryand metabolic biomarkers, and risk of Alzheimer's disease. JAlzheimers Dis 2010;22:483–92.

[128] H., Nelson, C., Munger, R. G. & Corcoran, C. Prospective study of ready-to-eat breakfast cereal consumption andcognitive decline among elderly men and women. J Nutr Health Aging. 15, 202–207 (2011).

[129] Loef, M. & Walach, H. Fruit, vegetables and prevention of cognitive decline or dementia: a systematic review of cohort studies. J NutrHealth Aging. 16, 626–630 (2012).

[130] Solfrizzi, V. et al. Dietary intake of unsaturated fatty acids and age-related cognitive decline: a 8.5-year follow-up of the ItalianLongitudinal Study on Aging. Neurobiol Aging. 27, 1694–1704 (2006).

[131] Martinez-Lapiscina, E. H. et al. Virgin olive oil supplementation and long-term cognition: the PREDIMED-NAVARRA randomized,trial. J Nutr Health Aging. 17, 544–552 (2013).

[132] Esposito, K. et al. Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. JAMA. 291,2978–2984 (2004).

[133] Chrysohoou, C., Panagiotakos, D. B., Pitsavos, C., Das, U. N. & Stefanadis, C. Adherence to the Mediterranean diet attenuatesinflammation and coagulation process in healthy adults: The ATTICA Study. J Am Coll Cardiol. 44, 152–158 (2004).

[134] Jula, A. et al. Effects of diet and simvastatin on serum lipids, insulin, and antioxidants in hypercholesterolemic men: a randomizedcontrolled trial. JAMA. 28, 598–605 (2002).

[135] Mecocci, P. Oxidative stress in mild cognitive impairment and Alzheimer disease: a continuum. J Alzheimers Dis. 6, 159–163 (2004).

[136] Yamaoka K, Tango T. Efficacy of lifestyle education to prevent type 2 diabetes:a meta-analysis of randomized controlled trials. Diabetes Care. 2005;28:2780-6. [PMID: 16249558]

[137] Lindstro¨m J, Ilanne-Parikka P, Peltonen M, Aunola S, Eriksson JG, Hemio¨K, et al; Finnish Diabetes Prevention Study Group. Sustained reduction in theincidence of type 2 diabetes by lifestyle intervention: follow-up of the FinnishDiabetes Prevention Study. Lancet. 2006;368:1673-9.

[138] Li G, Zhang P, Wang J, Gregg EW, Yang W, Gong Q, et al. The long-termeffect of lifestyle interventions to prevent diabetes in the China Da Qing DiabetesPrevention Study: a 20-year follow-up study. Lancet. 2008;371:1783-9. [PMID:18502303]

[139] Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, etal. Management of hyperglycemia in type 2 diabetes: A consensus algorithm forthe initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes.Diabetes Care. 2006;29:1963-72. [PMID: 16873813]

[140] Bantle JP, Wylie-Rosett J, Albright AL, Apovian CM, Clark NG, FranzMJ, et al; American Diabetes Association. Nutrition recommendations and interventionsfor diabetes: a position statement of the American Diabetes Association.Diabetes Care. 2008;31 Suppl 1:S61-78. [PMID: 18165339]

[141] Turner RC, Cull CA, Frighi V, Holman RR. Glycemic control withdiet, sulfonylurea, metformin, or insulin in patients with type 2 diabetesmellitus: progressive requirement for multiple therapies (UKPDS 49). UKProspective Diabetes Study (UKPDS) Group. JAMA. 1999;281:2005-12.[PMID: 10359389]

[142] Goldfine AB. Assessing the cardiovascular safety of diabetes therapies. N EnglJ Med. 2008;359:1092-5. [PMID: 18784098])

[143] Havas S. The ACCORD Trial and control of blood glucose level in type 2diabetes mellitus: time to challenge conventional wisdom. Arch Intern Med.2009;169:150-4. [PMID: 19171811]

[144] Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G,et al. Effect of a Mediterranean-style diet on endothelial dysfunction and markersof vascular inflammation in the metabolic syndrome: a randomized trial. JAMA.2004;292:1440-6. [PMID: 15383514]

[145] Due A, Larsen TM, Mu H, Hermansen K, Stender S, Astrup A. Comparisonof 3 ad libitum diets for weight-loss maintenance, risk of cardiovasculardisease, and diabetes: a 6-mo randomized, controlled trial. Am J Clin Nutr.2008;88:1232-41. [PMID: 18996857]

[146] Manley SE, Stratton IM, Cull CA, Frighi V, Eeley EA, Matthews DR, et al;United Kingdom Prospective Diabets Study Group. Effects of three months'diet after diagnosis of type 2 diabetes on plasma lipids and lipoproteins (UKPDS45). UK Prospective Diabetes Study Group. Diabet Med. 2000;17:518-23.[PMID: 10972581]

[147] Martı´nez-Gonza´lez MA, de la Fuente-Arrillaga C, Nunez-Cordoba JM,Basterra-Gortari FJ, Beunza JJ, Vazquez Z, et al. Adherence to Mediterraneandiet and risk of developing diabetes: prospective cohort study. BMJ. 2008;336:1348-51. [PMID: 18511765]

[148] Estruch R, Martı´nez-Gonza´lez MA, Corella D, Salas-Salvado´ J, Ruiz-Gutie´rrez V, Covas MI, et al; PREDIMED Study Investigators. Effects of a Mediterranean-style diet on cardiovascular risk factors: a randomized trial. AnnIntern Med. 2006;145:1-11. [PMID: 16818923]

[149] Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, BrayGA, Vogt TM, Cutler JA, Windhauser MM, et al: A clinical trial of the effectsof dietary patterns on blood pressure. DASH Collaborative ResearchGroup. New Engl J Med 1997, 336(16):1117–1124.

[150] Kastorini CM, Milionis HJ, Esposito K, Giugliano D, Goudevenos JA,Panagiotakos DB: The effect of Mediterranean diet on metabolicsyndrome and its components: a meta-analysis of 50 studies and534,906 individuals. J Am Coll Cardiol 2011, 57(11):1299–1313.

[151] World Health Organization. A global brief on hypertension. Available from:ish-world.com/downloads/pdf/global_brief_hypertension.pdf.

[152] James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, et al.2014 evidence-based guideline for the management of high blood pressure inadults: report from the panel members appointed to the Eighth Joint NationalCommittee (JNC 8). JAMA 2014;311:507–20.

[153] Beitz R, Mensink GBM, Fischer B. Blood pressure and vitamin C and fruit and vegetable intake. Annals of Nutr & Metabolism. 2003; 47:214–20.

[154] Alonso A, de la Fuente C, Martín-Arnau AM, de Irala J, Martínez JA, Martínez-González MA. Fruit and vegetable consumption is inversely associated with blood pressure in a Mediterranean population with a high vegetable-fat intake: the Seguimiento Universidad de Navarra (SUN) Study. Brit J Nutr. 2004; 92:311–319. 2004;92:311-9. [PubMed: 15333163].

[155] S. Klein, L. E. Burke, G. A. Bray et al., "Clinical implicationsof obesity with specific focus on cardiovascular disease: astatement for professionals from the American Heart AssociationCouncil on Nutrition, Physical Activity, andMetabolism,"Circulation, vol. 110, no. 18, pp. 2952–2967, 2004.

[156] P. Poirier and R. H. Eckel, "Obesity and cardiovascular disease,"Current Atherosclerosis Reports, vol. 4, no. 6, pp. 448–453, 2002.

[157] P. Zimmet and K. G. M. M. Alberti, "Global and societalimplications of the diabetes epidemic," Nature, vol. 414, no.6865, pp. 782–787, 2001.

[158] P. Hossain, B. Kawar, andM. El Nahas, "Obesity and diabetes inthe developing world—a growing challenge," The New EnglandJournal of Medicine, vol. 356, no. 3, pp. 213–215, 2007.

[159] G. A. Bray,AGuide toObesity andtheMetabolic Syndrome, CRCPress, 2011.

[160] H. C. Masouka and N. Chalasani, "Nonalcoholic fatty liverdisease: an emerging threat to obese and diabetic individuals,"Annals of the New York Academy of Sciences, vol. 1281, pp. 106–122, 2013.

[161] S. D. Hursting and S. M. Dunlap, "Obesity, metabolic dysregulation,and cancer: a growing concern ad an inflammatory (andmicroenvironmental) issue," Annals of the New York Academy of Sciences, vol. 1271, pp. 82–87, 2012.

[162] I. Vucenik and J. P. Stains, "Obesity and cancer risk: evidence,mechanisms, and recommendations," Annals of the New YorkAcademy of Sciences, vol. 1271, pp. 37–43, 2012.

[163] T. Gharibeh and R.Mehra, "Obstructive sleep apnea syndrome:natural history, diagnosis, and emerging treatment options,"Nature and Science of Sleep, vol. 2, pp. 233–255, 2010.

[164] F. Berenbaum, F. Eymard, and X. Houard, "Osteoarthritis,inflammation an obesity," Current Opinion in Rheumatology,vol. 25, pp. 114–118, 2013.

[165] (C. S. Farah and C. M. Salome, “Asthma and obesity: a knownassociation but unknown mechanism,” Respirology, vol. 17, no.3, pp. 412–421, 2012.

[166] (D.W.Haslam andW. P. T. James, “Obesity,” The Lancet, vol. 366,no. 9492, pp. 1197–1209, 2005.).

[167] M. I. McCarthy, “Genomics, type 2 diabetes, and obesity,” TheNew England Journal of Medicine, vol. 363, no. 24, pp. 2339–2350, 2010.

[168] J.-P.Despr´es and I. Lemieux, “Abdominal obesity and metabolicsyndrome,” Nature, vol. 444, no. 7121, pp. 881–887, 2006.

[169] A. Tchernof and J. P. Despr´es, “Pathophysiology of humanvisceral obesity: an update,” Physiological Reviews, vol. 93, pp.359–404, 2013.

[170] R.H. Eckel, “Nonsurgicalmanagement of obesity in adults,”TheNew England Journal of Medicine, vol. 358, no. 18, pp. 1941–1950,2008.

[171] V. Hainer, H. Toplak, and A. Mitrakou, “Treatmentmodalitiesof obesity: what fits whom?” Diabetes Care, vol. 31, no. 2, pp.S269–S277, 2008.

[172] G. Blackburn, “Effect of degreee of weight loss on healthbenefits,” Obesity Research, vol. 3, supplement 2, pp. 211–216,1995.

[173] D. J. Goldstein, “Beneficial health effects of modest weight loss,”International Journal of Obesity, vol. 16, no. 6, pp. 397–415, 1992.

[174] E. Heggen, T. O. Klemsdal, F. Haugen, I. Holme, and S.Tonstad, “Effect of a low-fat versus a low-gycemic-load dieton inflammatory biomarker and adipokine concentrations,”Metabolic Syndrome and Related Disorders, vol. 10, no. 6, pp.437–442, 2012.

[175] S. E. Shoelson, J. Lee, and A. B. Goldfine, “Inflammation andinsulin resistance,” Journal of Clinical Investigation, vol. 116, no.7, pp. 1793–1801, 2006.

[176] I. Shai, D. Schwarzfuchs, Y. Henkin et al., “Weight loss witha low-carbohydrate, Mediterranean, or low-fat diet,” The NewEngland Journal of Medicine, vol. 359, no. 3, pp. 229–241, 2008.

[177] A. C. Fernandez, A. V. Casariego, I. C. Rodreguez, and M. D.B. Pomar, “One-year effectiveness of two hypocaloric diets withdifferent protein/carbohydrate ratios in weight loss and insulinresistance,” Nutricion Hospitalaria, vol. 27, no. 6, pp. 2093–2101,2012.

[178] K. Esposito, R. Marfella, M. Ciotola et al., “Effect of a Mediterranean-style diet on endothelial dysfunction and markersof vascular inflammation in the metabolic syndrome: arandomized trial,” Journal of the AmericanMedical Association,vol. 292, no. 12, pp. 1440–1446, 2004.

[179] K. A. Varady, L. Tussing, S. Bhutani, and C. L. Braunschweig,“Degree of weight loss required to improve adipokine concentrationsand decrease fat cell size in severely obese women,”Metabolism: Clinical and Experimental, vol. 58, no. 8, pp. 1096–1101, 2009.

[180] Y. Deng and P. E. Scherer, “Adipokines as novel biomarkers andregulators of the metabolic syndrome,” Annals of the New YorkAcademy of Sciences, vol. 1212, pp. E1–E19, 2010.

[181] E. E. Kershaw and J. S. Flier, “Adipose tissue as an endocrineorgan,” Journal of Clinical Endocrinology and Metabolism, vol.89, no. 6, pp. 2548–2556, 2004.

[182] S. Galic, J. S. Oakhill, and G. R. Steinberg, “Adipose tissue asan endocrine organ,”Molecular and Cellular Endocrinology, vol.316, no. 2, pp. 129–139, 2010.

[183] Y. Arita, S. Kihara, N. Ouchi et al., “Paradoxical decrease of anadipose-specific protein, adiponectin, in obesity,” Biochemicaland Biophysical Research Communications, vol. 257, no. 1, pp.79–83, 1999.

[184] J. Wauman and J. Tavernier, “Leptin receptor signaling: pathwaysto leptin resistance,” Frontiers in Bioscience, vol. 16, no. 7,pp. 2771–2793, 2011.

[185] J. R. Vasselli, P. J. Scarpace, R. B. Harris, and W. A. Banks,“Dietary components in the development of leptin resistance,”Advances in Nutrition, vol. 4, no. 2, pp. 164–175, 2013.

[186] S. Dagogo-Jack, C. Fanelli, D. Paramore, J. Brothers, and M.Landt, “Plasma leptin and insulin

relationships in obese andnonobese humans," Diabetes, vol. 45, no. 5, pp. 695–698, 1996.

[187] M. W. Schwartz, R. L. Prigeon, S. E. Kahn et al., "Evidencethat plasma leptin and insulin levels are associated with bodyadiposity via different mechanisms," Diabetes Care, vol. 20, no.9, pp. 1476–1481, 1997.

[188] E. Klimcakova, M. Kovacikova, V. Stich, and D. Langin,"Adipokines and dietary interventions in human obesity," ObesityReviews, vol. 11, no. 6, pp. 446–456, 2010.

[189] M. C. Klempel and K. A. Varady, "Reliability of leptin, but notadiponectin, as a biomarker for diet-induced weight loss inhumans," Nutrition Reviews, vol. 69, no. 3, pp. 145–154, 2011.

[190] G. Carpenter and S. Cohen, "Epidermal growth factor," TheJournal of Biological Chemistry, vol. 265, no. 14, pp. 7709–7712,1990.

[191] M. Grau, C. Rodr´ıguez, M. Soley, and I. Ram´ırez, "Relationshipbetween epidermal growth factor in mouse submandibularglands, plasma, and bile: effects of catecholamines and fasting,"Endocrinology, vol. 135, no. 5, pp. 1854–1862, 1994.

[192] S.Gogg andU. Smith, "Epidermal growth factor and transforminggrowth factor α mimic the effects of insulin in human fatcells and augment downstream signaling in insulin resistance,"Journal of Biological Chemistry, vol. 277, no. 39, pp. 36045–36051, 2002.

[193] S. Kasayama, Y. Ohba, and T. Oka, "Epidermal growth factordeficiency associated with diabetes mellitus," Proceedings of theNational Academy of Sciences of the United States of America,vol. 86, no. 19, pp. 7644–7648, 1989.

[194] K. J. Strissel, Z. Stancheva, H. Miyoshi et al., "Adipocytedeath, adipose tissue remodeling, and obesity complications,"Diabetes, vol. 56, no. 12, pp. 2910–2918, 2007.

[195] T. Skurk, C. Alberti-Huber, C. Herder, and H. Hauner, "Relationshipbetween adipocyte size and adipokine expression andsecretion," Journal of Clinical Endocrinology and Metabolism,vol. 92, no. 3, pp. 1023–1033, 2007.

[196] C. Lelliott and A. J. Vidal-Puig, "Lipotoxicity, an imbalancebetween lipogenesis de novo and fatty acid oxidation," InternationalJournal of Obesity, vol. 28, no. 4, pp. S22–S28, 2004.

[197] American Cancer Society. Cancer prevention &early detection facts & figures 2012. [online],http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-033423.pdf (2012).

[198] Rey-Ares, L., Ciapponi, A. & Pichon-Riviere, A. Efficacyand safety of human papilloma virus vaccine in cervicalcancer prevention: systematic review and metaanalysis.Arch. Argent. Pediatr. 110, 483–489 (2012).

[199] World Cancer Research Fund/American Institute forCancer Research. Food, nutrition, physical activity, andthe prevention of cancer: a global perspective. [online], http://www.aicr.org/assets/docs/pdf/reports/Second_Expert_Report.pdf (2007).

[200] Albanes, D. et al. Effects of alpha-tocopherol andbeta-carotene supplements on cancer incidencein the Alpha-Tocopherol Beta-Carotene CancerPrevention Study. Am. J. Clin. Nutr. 62, 1427S–1430S(1995).

[201] J. Schlessinger and A. Ullrich, "Growth factor signaling byreceptor tyrosine kinases," Neuron, vol. 9, no. 3, pp. 383–391,1992.

[202] World Cancer Research Fund International.Our cancer prevention recommendations.[online],http://www.wcrf.org/int/research-we-fund/our-cancerprevention-recommendations (2016).

[203] Kushi, L. H. et al. American Cancer Society Guidelineson nutrition and physical activity for cancerprevention: reducing the risk of cancer with healthyfood choices and physical activity. CA Cancer J. Clin.62, 30–67 (2012).

[204] Franz, M. J. et al. Evidence-based nutrition principlesand recommendations for the treatment andprevention of diabetes and related complications.Diabetes Care 26 (Suppl. 1), S51–S61 (2003).

[205] Eckel, R. H. et al. 2013 AHA/ACC guideline on lifestylemanagement to reduce

cardiovascular risk: a reportof the American College of Cardiology/AmericanHeart Association Task Force on Practice Guidelines.J. Am. Coll. Cardiol. 63, 2960–2984 (2014).

[206] World Cancer Research Fund/American Institute forCancer Research. Ovarian cancer 2014 report: food,nutrition, physical activity, and the prevention ofovarian cancer 2014. [online], http://www.aicr.org/continuous-update-project/reports/ovarian-cancer-2014-report.pdf (2014).

[207] Prabhu, A., Obi, K. O. & Rubenstein, J. H. Thesynergistic effects of alcohol and tobacco consumptionon the risk of esophageal squamous cell carcinoma:a meta-analysis. Am. J. Gastroenterol. 109, 822–827(2014).

[208] Freedman, N. D. et al. A prospective study of tobacco,alcohol, and the risk of esophageal and gastric cancersubtypes. Am. J. Epidemiol. 165, 1424–1433 (2007).

[209] He, Z. et al. Prevalence and risk factors for esophagealsquamous cell cancer and precursor lesions in Anyang,China: a population-based endoscopic survey.Br. J. Cancer 103, 1085–1088 (2010).

[210] Hardefeldt, H. A., Cox, M. R. & Eslick, G. D.Association between human papillomavirus (HPV)and oesophageal squamous cell carcinoma: a metaanalysis.Epidemiol. Infect. 142, 1119–1137 (2014).

[211] Hoyo, C. et al. Body mass index in relation tooesophageal and oesophagogastric junctionadenocarcinomas: a pooled analysis from theInternational BEACON Consortium. Int. J. Epidemiol.41, 1706–1718 (2012).

[212] Coleman, H. G. et al. Dietary fiber and the risk ofprecancerous lesions and cancer of the esophagus:a systematic review and meta-analysis. Nutr. Rev. 71,474–482 (2013).

[213] Larsson, S. C., Giovannucci, E. & Wolk, A. Folateintake, MTHFR polymorphisms, and risk ofesophageal, gastric, and pancreatic cancer: a metaanalysis.Gastroenterology 131, 1271–1283(2006).

[214] Yang, H. P. et al. Endometrial cancer risk factors by 2main histologic subtypes: the NIH–AARP Diet andHealth Study. Am. J. Epidemiol. 177, 142–151(2013).

[215] Neill, A. S. et al. Dietary phyto-oestrogens and the riskof ovarian and endometrial cancers: findings from twoAustralian case–control studies. Br. J. Nutr. 111,1430–1440 (2014).

[216] Thomson, C. A. & Thompson, P. A. Fruit and vegetableintake and breast cancer risk: a case for subtypespecificrisk? J. Natl Cancer Inst. 105, 164–165(2013).

[217] Jung, S. et al. Fruit and vegetable intake and risk ofbreast cancer by hormone receptor status. J. NatlCancer Inst. 105, 219–236 (2013).

[218] World Cancer Research Fund/American Institute forCancer Research. Food, Nutrition and the Preventionof Cancer: a Global Perspective. (American Institutefor Cancer Research, Washington, DC, USA 1997).

[219] Eussen, S. J. et al. Plasma folate, related geneticvariants, and colorectal cancer risk in EPIC.Cancer Epidemiol. Biomarkers Prev. 19, 1328–1340(2010).

[220] Ulrich, C. M. et al. Colorectal adenomas and theC677T MTHFR polymorphism: evidence for gene environment interaction? Cancer Epidemiol.Biomarkers Prev. 8, 659–668 (1999).

[221] Sharafeldin, N. et al. A candidate-pathway approach to identify gene-environment interactions: analyses of colon cancer risk and survival. J. Natl Cancer Inst.107, djv160 (2015).

[222] Wild, C. P. The exposome: from concept to utility.Int. J. Epidemiol. 41, 24–32 (2012) .

[223] Youngson, N. A. & Whitelaw, E. Transgenerationalepigenetic effects. Annu. Rev. Genom. Hum. Genet.9, 233–257 (2008).

[224] Jimenez-Chillaron, J. C. et al. The role of nutritionon epigenetic modifications and their implications onhealth. Biochimie 94, 2242–2263 (2012).

[225] Coşkun, Turgay. “Fonksiyonel besinlerin sağlığımız üzerine etkileri.” Çocuk Sağlığı ve Hastalıkları Dergisi 48.1(2005): 61-84.

[226] Kwan, Hiu Yee, et al. “The anticancer and anti-obesity effects of Mediterranean diet.”

Critical Reviews in FoodScience and Nutrition 57.1 (2017): 82-94.

[227] Hacettepe University, Faculty of Health Sciences, Nutrition and Dietetics Department. Turkey's Food andNutrition Guide Ankara 2015. TR Ministry of Health, Public Health Institution of Turkey. Turkey Nutrition Guide 2015 (TÜBER). Ankara 2016.

[228] Barbaros B ve Kabaran S. Mediterranean diet and health protective properties. Beslenme ve Diyet Dergisi 42.2(2014):140-147.

[229] Garrett, W. S. Cancer and the microbiota. Science348, 80–86 (2015).

[230] Wu, G. D. et al. Linking long-term dietary patternswith gut microbial enterotypes. Science 334,105–108 (2011).

[231] Hullar, M. A., Burnett-Hartman, A. N. & Lampe, J. W.Gut microbes, diet, and cancer. Cancer Treat. Res.159, 377–399 (2014).In this paper, the authors provide an overviewof the role of the gut-microbial community incarcinogenesis, including in tissues outside of thegastrointestinal tract, with implications for dietand nutrition.

[232] Turnbaugh, P. J. et al. The human microbiome project.Nature 449, 804–810 (2007).

[233] Schloissnig, S. et al. Genomic variation landscape of the human gut microbiome. Nature 493, 45–50(2013).

[234] Halliwell B, Rafter J, Jenner A: Health promotion by flavonoid,tocopherols, tocotrienols and other phenols: direct or indirect effects?Antioxidant or not? Am J Clin Nutr 2005, 81:68S-76S.) (Betteridge DJ: What is oxidative stress? Metabolism 2000, 49:3-8.

[235] Robertson RM, Smaha L: Can a Mediterranean-Style Diet Reduce HeartDisease? Circulation 2001, 103:1821-1822.

[236] Mori TA, Beilin LJ, Burke V, Morris J, Ritchie J: Interactions between dietaryfat, fish, and fish oils and their effects on platelet function in men at riskof cardiovascular disease. Arterioscler Thromb Vasc Biol 1997, 17(2):279-286.

[237] Singh RB, Dubnov G, Niaz MA, Ghosh S, Singh R, Rastogi SS, Manor O,Pella D, Berry EM: Berry Effect of an Indo-Mediterranean diet onprogression of coronary artery disease in high risk patients (Indo-Mediterranean Diet Heart Study): a randomised single-blind trial. Lancet2002, 360(9344):1455-61.

[238] Meyer AS, Frankel EN: Antioxidant activity of hydroxycinnamic acids onhuman low-density lipoprotein oxidation. Methods Enzymol 2001,335:256-65.

[239] Chopra M, O'Neill ME, Keogh N, Wortley G, Southon S, Thurnham DI:Influence of increased fruit and vegetable intake on plasma andlipoprotein carotenoids and LDL oxidation in smokers and nonsmokers.Clin Chem 2000, 46(11):1818-29.

[240] Pino-Lagos K, Benson MJ, Noelle RJ: Retinoic Acid in the Immune System.Ann N Y Acad Sci 2008, 114:170-87.

[241] Freese R, Alfthan G, Jauhiainen M, Basu S, Erlund I, Salminen I, Aro A,Mutanen M: High intake of vegetables, berries, and apples combinedwith a hig intake of linoleic or oleic acid only slightly affect markers oflipid peroxidation and lipoprotein metabolism in healthy subjects. Am JClin Nutr 2002, 79:950-960.

[242] Bazzano LA, Serdula MK, Liu S: Dietary intake of fruits and vegetables andrisk of cardiovascular disease. Curr Atheroscler Rep 2003, 5:492-499.

[243] Stahl W, van den Berg H, Arthur J, Bast A, Dainty J, Faulks RM, Gärtner C,Haenen G, Hollman P, Holst B, Kelly FJ, Polidori MC, Rice-Evans C,Southon S, van Vliet T, Viña-Ribes J, Williamson G, Astley SB: Bioavailabilityand metabolism. Mol Asp Medicine 2002, 23:39-100.

[244] Garsetti M, Pellegrini N, Baggio C, Brighenti F: Antioxidant activity inhuman faeces. Br J Nutr 2000, 84:705-710.

[245] Ghiselli M, Serafini F, Natella , Scaccini C: Total antioxidant capacity as atool to assess redox status: critical view and experimental data. Free RadBiol Med 2000, 29:1106-1114.

[246] Sies H: Total antioxidant capacity: appraisal of a concept. J Nutr 2007,137:1493-1495.

[247] Bartosz G: Total antioxidant capacity. Adv Clin Chem 2003, 37:219-92.

[248] Ndhlala AR, Moyo M, Van Staden J: Natural Antioxidants: Fascinating orMythical Biomolecules? Molecules 2010, 15:6905-6930.

[249] Pitsavos C, Panagiotakos DB, Tzima N, Chrysohoou C, Economou M,Zampelas A, Stefanadis C: Adherence to the Mediterranean diet isasoiated with total antioxidant capacity in healthy adults: the ATTICAstudy. Am J Clin Nutr 2005, 82(3):694-9.

[250] Record IR, Dreosti IE, Mcinerney JK: Changes in plasma antioxidant statusfollowing consumption of diets high or low in fruit and vegetables orfollowing dietary supplementation with an antioxidant mixture. Br J Nutr2001, 85:459-464.)

[251] Fitó M, Guxens M, Corella D, Sáez G, Estruch R, de la Torre R, Francés F,Cabezas C, López-Sabater Mdel C, Marrugat J, García-Arellano A, Arós F,Ruiz-Gutierrez V, Ros E, Salas-Salvadó J, Fiol M, Solá R, Covas MI, for thePREDIMED Study Investigators: Effect of a traditional Mediterranean dieton lipoprotein oxidation: a randomized controlled trial. Arch Intern Med2007, 167(11):1195-203.

[252] Galland L: Diet and inflammation. Nutr Clin Pract 2010, 25(6):634-40.

[253] Bloomfield, Hanna E., et al. "Effects on health outcomes of a Mediterranean Diet with no restriction on fatintake: A systematic review and meta-analysis: Mediterranean diet with no restriction on fat intake." Annals ofInternal Medicine 165.7 (2016): 491-500.