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The Efficacy of a Mediterranean Diet in Reducing the Risk of Cardiovascular and Cerebrovascular Disease Incidence and Mortality in Patients with Known Risk Factors

Kendra Cutter
Pacific University

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Abstract

Background: Heart disease and stroke are two leading causes of disability and death in the United States. The Mediterranean diet has been shown to reduce recurrent cardiovascular events and decrease inflammatory biomarkers that contribute to atherosclerotic progression. Should the Mediterranean diet be recommended to patients with known risk factors for cardiovascular disease to reduce risk of first incident or mortality associated with cardiovascular and cerebrovascular disease?

Methods: An exhaustive search of available medical literature was conducted using Medline-OVID, CINAHL and EBSCO-Host. The key words that were used individually and in combination included: Mediterranean diet, vascular inflammation, cardiovascular disease treatment, cerebrovascular disease, coronary heart disease, myocardial infarction, CRP and IL-6. Relevant articles were assessed for quality using GRADE.

Results: Three studies met inclusion and exclusion criteria and were used in this review. The first is a large prospective Greek-population cohort study, which found a decrease in mortality from coronary heart disease with greater Mediterranean diet adherence. The second is a large prospective Manhattan-population cohort study, which found no association for diet adherence and ischemic stroke and a reduced risk of myocardial infarction and vascular death up to a score of four. The third is a large prospective Mediterranean-population based cohort study, which found a reduction in cerebrovascular incident with diet scores greater than four.

Conclusion: The Mediterranean diet has been shown to reduce the risk of cardiovascular disease incidence and mortality. There is conflicting evidence regarding reduction of cerebrovascular disease incidence and mortality. The overall study quality is very low due to design and follow up time, however, a dose response gradient is evident in each study. Providers should advise patients without disease but with known risk factors to implement complete adherence to the Mediterranean diet for best risk reduction.

Keywords: Mediterranean diet, myocardial infarction, cerebrovascular disease, coronary heart disease, vascular inflammation.

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The Efficacy of a Mediterranean Diet in Reducing the Risk of Cardiovascular and Cerebrovascular Disease Incidence and Mortality in Patients with Known Risk Factors

Kendra M. Cutter

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Faculty Advisor: James Ferguson, PA-C

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS

Biography

[Redacted for privacy]

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List of Abbreviations

MD……..……..…..Mediterranean Diet
CHD……..…….…..Coronary Heart Disease
CVD…...……..Cardiovascular Disease
CBVD…...…..…….Cerebrovascular Disease
CAD….……..Coronary Artery Disease
CV……..……Cardiovascular
MI…….……..Myocardial Infarction
HTN……..……Hypertension
DM……..……Diabetes
BMI…...…….Body Mass Index
TLC……...……Therapeutic Lifestyle Changes
AHA…....…….American Heart Association
NCEP……National Cholesterol Education Program
ATP III……..Adult Treatment Panel III

The Efficacy of a Mediterranean Diet in Reducing the Risk of Cardiovascular Disease Progression in Patients with Known Risk Factors

BACKGROUND

Heart disease and stroke are two of the leading causes of disability and death in the United States, with an estimated one in three adults being affected and over 811 000 deaths occurring annually (http://www.heart.org/idc/groups/heart-public/@wcm/@adt/documents/downloadable/ucm_449081.pdf).[1] This statistic has increased from American Heart Association (AHA) statistics in 2005, where one in five deaths were attributed to coronary heart disease (CHD).[2] Camargo et al[3] describes cardiovascular disease (CVD) as an inflammatory process caused by aging, oxidative stress, and an increase in pro-inflammatory molecules which are affected by dietary fat intake. An important factor in atherosclerotic development is plaque stability, as rupture of plaque particles can cause significant cardiovascular (CV) events like myocardial infarction (MI), cerebrovascular disease (CBVD) like stroke, and death. Camargo et al[3] describes the determining factors of plaque stability and rupture as chronic lipid accumulation within the vascular endothelium, chronic low-grade inflammation, and subsequent weakening of plaque caps over time. Patients most at risk for CVD or CBVD incidents are males over the age of 45, females over the age of 55, current smokers, high-density lipid value less than 40, stage one hypertension, or use of hypertensive medication and family history of coronary artery disease (CAD).

Therapeutic lifestyle changes (TLC) are first line therapy for those at risk and with a current diagnosis of heart disease, however there are many dietary

recommendations available that can be confusing to providers when advising patients on how to improve their long term health. Past dietary recommendations by the AHA, National Cholesterol Education Program (NCEP), and Adult Treatment Panel III (ATP III) have failed to reduce the incidence of CHD, which prompts investigation into developing other, more effective, dietary guidelines.[2] Extensive research on the traditional Mediterranean diet (MD) has been completed over the last 60 years since Ancel Keys, a U.S. nutritionist, concluded that death from CHD was lower in Mediterranean populations compared with other areas of the world.[2] According to the AHA, an MD consists of high consumption of fruits, vegetables, bread and other cereals, potatoes, beans, nuts and seeds, olive oil as the main fat source, low to moderate intake of dairy products, fish and poultry, little intake of red meat, none or little intake of eggs, and low to moderate intake of wine (see Figure 1). The MD has been studied extensively for its ability to decrease the incidence of future CV events in patients with existing CVD or previous MI.[4,5] Many studies have been performed that measure short term (<2 years) outcomes like inflammatory markers, immune cell activation, pro-atherogenic genes, and endothelial function in patients who adhere to the MD.[3,6,7] Although these studies showed improved outcomes with MD intervention, long term (>5years) evidence of risk reduction is necessary to evaluate the sustainability of such a recommendation. It is also important to consider a population without disease to evaluate the ability of the MD to prevent incidents in those patients most at risk. Evidence of a decrease in incident of CV and cerebrovascular events in patients with known risk factors for CVD but without current disease diagnosis is important to consider when advising patients on effective lifestyle changes. The goal of preventative medicine is to make lifestyle changes that prevent

these events from ever occurring, and the MD seems to be a viable option for disease prevention. Should the MD be recommended to patients with known risk factors for CVD to reduce risk of incident or mortality associated with cardiovascular and cerebrovascular disease?

METHODS

An exhaustive search of available medical literature was conducted using Medline-OVID, CINAHL and EBSCO-Host using the following key words individually or in combination: Mediterranean diet, vascular inflammation, cardiovascular disease treatment, cerebrovascular disease, myocardial infarction, CRP, and IL-6. The search was narrowed to include only studies with a mean follow-up time greater than five years, published no sooner than 2008, that were either randomized controlled trials, cohorts, or randomized crossover studies, in the English language, and only on human subjects. Articles evaluating patient populations without current or previous diagnosis of CVD or CBVD were included. Relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).[8]

RESULTS

The initial search yielded 130 articles for review. After assessing the articles for relevancy, nine articles were further reviewed based on inclusion criteria. Of these, three articles met both inclusion and exclusion criteria. All three articles are large prospective cohort studies.[9-11] See Table 1.

Dilis, et al

This large population-based prospective cohort study[9] assessed the association between MD adherence and CHD incidence and mortality in a Greek population. This population was a subgroup of the EPIC cohort (European Prospective Investigation into Cancer and Nutrition), a large database of 520 000 participants from ten European countries. The EPIC cohort "provides data on diet, anthropometry, lifestyle, socio-economic variables, as well as genetic and biomarker data in relation to cancer and other chronic diseases." Primary outcomes measured were CHD incident which included angina, myocardial infarction or other CHD event. Mortality was measured if the CV event resulted in death.[9]

The Greek segment of the EPIC cohort consists of 28 572 male and female participants. Participants were excluded if they had a previous diagnosis of CVD or cancer at time of enrollment, if follow up data was insufficient, or if patients were not able to provide data for one or more of the study variables. The final study consisted of 23 929 participants (9740 men and 14 189 women) who met eligibility criteria. All participants signed an informed consent and the study was approved by the International Agency for Research on Cancer and the Medical School of the University of Athens ethics committee.[9]

The intervention assessed was adherence to a traditional MD, which ranged from non-adherent to completely adherent. Baseline data collected included dietary habits for each participant using a quantitative food questionnaire administered by an interviewer that assessed intake and frequency of intake of 200 of the most common Greek foods. Portion sizes were confirmed with photographs. MD adherence was assessed using a 10-point score as developed by Trichopoulou et al.[12] A score of zero or one was assigned to

those who did not frequently or who frequently consumed foods typical of the MD, respectively (vegetables, legumes, fruits and nuts, cereals, fish and seafood, high ratio of monounsaturated to saturated fats). A score of zero or one was given to those who frequently or infrequently consumed foods *not* consistent with the MD, respectively (dairy, meat or meat products). A score of one was assigned to those consuming a moderate amount of alcohol daily, and a score of zero was assigned otherwise. A score of zero correlated with non-adherence and a score of nine correlated with complete adherence to the MD. Participants were grouped into three score ranges (0-3, 4-5, 6-9) based on frequency of consumption of these nine different food types. Patient characteristics were also recorded at baseline and included the following: age, years of schooling, height, BMI, level of physical activity, alcohol intake, smoking status, and blood pressure.[9]

Follow up was completed via telephone interviews by "specially trained health professionals" although no indication of blinding is discussed. There is also no mention of the frequency of follow up with each participant. Next of kin was contacted in the event of participant death during the follow up period. Outcomes reported by participants or next of kin during the follow up period were confirmed via hospital discharge data, medical records or death certificates.[9]

The association between MD and outcome measures (MI, angina and CHD other than MI, or angina and death) was assessed using Cox regression and adjusted for age, BMI, height, physical activity, years of schooling, energy intake, and sex. Over a mean follow up period of 10 years, 636 volunteers developed CHD (426 males and 210 females), and 240 of these people died from the disease (150 males and 90 females). The

study recognized certain baseline characteristics of the participants, such as there being more women than men in the study, a greater percentage of participants with lower education level, and most participants being overweight or obese.[9]

Independent of MD adherence, the association between risk factors for CHD and CHD incidence and mortality were assessed for men and women separately. These risk factors for CHD include age > 45 for men, > 55 for women, current smokers and hypertension (HTN). For men, there was a statistically significant 2-fold, 3-fold and 6-fold increase in CHD incidence at 45-54 years, 55-64 years, and $\geq$ 65 years old, respectively, and a 3-fold and 14-fold increase in CHD mortality at 55-64 years and $\geq$ 65 years old, respectively. Male smokers and with Stage 1 HTN or on hypertensive agents were at a statistically significant 2-fold increased risk of CHD incidence and mortality (see Table 2). For women, there was a statistically significant 6-fold and 12-fold increase in CHD incidence at 55-64 years and $\geq$ 65 years old, respectively, and a 9-fold and 36-fold increase in CHD mortality at 55-64 years and $\geq$ 65 years old, respectively. Female smokers were at a statistically significant 2-fold increased risk of CHD incidence and mortality. Females with Stage 1 HTN or on hypertensive agents were at a statistically significant 3-fold increased risk of CHD incidence and 2-fold risk of CHD mortality (see Table 3).[9]

In regards to MD adherence and CHD incidence and mortality, after being adjusted for sex, age, BMI, height, physical activity, years of schooling, and energy intake, a statistically significant reduction in CHD mortality was seen in those participants with MD scores of 6-9. There was a "suggestive reduction" in CHD incidence with greater adherence to the MD (scores 4-5 and 6-9), indicating a dose

response gradient. When applying a 2-point increase to the MD scores to assess if greater adherence had an effect on incidence and mortality, there was a statistically significant 25% reduction in CHD mortality among women and 19% reduction in CHD mortality among men.[9] See Table 4.

Gardener et al

This large population-based prospective cohort study[10] assessed the relationship between MD adherence and risk of stroke incidence, MI incident, and vascular death in white, black, and Hispanic communities in Manhattan, New York. The study was derived from the NOMAS cohort study, which was designed to evaluate stroke incidence in relation to risk factors and prognosis in Manhattan communities. Primary outcomes measured were ischemic stroke incidence, MI incidence, and vascular death.[10]

Eligible participants included those who did not have a previous incident of ischemic stroke, were > 40 years of age, and had lived in Northern Manhattan for at least 3 months with telephone access. Participants with a history of MI prior to enrollment were excluded. Participants were contacted via random-digit dialing and interviewed by trained bilingual interviewers and research assistants. An in-person baseline interview and assessment by study neurologists was conducted after the telephone interview. A total of 2568 participants were included in the study. All participants signed an informed consent and the study was approved by the Columbia University and University of Miami review boards.[10]

The intervention assessed was adherence to the MD, as determined by a modified Block National Cancer Institute food-frequency questionnaire given by bilingual research assistants. Due to the overwhelming Hispanic population percentage in the study group,

the food-frequency questionnaire was modified to include Hispanic foods. Each participant was assigned a value of one for each of the following foods consumed at or above the median: fruit, vegetables, legumes, cereals and fish. A value of one was assigned for meat and dairy products if consumed at or below the median. A value of one was assigned if the ratio of monounsaturated to saturated fats was at or above the median, and for mild-to-moderate alcohol consumption. Participants were categorized into quintiles (0-2, 3, 4, 5, 6-9) based on their responses. A higher response correlated to greater adherence to the MD. Baseline assessment was completed using standardized questions from the Behavioral Risk Factor Surveillance System by the CDC. Risk factor evaluation included presence of hypertension, diabetes, hyperlipidemia, and low level of physical activity.[10]

Participants were followed up with annually by telephone to assess for "changes in vital status, detect neurologic events, document interval hospitalizations, and review risk factor status, medication changes, and changes in functional status." If a positive response was found, an in-person interview with neurologic assessment was completed. Incident events were confirmed via hospital discharge records.[10]

The association between adherence and outcome measures (stroke, MI, and vascular death) was assessed using chi-square tests, ANOVA, Cox hazard models and 95% CI, and adjusted for age, sex, race-ethnicity, education, moderate-to-heavy physical activity, average total daily kilocalorie consumption, and smoking. A second model adjusted for these variables and confounders like diabetes (DM), HTN, hypercholesterolemia and history of self-reported CV disease. A binary variable was used to account for missing dietary data in attempts to minimize potential bias. Additionally,

participants reporting <500 or >4000 kilocalorie intake values were excluded, as this was likely inaccurate reporting of dietary intake. Over a mean follow up period of 9 +/- 3.5 years, 518 vascular events occurred, which included 171 ischemic strokes, 133 myocardial infarctions, and 314 vascular deaths.[10]

In regards to MD adherence and outcome events, no significant association was found for MD adherence and reduced risk of ischemic stroke. For MI, there was a decreased risk of event up to an MD score of four, at which point higher MD adherence seemed to provide no additional risk reduction indicating a threshold effect without a dose-response relationship. These results were not statistically significant. For vascular death, there was a decreased risk of event up to an MD score of four as well, and beyond this score there was a similar threshold effect. These results were also not statistically significant. When applying a 1-point increase to the MD score, there was a 9% decrease in risk of vascular death. When evaluating the association between MD and all events combined, statistical significance was achieved only for MD scores of 4 and 5, however, there was risk reduction evident for scores >3 with threshold effect beyond a score of four. In addition, those in the highest quintile (6-9) experienced the greatest risk reduction in vascular event (33%) compared to the lowest quintile (0-2). The study suggests a possible threshold effect beyond the 3rd quintile.[10] See Table 4.

Miserli et al

This large population-based prospective cohort study[11] assessed the association between MD adherence and risk of incidence and mortality from cerebrovascular disease (CBVD), specifically ischemic vs. hemorrhagic stroke. This population was a subgroup

of the EPIC cohort. Primary outcomes were CBVD incident (ischemic stroke and hemorrhagic stroke) and CBVD mortality.[11]

Participants were invited volunteers from the general Greek population who were already participants in the Greek EPIC cohort. Participants were excluded if they had a history of CBVD, CVD, or cancer at time of enrollment and insufficient follow up due to loss of contact or missing variable information like socio-economic, lifestyle, dietary, or anthropometric data. The final study included 23 601 participants who met eligibility criteria. All participants signed an informed consent and the study was approved by the University of Athens Medical School Bioethics Committee.[11]

The intervention assessed was MD adherence. Baseline dietary data was collected by interviewers who recorded participant's dietary habits after a validated semiquantitative food frequency questionnaire which included about 150 food and drink items common to the traditional Greek diet. Participants visited the study center every month for one year to give a 24-hour recall of their diet to assess habits. Participants were assigned to an MD adherence group (0-3, 4-5, 6-9) based on Trichopoulou et al's[12] study design after assessment of baseline dietary habits was completed. Baseline characteristics like physical activity, blood pressure, health problems, medication use, and smoking habits were recorded as well.[11]

Follow up was conducted by telephone to record changes in health status, diet, and lifestyle. Next of kin was contacted in the event of death of a participant. The study admits to lack of information on lifestyle changes for a large percentage of the study participants. Outcomes reported by participants or next of kin were confirmed by hospital

records, discharge data, or death certificates. Local death registries were consulted to confirm cause of death.[11]

The association of MD adherence and outcome measures (ischemic stroke, hemorrhagic stroke, and mortality) were analyzed using Cox regression models and Nelson-Aalen cumulative hazard curves, with controlling for sex, age, education, smoking status, BMI, level of physical activity, HTN, DM, and total energy intake. Data was analyzed with the STATA SE statistical package, 11th edition. Over a mean follow up period of 10.6 years, 395 first-ever CBVD events occurred and 1446 deaths occurred, with 196 of those being due to CBVD.[11]

Independent of MD adherence, the association between known risk factors for CHD and CBVD incidence and mortality were assessed for the participants. For participants aged 55-64, there was a statistically significant 3-fold and 4-fold increase in CBVD incident and mortality, respectively. For those aged $\geq$ 65, there was a statistically significant 9-fold and 18-fold increase in risk of incidence and mortality, respectively. There was no statistical significant increase in incident and mortality for current smokers or those with BMI >25. For participants with HTN, there was a statistically significant 1.39x risk of CBVD incident and no statistical significance in mortality. This was the same for participants with diabetes (DM), with a statistically significant 1.44x risk of CBVD incident without statistically significant risk of mortality (see Table 5).[11]

In regards to MD adherence and CBVD incidence and mortality, after being adjusted for sex, age, education, smoking status, BMI, level of physical activity, HTN, DM, and total energy intake, a statistically significant reduction in CBVD incident was seen in those participants with MD scores of >4. There is a suggestive reduction in

mortality, however, not statistically significant. A dose-response gradient was observed with an inverse relationship between increased adherence to the MD and decreased incident and mortality (see Table 4).[11]

In regards to incidence of ischemic versus hemorrhagic versus overall CBVD, after being adjusted for the same variables as above, the greatest risk reduction was seen in those in the MD score 6-9 category. Overall CBVD reduction was statistically significant, whereas ischemic was marginally significant versus hemorrhagic that was not significant. An inverse relationship between MD score and reduction of event or mortality was event for both ischemic and hemorrhagic stroke, indicating a dose response gradient. When applying a 2-point increase to the MD score to assess if greater adherence had an effect on incidence and mortality, there was a statistically significant reduction in CBVD incident only (HR = 0.85, 95% CI = 0.74, 0.96) (see Table 4).[11]

DISCUSSION

The Mediterranean diet has been shown in multiple studies as an effective intervention for the secondary prevention of CVD and CBVD events, improvement in endothelial function, decreasing inflammatory biomarkers, and decreasing the expression of pro-atherogenic genes.[3-7] ideally, providers should have a dietary recommendation for patients who do not have a diagnosis of CVD or CBVD in order to prevent these events from occurring. These three large prospective cohort studies[9-11] provide insight into the MD efficacy in reducing incidence and mortality in patients without CVD or CBVD diagnosis, and with risk factors for disease to help answer the question: Should the MD be recommended to patients with known risk factors for CVD to reduce risk of incident or mortality associated with cardiovascular and cerebrovascular disease?

Clinical Relevance

When comparing patient risk factors (age, smoking status, HTN, DM, BMI) with CVD and CBVD incidence and mortality, Dilis et al[9] and Misirli et al[11] found a statistically significant increase in events with increasing age. Dilis et al[9] found an increase in incidence and mortality in current smokers and patients with HTN, with a particularly higher incidence in women. Misirli et al[11] did not find statistically significant increase in events of smokers or those with a BMI >25. There was only a statistically significant increase in incidence, not mortality, in patients with DM and HTN[11] (see Tables 2-3, 5). These results, though not identical, support the rationale that patients with risk factors for CVD and CBVD are generally at a higher risk of either incident or mortality. This generalization supports the need to find an appropriate dietary recommendation for patients at risk to prevent future events from occurring.

When comparing MD adherence and CVD and CBVD incident and mortality, Dilis et al[9] found a statistically significance reduction in mortality only with MD scores of 6-9, indicating a dose response gradient. When a 2-point increase in the MD score was applied to the data, a 25% decrease in mortality in women and 19% decrease in mortality in men was found.[9] Gardener et al[10] found no association between MD adherence and stroke incident, and a threshold effect beyond an MD score of 3 for MI incident, vascular death and overall events. When comparing MD scores of 0-2 (least adherent) to MD scores of 6-9 (most adherent), a dose-response gradient is evident by a 33% decrease in event.[10] Misirli[11] et al found a statistically significant decrease in CBVD incident with an MD score greater than 4, again indicating a dose-response gradient. Overall event

(ischemic and hemorrhagic stroke) was decreased most with an MD score of 6-9 and was statistically significant, however when assessed independently, ischemic stroke was "marginally" significant and hemorrhagic stroke was not statistically significant.[11] All three studies[9-11] recognize that greater adherence to the MD point toward a decrease in either incident of or mortality from CVD or CBVD events. Though not all data is statistically significant, a generalization can be made that this dietary recommendation would likely benefit patients at risk for CVD and CBVD (see Table 4).

Limitations

All three studies[9-11] are limited by design. Each is a large prospective population-based cohort and lacks a control group. Each study has the potential for recall bias, since follow up times for each are long (>9 years). In addition, Dilis et al[9] and Gardener et al[10] do not mention blinding of interviewers or neurologists. Dilis et al[9] and Misirli et al[11] do not mention frequency of follow up for each participant (see Table 1). The combination of these limitations downgrades each study to a very low quality status based on GRADE criteria.[8] Dilis et al[9] does not provide recommendations for future studies. Gardener et al[10] recommends further studies in larger populations to evaluate the association between MD and stroke. Misirli et al[11] recommends more studies to replicate the protective effect of the MD against ischemic CBVD, as this was an unexpected finding.[11]

CONCLUSION

The Mediterranean diet has been demonstrated to reduce the risk of incident and mortality in patients at risk of developing CVD or CBVD. Patients with known risk factors for CVD are at a much greater risk of event and worse, mortality from an event. The overall combined quality of the studies reviewed is very low based on GRADE

criteria[8] due to cohort study design and long follow up periods that allow potential for recall bias. However, each study provides evidence of a dose-response gradient, where better risk reduction can be achieved with greater adherence to the diet.

Since there is no harm in implementing the Mediterranean diet, it should be recommended by providers as a preventative measure when advising patients about lifestyle changes prior to an event, with emphasis on the long term value of complete adherence rather than mild or moderate adherence to achieve the best risk reduction. However, even some adherence to the MD is beneficial. For patients with risk factors for heart disease and stroke but without a current diagnosis, implementing a lifestyle change now rather than waiting for an event to occur would greatly reduce risk of event or mortality from an event. Research studies that implement a randomized controlled trial design with monthly follow up frequency over several years would provide more concise outcomes.

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Table 1. Characteristics of Reviewed Studies

Quality Assessment								
		Downgrade Criteria					Quality	Importance
No. of Studies	Design	Limitations	Indirectness	Imprecision	Inconsistency	Publication Bias Likely		
Cerebrovascular Disease Incident (Ischemic and Hemorrhagic Stroke)								
2	Prospective Cohort	No control, potential for recall bias	No indirectness	No lack of precision	No inconsistencies	Unlikely	Very Low	Important
Cerebrovascular Disease Mortality								
1	Prospective Cohort	No control, potential for recall bias	No indirectness	No lack of precision	No inconsistencies	Unlikely	Very Low	Critical
Coronary Heart Disease Incident (MI, angina)								
2	Prospective Cohort	No control, potential for recall bias	No indirectness	No lack of precision	No inconsistencies	Unlikely	Very Low	Important
Coronary Heart Disease Mortality								
2	Prospective Cohort	No control, potential for recall bias	No indirectness	No lack of precision	No inconsistencies	Unlikely	Very Low	Critical

Table 2. Risk Factors and CHD Incidence and Mortality - Men

Age	**CHD Incidence**			**CHD Mortality**		
	HR	**95% CI**	**Statistically Significant?**	**HR**	**95% CI**	**Statistically Significant?**
45-54	2.32	1.62, 3.32	Y	1.99	0.86, 4.61	N
55-64	3.48	2.39, 5.08	Y	3.04	1.31, 7.06	Y
≥65	5.69	3.79, 8.54	Y	13.75	6.03, 31.36	Y
Current Smoker	2.01	1.56, 2.61	Y	2.22	1.43, 3.43	Y
HTN Stage 1 or HTN medication use	1.63	1.30, 2.03	Y	1.62	1.09, 2.40	Y

*Dilis et al

Table 3. Risk Factors and CHD Incidence and Mortality - Women

Age	**CHD Incidence**			**CHD Mortality**		
	HR	**95% CI**	**Statistically Significant?**	**HR**	**95% CI**	**Statistically Significant?**
55-64	5.72	3.09, 10.59	Y	9.26	2.54, 33.80	Y
≥65	12.18	6.51, 22.82	Y	36.14	10.02, 130.39	Y
Current Smoker	1.89	1.10, 3.23	Y	2.35	1.03, 5.34	Y
HTN Stage 1 or HTN medication use	2.62	1.76, 3.90	Y	1.88	1.05, 3.34	Y

*Dilis et al

Table 4. Summary of Findings

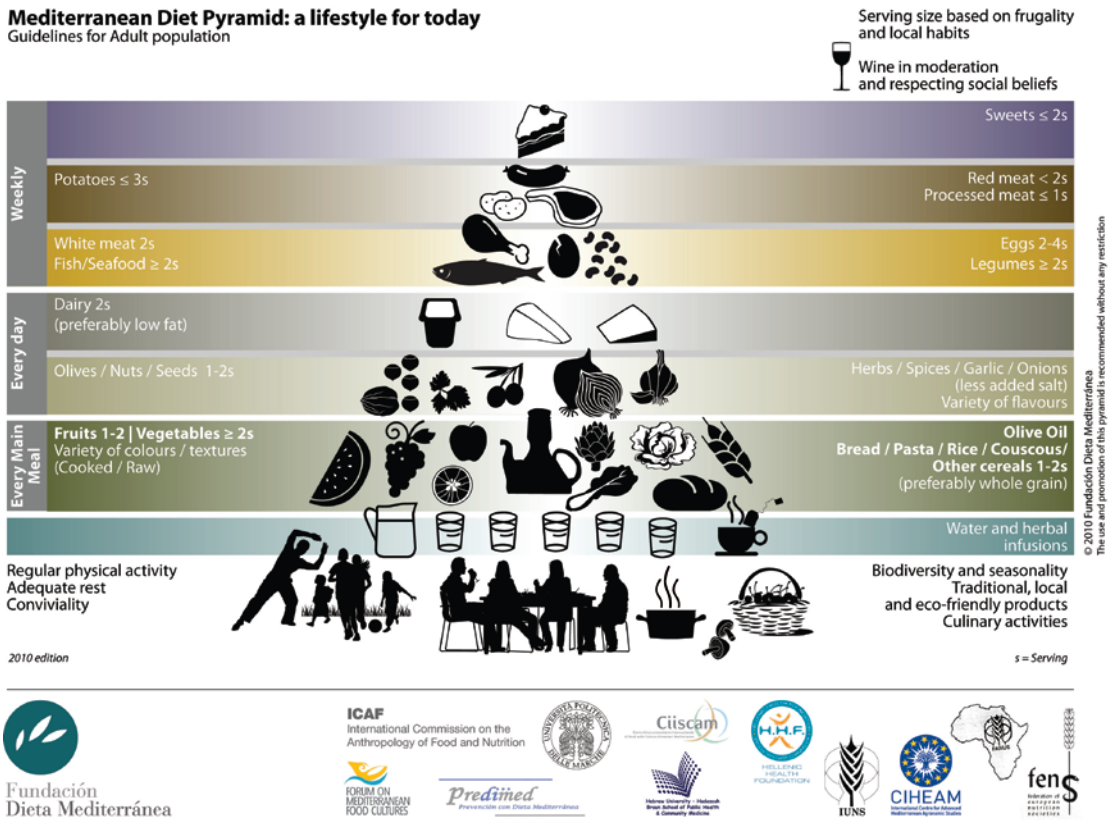
	Number of Patients			**Outcomes**					
Study	*Treatment (total)*	*Placebo or no treatment (total)*	*MD score*	*CHD Incident (MI, angina, other acute/chronic ischemic heart disease, n=636)*		*CHD Mortality (n=240)*			
				HR	95% CI	HR	95% CI		
Dilis et al	23 929	*	0-3	1	Reference	1	Reference		
			4-5	0.86	0.72, 1.03	0.82	0.62, 1.09		
			6-9	0.82	0.66, 1.02	0.54	0.37, 0.81		
				CBVD Incident (Ischemic stroke, n=171)		*CHD Incident (MI, n=133)*		*CHD Mortality (Vascular death, n=314)*	
Gardener et al	2568	*	0-2	1	Reference	1	Reference	1	Reference
			3	1.18	0.69, 2.01	0.57	0.32, 1.03	0.87	0.60, 1.26
			4	0.91	0.53, 1.55	0.62	0.37, 1.06	0.74	0.52, 1.06
			5	0.96	0.56, 1.63	0.60	0.34, 1.04	0.69	0.47, 1.00
			6-9	1.03	0.61, 1.73	0.65	0.38, 1.12	0.71	0.49, 10.4
				CBVD Incident (Ischemic Stroke, n=95)		*CBVD Incident (Hemorrhagic Stroke, n=59)*		*CBVD Mortality (n=196)*	
Misirli et al	23 601	*	0-3	1	Reference	1	Reference	1	Reference
			4-5	0.77	0.50, 1.21	1.25	0.69, 2.26	0.79	0.57, 1.08
			6-9	0.54	0.29, 1.01	0.86	0.40, 1.87	0.76	0.50, 1.16

Table 5. Risk Factors and CBVD Incidence and Mortality

Age	**CBVD Incidence**			**CBVD Mortality**		
	HR	**95% CI**	**Statistically Significant?**	**HR**	**95% CI**	**Statistically Significant?**
55-64	3.32	2.22, 4.97	Y	3.56	1.77, 7.15	Y
≥65	9.29	6.21, 13.88	Y	17.50	8.97, 34.15	Y
Current Smoker	1.23	0.90, 1.68	N	1.50	0.96, 2.36	N
NHTN Stage 1 or HTN medication use	1.39	1.09, 1.77	Y	1.35	0.95, 1.93	
DM	1.44	1.16, 1.79	Y	1.32	0.97, 1.79	N

*Misirli et al

Figure 1. Mediterranean Diet Pyramid



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