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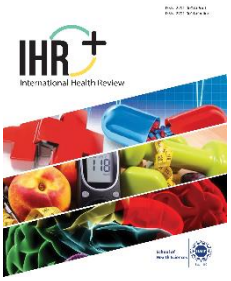

Title: **Impact of the Mediterranean Diet (Med-Diet) on Cancer and Cardiovascular Disease (CVD) Prevention and Management: A Narrative Review**

Author (s): Ifra Chaudhary[1,2], and Hassan Anwar[3]

Affiliation (s): [1]Department of Pathobiology & Biomedical Sciences, MNS-University of Agriculture, Multan, Pakistan
[2]District Program Coordinator, Qatar Charity, District Multan, Pakistan
[3]Department of Food Safety & Quality Management, Bahauddin Zakariya University, Multan, Pakistan

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Impact of the Mediterranean Diet (Med-Diet) on Cancer and Cardiovascular Disease (CVD) Prevention and Management: A Narrative Review

Ifra Chaudhary[1,2], and Hassan Anwar[3*]

[1]Department of Pathobiology & Biomedical Sciences, MNS-University of Agriculture, Multan, Pakistan
[2]District Program Coordinator, Qatar Charity, District Multan, Pakistan
[3]Department of Food Safety & Quality Management, Bahauddin Zakariya University, Multan, Pakistan

ABSTRACT

Cancer and cardiovascular diseases (CVD) are the leading causes of mortality and morbidity worldwide. Dietary patterns play a crucial role in the prevention and management of these life-threatening diseases. Moreover, the Mediterranean diet (Med-Diet) is consistently associated with health benefits. Therefore, the current study attempted to synthesize the contemporary scientific evidence, outlining the impact of Med-Diet on CVD. The key components of this dietary pattern include a high intake of fruits, vegetables, whole grains, seafood, olive oil, and moderate consumption of poultry and dairy products which interact to provide protective effects against these diseases. The Med-Diet emphasizes the use of monounsaturated fats from olive oil and polyunsaturated fats from seafood, which significantly contribute to cardiovascular health. This diet is also rich in antioxidants and phytochemicals, offering potential protective qualities against cancer through combating inflammation and oxidative stress. High fiber content contributes to a healthy digestive system and potentially reduces the incidence of colorectal cancers. While, the Med-Diet alone cannot guarantee complete immunity against these diseases, it is an essential element of a holistic approach to disease prevention and management. Moreover, it also reinforces the importance of incorporating dietary patterns into public health strategies. To strengthen the evidence base, future research should focus on long-term randomized controlled trials in diverse populations.

Keywords: cancer, cardiovascular diseases (CVD), mediterranean diet (Med-Diet), nutrition, public health

*Corresponding Author: hassan.anwarft@gmail.com

1.INTRODUCTION

The evolving effect of nutritional variables on human health has revealed the crucial role of various foods and nutrients in promoting health and preventing diseases. Particularly, certain dietary patterns are increasingly emerging as effective strategies for optimizing health outcomes, reducing disease risks, and managing specific health conditions. Among the primary causes of death across the globe, cancer and cardiovascular diseases (CVD) feature prominently [1]. It is a widely understood fact that our choices regarding our daily lifestyle including the consumption of food have profound implications for the prevention and regulation of these diseases [2, 3]. Over time, one such dietary pattern which has consistently attracted considerable interest within scientific circles is the Mediterranean diet (Med-Diet) [4, 5]. The current study focused on the Med-Diet, which is influential due to its prospective impacts on these illnesses.

1.1 Cardiovascular Disease (CVD)

Over half a billion people worldwide are still impacted by CVD. In 2021, these diseases were responsible for approximately 20.54 million deaths, nearly one-third of all global mortalities and a rise compared to the estimated 121 million CVD fatalities. Prevention methods could potentially prevent up to 80% of strokes and heart attacks [6]. CVD is an expansive term which includes numerous disorders related to various blood vessels and heart. This encompasses diseases, such as cerebrovascular disease, coronary heart disease, and venous thromboembolism [7, 8]. Lifestyle choices, such as unhealthy eating, physical inactivity, tobacco usage, and harmful alcohol consumption are usually linked to CVD [9].

1.2 Cancer

Cancer is a primary cause of mortality globally, contributing to almost 10 million deaths in 2020, which equals to about one in six deaths. The most frequently occurring cancers include those of the lungs, breast, prostate, rectum, and colon. About a third of cancer-related deaths can be attributed to lifestyle choices, such as obesity, alcohol consumption, smoking, insufficient intake of fruit and vegetables, and a sedentary lifestyle. Each year, around 400,000 children are diagnosed with cancer. The incidence of specific cancers differs between countries, with cervical cancer being the most prevalent in 23 countries [10]. The invasive nature of cancer is

manifested through abnormal cell growth, which holds the potential to spread and overwhelm different parts of the body [11]. The types of cancer vary, each possessing different rates of advancement, future predictions, and treatment methodologies. Age, familial history of cancer, exposure to specific chemicals or substances, and particular behavioral patterns contribute to increasing cancer risks [12]. These behaviors may include lack of physical activity, alcohol and tobacco consumption, and improper dieting habits.

1.3 Mediterranean Diet (Med-Diet)

Med-Diet, a distinct eating pattern seen in countries situated along the Mediterranean Sea, has often been connected to lower the instances of both cancer and CVD [13–15]. This diet primarily includes a considerable consumption of whole grains, vegetables, fruits, seafood, and olive oil. Moreover, this diet is also distinguished by its moderate consumption of dairy products, chicken, and wine, with a lower intake of red meat [16–18]. These components work together interactively, providing a myriad of protective effects on health.

2.METHODOLOGY

The current study was based on a narrative review which focused on showing the potential health effects of Med-Diet on CVD and cancer. A total of 87 studies were evaluated using different sources, such as PubMed, Scopus, and Google Scholar, however, only 58 studies met the inclusion criteria. Different keywords were searched, such as Med-Diet, cardiovascular, cancer, Mediterranean diet, heart, and diseases in different combinations. The studies that were included to elaborate the effect were mainly cross-sectional, prospective, cohort, and case studies.

3. Mediterranean Diet (Med-Diet) and its Health Benefits

A significant aspect of this diet prefers healthy fats, particularly monounsaturated fats from olive oil and polyunsaturated fats from seafood [19–21]. Prominent use of olive oil, in place of saturated and trans fats, can translate to reduced LDL (bad cholesterol) levels [22, 23]. Omega-3 fatty acids are abundant in fish which have been shown to lower the blood pressure and triglyceride levels along with limiting the growth rate of atherosclerotic plaques [24–27]. These factors contribute significantly to cardiovascular health.

Concerning cancer, the Med-Diet offers potential protective qualities. This particular eating pattern is rich in antioxidants and phytochemicals, which are sourced from a wide array of fruits, vegetables, herbs, and spices. These bioactive compounds are known for their potential to fight inflammation and oxidative stress, both of which are key players in the progression and development of cancer [28–32].

Additionally, the high fiber content present in the Med-Diet contributes to maintaining a healthy digestive system, reducing the incidence of colorectal cancers [33–36]. Dietary fiber aids in digestion, leading to a healthier gastrointestinal tract, while also helping to maintain normal body weight, reducing obesity risk, a known contributing factor in several types of cancer [37–40]. Figure 1 shows the process by which Med-Diet could prevent or reduce the CVD and cancer burden in population. Med-Diet has shown promising effects in preventing CVD and cancer as shown in Table 1.

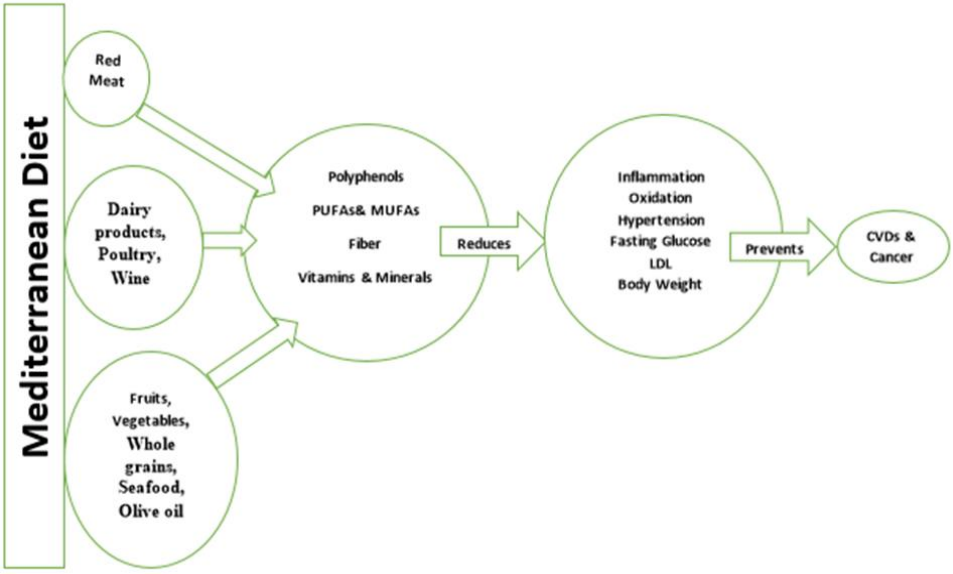

Figure 1. Mechanism of Prevention of CVDs and Cancer

3.1 Mediterranean Diet (Med-Diet) and Cardiovascular Diseases (CVDs)

Significant positive changes were detected in health in a cross-sectional study aimed at analyzing the impact of a 12-month Med-Diet on the lipid

profile and carotid intima-media thickness (cIMT) in pre-pubertal hypercholesterolaemic children. The preliminary phase of the study revealed that hypercholesterolaemic children exhibited an elevated cIMT in both carotid arteries, relative to control subjects. Upon introducing the Med-Diet intervention among the hypercholesterolaemic children for 12 months, there was a noteworthy decrease in LDL-cholesterol, total cholesterol levels, and cIMT. More significantly, following dietary intervention, changes in LDL-cholesterol (delta LDL-cholesterol) and body mass standard deviation score (delta BMI-SD) demonstrated a statistically significant and independent relationship with alterations in cIMT metrics. The adoption of a Med-Diet strategy has several potential benefits for CVD prevention in hypercholesterolaemic children [41].

In the context of preventing CVD through dietary measures, Med-Diet has demonstrated promising potential in reducing cardiovascular events, particularly in patients with atrial fibrillation (AF). With AF being marked by increased oxidative stress and related CVD complications, anticoagulant treatment has achieved only partial prevention [42]. To explore this aspect, a prospective study of 709 anticoagulated AF patients was conducted. The focus of this study was to assess the impact of adherence to Med-Diet. The participants were categorized based on their Med-Diet scores into high (7-9 scores), medium (4-6 scores), and low (0-3 scores) adherence groups. The study's observations were recorded during a mean follow-up period of 39.9 months. It was found that the prevalence of cardiovascular events showed an inverse correlation towards Med-Diet stickiness, that is, 23.4% in the low-stickiness group, 8.4% in the intermediate group, and finally 5.3% among high-adherers ($p<0.001$). The findings add weight to the proposition that higher stickiness to Med-Diet could contribute to a notable reduction in CVEs, potentially mediated by an antioxidant effect [43].

In the context of dietary practices impacting the prevention of CVD, adherence to a Med-Diet has emerged as a crucial protective factor. Research conducted between 2005 and 2015 involved the assessment of lifestyle options, such as physical activity and diet. The research encompassed 2,749 older individuals between the age of 65-100 years across 21 Mediterranean islands and the Greece rural region of Mani. The traditional risk factors of CVD included hypertension (62.4%), diabetes mellitus type 2 (22.3%), and hypercholesterolemia (47.7%). Factors affecting CVD risk included age, body mass index (BMI), social habits,

frequency of midday sleep, and residential environment among others. A notable aspect observed was that the urban residential environment increases the possibility of diabetes mellitus after adjusting for other influences. These findings underscore the connection between lifestyle attributes including daily habits, community life, midday sleep patterns, and residing settings with the prevalence of CVD risk factors in elderly population. Accordingly, comprehensive strategies are aimed at CVD prevention since these elements effectively mitigate the diseases' burden [44].

A study was conducted in Iran within the body of work focusing on dietary trends and CVD prevention. This prospective cohort study was based on population (2001-2009) of 4834 randomly selected adults aged 35 and above from both rural and urban settings. The researchers evaluated dietary intakes based on the frequency of food questionnaires and also identified the major patterns of food consumption using exploratory factor analysis. About 118 CVD mortality was identified over the average follow-up time frame of 9.0 years. Four primary dietary patterns emerged, that is, 'Mediterranean', 'Western' 'Fast food', and 'Animal fat'. Of note, adherence to Med-Dietary patterns demonstrated a protective association with CVD mortality. Participants in the highest percentile of this pattern's adherence were shown to be 46% less likely to develop incident CVD mortality than those in the lowest quartile. Interestingly, no corresponding association was observed between adherence to western food, animal fat, and fast food dietary consumption trends and CVD mortality. Hence, it can be concluded that the intake of Med-Diet is linked with a lower risk for CVD mortality [45].

In a large-scale prospective cohort study, researchers investigated whether adherence to a Med-Diet influenced the association between prolonged exposure to pollutants in the atmosphere and CVD mortality. The study comprised 548,845 participants from across the United States, with follow-up consisting of 17 years. Participants' exposure was calculated to fine particulate matter (PM) and nitrogen dioxide through the census-tract level and by building a substitute Med-Diet Index based on their starting point eating habits' questionnaires. It was observed that prolonged exposure to fine particulate matter was strongly linked with a higher likelihood of CVD, ischemic heart disease, and cerebrovascular disease. Likewise, exposure to nitrogen dioxide was significantly associated with CVD and

ischemic heart disease. On the other hand, individuals with higher scores on the alternative Med-Diet Index had considerably decreased rates of CVD mortality associated with long-term air pollution exposure. This data suggests that adhering to a Med-Diet may mitigate the negative health impacts of air pollution [46].

In a randomized, controlled trial spanning 12 weeks, the effectiveness of Med-Diet was assessed in reducing the risk factors associated with CVD in a population within the southeastern United States which was considered to be at a higher risk. Participants were randomized into two groups, that is, control and intervention, with a prerequisite BMI of 24.9 and at least two major CVD risk factors. Evidence from this trial indicated that the implementation and adherence to a Med-Diet may lead towards significant improvements in multiple health outcomes related to CVD risk. Particularly, the influence of an increased nutritional knowledge and adherence to Med-Diet is noteworthy which is strongly correlated with changes in blood glucose and cholesterol levels. Furthermore, intriguing associations between nut and extra-virgin olive oil intake, crucial components of Med-Diet, and several vital health indicators, such as HDLC (high-density lipoprotein cholesterol) levels and systolic blood pressure were observed. The outcomes suggest that scaling up the implementation of a Med-Diet may have far-reaching positive impacts on the prevention of CVD [47].

In accordance with new empirical findings, commitment to a Med-Diet may positively alter circulating microvesicles, which contribute to the atherothrombotic process and are the biomarkers of CVD progression. Microvesicle shedding, a measure of cell activation and vascular injury, appears responsive to dietary changes, spotlighting the role of nutrition in CVD prevention. The beneficial impact was observed from a Med-Diet supplemented with extra-virgin olive oil and mixed nuts. Patients at high CVD risk who followed Med-Diet diet for a year recorded lower concentrations of prothrombotic microvesicles, suggestive of less cell activation towards a pro-atherothrombotic phenotype, potentially delaying the development of cardiovascular complications as compared to those on a low-fat diet. This correlation between a Med-Diet and reduced CVD biomarker progression reinforces its potential for preventing CVD [48].

A retrospective study of individuals who suffered from congestive heart failure (CHF) from the time period 2008-2014 investigated the relationship

between commitment to a Med-Diet and CHF, as well as its level of severity and pathophysiology. Data was collected from 209 patients suffering from CHF. Moreover, data from 200 controls was also reviewed which revealed that there was an appreciable difference in the average Med-Diet score of CHF patients as compared to controls, with CHF patients consistently exhibiting lower scores. Through sensitivity and specificity analysis of mean Med-Diet scores, it could be inferred that these scores were effective in predicting the instances of CHF. Moreover, evidence suggested a positive correlation between Med-Diet scores and ischemic causes of CHF [49].

In the CORDIOPREV study conducted in Cordoba, Spain, a Med-Diet was studied in terms of its effects on patients with established coronary heart disease. Over a 7-year period, major cardiovascular events, such as myocardial infarction, revascularization, peripheral artery disease, ischemic stroke, and cardiovascular death were less likely among those who followed a Med-Diet. Approximately, 502 people were enrolled over the experiment duration. The data highlighted that in secondary prevention of CVD, the Med-Diet showed considerably good results. Hence, for those working towards CVD prevention, these findings underscore the potential benefits attributable to following a Med-Diet [50].

A cross-sectional association was explored between sex-stratified Med-Diet adherence. The study incorporated three Med-Diet scores, that is,- MEDAS, MEDAS continuous, and Pyramid- in addition to a Western diet score. The association between cardiovascular health and Med-Diet score was tested using linear regression and linear mixed effects models. To boost causality inferences from the collected data, propensity scores were computed and utilized as covariates along with total energy intake and Western diet scores. The sample comprised 533 participants, predominantly women (60.0%), with an average age of 51.25 years. Across all three scoring methods, women held superior Med-Diet scores, consumed fewer total calories, and scored lower in the Western diet category. Improved Med-Diet scores correlated with a decrease in blood pressure and BMI as well as reduced cardiovascular risk overall. On examining by sex, significant positive associations were determined for women regarding lower blood pressure, BMI, and glycemia against better Med-Diet scores. However, men only demonstrated significant associations for reduced BMI against better Med-Diet scores. Based on these findings, it is evident that an enhanced adherence to Med-Diet is associated with improvements in

numerous cardiovascular health outcome measurements. These associations are more pronounced in women than men. This potentially implicates the development of individualized nutritional suggestions to enhance cardiovascular health [51].

To summarize the findings, research indicated that maintaining adherence to the Med-Diet could potentially have protective implications against CVDs through its associated biochemical effects, such as anti-inflammation and antioxidant activities. This insight adds depth to understanding of the relationship between Med-Diet and CVDs prevention.

3.2 Mediterranean Diet (Med-Diet) and Cancer

A case-control study was conducted in Italy which examined the recurrence of breast cancer in women who followed a standard diet versus those following a Med-Diet. Over a follow-up period of three years, results evidenced a significant reduction in breast cancer recurrence among women adhering to a Med-Diet. A strong correlation was also identified between levels of carotene in blood and compliance with the Med-Diet, suggesting that these levels could be an effective way to monitor adherence to Med-Diet [52].

A standardized frequency of food questionnaire covering over 25 food items was used to measure dietary intake for 226 patients and 444 controls in an Italian case-control research. Commitment to the traditional Med-Dietary pattern was accessed using a Med-Diet level. Multiple logistic regression models were used to construct 95% confidence intervals (CI) indicating a lower risk of stomach cancer with higher adherence to the Med-Diet. This risk reduction was consistent across various age and gender groups. Focusing on specific components of this dietary regimen, substantial consumption of fruits (CI: 0.67-0.84), vegetables (CI: 0.53-0.75), and legumes (CI: 0.66-0.98) revealed a significant correlation with lower risk of developing gastric cancer [53].

From 1993-2008, the E3 N prospective cohort study recruited 67,332 French women aged 40 to 65 years and reported skin cancer cases: 232 squamous-cell carcinoma (SCC), 404 melanoma, and 1367 basal-cell carcinoma (BCC). A validated food frequency questionnaire was used to analyze dietary habits, and commitment to the Med-Diet was graded from 0 to 9 according to various dietary components. Adherence to the Med-Diet demonstrated an overall decreased risk of skin cancer. The risk of non-

melanoma skin cancers showed a linear decline with higher Med-Diet scores, particularly BCC. While there was no authentication of a linear association with melanoma, higher Med-Diet scores suggested a marginal decreased risk of melanoma. No heterogeneity was discovered among different skin cancer types. Therefore, the results from this comprehensive prospective cohort study ascertain that adherence to a Med-Diet may contribute to mitigating the overall risk of skin cancer in women, particularly BCC and potentially melanoma as well [54].

Within the recently discovered mammary gland-specific microbiome, evidence suggests the presence of varying population of bacteria in breast cancer. Lactobacillus levels in malignant breast tumors were lower than in benign lesions, establishing Lactobacillus as a possible opponent of breast cancer development. Diet is an important driver of gut microbial diversity, however, its influence on breast microbiome populations is unknown. The ingestion of a Western or Med-Diet changed the microbiota and metabolite profiles of the breast milk gland in a non-human primate research. The Med-Diet in particular was linked to increased *Lactobacillus* abundance in the mammary gland as compared to those fed with a Western diet. Higher levels of bile acid metabolites and bacterial-processed bioactive compounds were also found in mammary glands from monkeys who were fed the Med-Diet. It indicates that Med-Diet has a direct influence on microbiome populations outside the intestinal tract, extending to distal sites, such as the mammary gland. Hence, this reinforces an alternative mechanism through which dietary choices play a role in breast cancer prevention by directly affecting the mammary gland microbiome [55].

In examining the link between the Med-Diet and rates of breast cancer among postmenopausal Arab Saudi women in the region of Makkah, the study found significant evidence of a protective effect. A case-control study was conducted using a self-admistered questionnaire on 432 Saudi female subjects, who were of postmenopausal and around the same age. The study spanned over 2 yearsand produced convincing results. The consumption of 1-2 servings of legumes on weekly basis, 1-5 servings of fish, and a daily intake of 1-5 servings of dairy products, along with more than one cup of black tea and coffee per day, coupled with a daily consumption of 3-5 servings of fruits and vegetables, significantly lowers the risk of breast cancer. Thus, it was discovered that consuming a Med-Diet can act as a

preventive intervention against breast cancer in postmenopausal females [56].

The collected evidence supports the conclusion that a strong adherence to the Mediterranean-Dietary pattern can be advantageous in reducing cancer risks, thereby enhancing the potential value of this diet for cancer preventive measures.

3.3. Prevention and Management of Diseases through Lifestyle Modifications

Preventing and controlling diseases, such as cancer and CVD requires the adoption of healthier lifestyles that incorporate a balanced diet, routine physical activity, avoidance of smoking, and controlled consumption of alcohol [57, 58]. The Med-Diet provides an effective blueprint for healthy eating habits by emphasizing not just individual nutrients, however, also a well-rounded eating pattern.

However, the prevention and treatment of these diseases involves more than merely sticking to a healthy diet. Regular health screenings, early detection, appropriate medical care, and additional lifestyle adaptations are the key to successful disease management.

5.CONCLUSION AND FUTURE PERSPECTIVES

Med-Diet has shown significant potential in reducing cancer and CVD risks. This diet emphasizes food quality, diversity, and pleasure which could act assubstantial ingredients in making healthier lifestyle choices. Broadly, the Med-Diet contributes to achieve improved health outcomes. For instance, its rich content of bioactive compounds, such as antioxidants and phytochemicals are helpful in combating inflammation, oxidative stress, and cancer development. Furthermore, the excessive use of olive oil rich in monounsaturated fats and the extensive use of seafood loaded with omega-3 fatty acids, reduce bad cholesterol levels and blood pressure, promoting overall cardiovascular health. Large-scale studies have demonstrated the diet's protective influence on cardiovascular health. Its high adherence produces significant reductions in cardiovascular events and mortality rates. Similarly, evidence suggests that this diet also contributes to lower breast and gastric cancer risks. Therefore, the adoption of Med-Diet may substantially enhance defense mechanism against global killers.

Table 1. Summary of Studies Showing Med-Diet and its Impact on CVD and Cancer

Author & Year	Study Type	Study Period	Targeted Population	Effect of Mediterranean diet
Cardiovascular Diseases (CVDs)				
Giannini et al. [41]	Cross-sectional	12 Months	Pre-pubertal hypercholesterolaemic children	Decrease in total cholesterol levels, LDL-cholesterol, and cIMT
Pastori et al. [43]	Prospective	39.9 months	Patients with atrial fibrillation	Prevalence of cardiovascular events showed an inverse correlation with adherence to Med-Diet, potentially mediated by an antioxidant effect
Georgousopoulou et al. [44]	Cross-sectional	10 years	65-100 years old people across the rural region of Mani in Greece and Mediterranean islands	CVD prevention should consider daily habits, community life, midday sleep patterns with Med- diet
Mohammadifard et al. [45]	Prospective cohort	9 years	Participants aged 35 and up were chosen at random.	Med-Diet lowers the risk for CVD mortality as contrasted to fast food, western food, and animal fat diet
Lim et al. [46]	Prospective cohort	17 years	Participants from across the United States.	Adherence to Med-Diet can modify the adverse health effects of air pollution
Willis et al. [47]	Randomized controlled trial	12 Weeks	Adults with a minimum BMI of 24.9 plus at least 2 other CVD risk factors	Implementation of a Med-Diet may have far-reaching positive impacts on prevention of CVD
Tuttolomondo et al. [49]	Retrospective	6 years	Patients diagnosed with CHF	Med-Diet decreases the chances of CHF
Delgado-Lista et al. [50]	CORDIOPREV	7 years	Patients with established coronary heart disease	Med-Diet plays significant role in CVD prevention
Cancer				
Biasini et al. [52]	Case-control	3 years	Women with breast cancer	Results evidenced a significant reduction in breast cancer recurrence among women adhering to a Med-Diet
Mahamat-Saleh et al. [54]	Prospective cohort	15 years	women between the age of 40–65 years	Adherence to Med-Diet demonstrated an overall reduction in skin cancer risk
Azzeh et al. [56]	Case Control	2 years	Postmenopausal women	Adherence to Med-Diet serves as a preventive measure against breast cancer.

Looking ahead, more research on this specific diet's potential may broaden the understanding of its protective elements in managing other health conditions. Additionally, future research could focus on long-term randomized controlled trials in diverse populations for more definitive insights. Furthermore, health policies should also prioritize the promotion of public awareness and accessibility to healthy food. While the Med-Diet alone does not guarantee complete immunity from diseases, such as cancer and CVD, it offers a well-rounded approach toward healthier living. The combination of Med-Diet with other lifestyle modifications may offer a powerful weapon against these diseases' development and management. In conclusion, the future of Med-Diet's role in disease prevention looks promising and can potentially reshape global health outcomes significantly.

CONFLICT OF INTEREST

The author of the manuscript has no financial or non-financial conflict of interest in the subject matter or materials discussed in this manuscript.

DATA AVAILABILITY STATEMENT

Data availability is not applicable as no new data was created.

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