**SUPPLEMENTAL MATERIAL**

Table 3. Main prospective observational studies and randomized controlled trials published until May 2017, assessing the effects of the Mediterranean diet on mortality from or incidence of cardiovascular disease.

| Author, year | Study | Location | Outcome(s) | Exposure | n     | Follow-up | Results/observations |
|--------------|-------|----------|------------|----------|-------|-----------|---------------------|
| De Lorgeril, 1994 | Lyon Diet Heart Study | France | CV deaths, non-fatal MI and total mortality | MedDiet rich in alpha-linolenic diet vs usual post-infarct prudent diet | 605 | 27 months | In the experimental group the adjusted RR of CV deaths and of total major primary endpoints were 0.24 (95%CI: 0.07-0.85) and 0.27 (95%CI: 0.12-0.59) respectively |
| Trichopoulou, 2003 | Greek population | Greece | Total mortality, CV mortality and cancer mortality | MedDiet (range of score 0-9) | 22043 | 44 months | A higher adherence to MedDiet was associated with lower risk of mortality due CHD [HR=0.67 (95%CI: 0.47-0.94)] |
| Knoops, 2004 | The HALE Project | 13 European countries | Mortality from all causes, CHD, CVD and cancer | MedDiet score (0-8 range) and lifestyle factors | 2339 | 10 years | Adhering to MedDiet was associated with a lower risk of mortality from CVD [HR= 0.71 (95 % CI: 0.58-0.88)] and from CHD [HR= 0.61 (95 % CI (0.43-0.88)] |
| Mitrou, 2007 | NIH-AARP Diet and Health Study | US | All-cause, CVD and cancer mortality | MedDiet (9 point score) | 214284 men and 166012 women | 5 years | The higher adherence to MedDiet was associated with reduced CVD mortality in men [HR=0.78 (95 % CI:0.69-0.87)] and in women [HR=0.81 (95 % CI: 0.68-0.97)] |
| Fung, 2009 | Nurses’ Health Study | US | CHD, stroke and CVD deaths | Alternate MedDiet Score (0-9 range) | 76522 | 20 years | Women in the top Alternate MedDiet score were at lower risk for CHD, stroke and CVD mortality [RR=0.71 (95 % CI 0.62-0.82)], [RR=0.87 (0.73-1.02)] and [RR=0.61 (0.49-0.76)] respectively. |
| Author, year | Study | Location | Outcome(s) | Exposure | n     | Follow-up | Results/observations |
|--------------|-------|----------|------------|----------|-------|-----------|----------------------|
| Buckland, 2009 | Spanish EPIC cohort Study | Spain | CHD events | Relative MedDiet score (18-unit) | 41078 | 10.4 years | A 1-unit increase in rMedDiet score was associated with a 6% reduced risk of CHD (95% CI: 0.91, 0.97) |
| Martinez-González, 2011 | SUN cohort study | Spain | Composite (CVD death, CHD, MI, revascularization procedures, or fatal or nonfatal stroke) | MedDiet (A 9-point score) | 13609 | 12.3 | The highest adherence to the MedDiet exhibited a lower CV risk [HR=0.41 (95% CI: 0.18-0.95)]. For each 2-point increment in the score, the adjusted HR were 0.80 (95% CI: 0.62-1.02) for total CVD and 0.74 (0.55-0.99) for CHD |
| Gardener, 2011 | NOMAS cohort | US | Stroke, MI and Vascular death | MedDiet (0-9 scale) | 2568 | 9 years | A point increase of the MedDiet score was inversely associated with risk of vascular death [HR= 0.91 (95% CI 0.85-0.98)] |
| Buckland, 2011 | Spanish EPIC cohort Study | Spain | All-cause and cause-specific mortality | Relative MedDiet score (18-unit) | 40622 | 13.4 years | A 2-unit increase in rMed score was associated with a 12% decreased risk of CVD deaths [HR=0.88 (95% CI 0.81-0.95)] |
| Tognon, 2012 | VIP study | Northern Sweeden | Total or cause-specific mortality | Modified MedDiet score (0-8 range) | 77151 | | CVD mortality was inversely associated with the modified MedDiet score in women [HR=0.90 (95% CI:0.82-0.99)] |
| Misirli, 2012 | EPIC- Greece | Greece | Incidence of and mortality from cerebrovascular diseases | MedDiet (10-point scale) | 23601 | 10.6 | Increased adherence to the MedDiet, as measured by 2-point increments, was inversely associated with cerebrovascular diseases incidence [HR=0.85 (95% CI:0.74-0.96)]. In men [HR=0.88 (95% CI:0.74-1.04)] and in women [HR=0.81 (95% CI:0.67-0.98)] |
| Author, year | Study | Location | Outcome(s) | Exposure | n     | Follow-up | Results/observations |
|--------------|-------|----------|------------|----------|-------|-----------|---------------------|
| Dilis, 2012  | EPIC- Greece | Greece | CHD event | MedDiet (range 0-9 points) | 23929 | 10.6      | A 2-point increase in the MedDiet score was associated with lower CHD mortality [HR=0.75 (95% CI: 0.57-0.98)] among women and [HR=0.81 (95% CI: 0.67-0.99)] among men. |
| Hoevenaar-Blom, 2012 | EPIC-NL-Germany | Germany | Incidence of total and specific CVD | MedDiet (range 0-9) | 40011 | 11.8      | A 2-unit increment in MedDiet score was inversely associated with fatal CVD [HR=0.78 (95% CI: 0.69-0.88)], total CVD [HR=0.95 (95% CI: 0.91-0.98)], MI [HR=0.86 (95% CI: 0.79-0.93)], stroke [HR=0.88 (95% CI: 0.78-1.00)] and composite CVD [HR=0.85 (95% CI: 0.80-0.91)] |
| Tognon, 2014 | Danish cohort study | Denmark | Total mortality, CV incidence and mortality | Three different MedDiet scores | 1849 | 13 years  | The modified MedDiet score was inversely associated with total mortality and with CVD and MI incidence and mortality. |
| Estruch, 2013 | PREDIMED TRIAL | Spain | CV events and mortality | MedDiet+extra virgin olive oil; MedDiet + nuts; Low fat diet | 7447 | 4.8 years | A MedDiet supplemented with extra-virgin olive oil or nuts reduced the incidence of major CV events [HR=0.70 (95% CI: 0.54-0.92)] and [HR=0.72 (95% CI: 0.54-0.96)] respectively |
| Sotos-Prieto, 2015 | HPFUS NHS | US | CHD and stroke | Several food patterns. Alternative MedDiet score (range 0-9) | 80538 | 17.3 years | Improving adherence to MedDiet during the first 4 years of follow-up associated with a lower risk of CVD [HR=0.91 (95% CI: 0.86-0.97)] |
| Author, year   | Study                   | Location                   | Outcome(s)                              | Exposure                              | n     | Follow-up | Results/observations                                                                                                                                                                                                 |
|---------------|-------------------------|----------------------------|-----------------------------------------|---------------------------------------|-------|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Panagiotakos, 2015 | ATTICA                  | Greece                     | CVD and all-cause mortality             | MedDiet (score 0-55) and lifestyles   | 2583  | 10 years  | MedDiet associated with lower risk of CVD [RR=0.98 (95% CI: 0.95-1.01)], for each additional unit in a 0-55 score, equivalent to a [HR=0.78 (95% CI: 0.53-1.13)] for 2 units in the score |
| Tektonidis, 2015 | SMC                     | Sweden                     | MI, stroke, HF                          | MedDiet (0-8 scale)                   | 32921 | 10 years  | MedDiet associated with lower risk of MI [RR=0.74 (95% CI:0.61-0.90)], HF [RR=0.79 (95% CI:0.68-0.93)] and ischemic stroke [RR=0.78 (95% CI:0.65-0.93)], but not hemorrhagic stroke [RR=0.88 (95% CI:0.61-1.29)]. |
| Tektonidis, 2016 | COSM                    | Sweden                     | Heart failure                           | MedDiet (0-8 score)                   | 37308 | 10.9 years| Inverse association of the MedDiet with heart failure [HR=0.85 (95% CI:0.78-0.91)] for each 2 additional points in the score                                                                  |
| Bo, 2016       | Turin study             | Italy                      | Mortality and CVD                       | MedDiet (0-9 scale)                   | 1658  | 12 years  | High adherence to MedDiet inversely associated with all-cause mortality [HR=0.83 (95% CI: 0.72–0.96)] and CVD [HR=0.79, (95% CI:0.65–0.97)]. No association with mortality among high risk subjects |
| Tong, 2016     | UK-based EPIC-Norfolk cohort | UK                        | Incident CVD, CVD mortality and all-cause mortality | MedDiet score (0-18 range)           | 23902 | 17 years  | The MedDiet score was significantly associated with lower incidence of the incidence of CVD [HR=0.97 (95% CI:0.94–0.99)]                                                                                           |
| Stefler, 2017  | HAPIEE                  | Czech Republic, Poland, Russia | Mortality, CVD                          | MedDiet (0-17 points)                 | 19333 | 7 years   | One standard deviation (SD) in MedDiet adherence inversely associated with all-cause death (HR, 95 % CI 0.93, 0.88–0.98) and CVD (0.90, CI 0.81–0.99)                                           |

CV: Cardiovascular. CHD: Coronary Heart Disease. CVD: Cardiovascular Disease. MI: myocardial infarction. MedDiet: Mediterranean Diet.
CI: Confidence Interval. HR: Hazard Ratio. RR: Relative Risk.
INTRODUCTION

Cardiovascular diseases, together diabetes, cancer and other chronic diseases, are among the leading causes of morbidity and mortality in developed and non-developed countries. The traditional Mediterranean diet (MedDiet) pattern has been widely recommended for the prevention of the chronic disease. Several observational studies and a few clinical trials have examined the association between this food pattern and different health outcomes. However, the evidence on the prevention of cardiovascular disease by MedDiet deserves to be systematically reviewed.

The purpose of this cumulative meta-analysis is to quantify the association between the adherence to the MedDiet and risk of mortality from or incidence of cardiovascular disease and to assess the consistency of previous observational findings with those of randomised controlled trials (RCT).

SEARCH STRATEGY AND STUDY SELECTION

We will conduct electronic searches in PubMed, Embase, Google Scholar and Web of Science. Search terms: “Mediterranean diet” in combination with keywords relating to cardiovascular events (“cardiovascular disease”, or “cerebrovascular”, or “ischemic”, or “stroke”, or “coronary”). We also will review the bibliographies of the extracted articles and reviews to locate additional publications.

The parameters of search strategy will include the following filters: language (English, Spanish, Italian, French), age (up to 18 years old) and human studies. No time period limit will be established. Originals published up until May 2017 will be included in this search.
INCLUSION AND EXCLUSION CRITERIA

*Inclusion criteria*

- Clinical trials or prospective cohort studies with appropriate control of confounding, originals and primary prevention of mortality or incidence of cardiovascular disease through MedDiet.
- The exposure of interest was the adherence to the MedDiet
- The outcome was mortality from cardiovascular disease or incidence of cardiovascular events (coronary heart disease or stroke)

*Exclusion criteria*

- Presence of previous cardiovascular disease
- Reviews, editorials, comments, letters without sufficient data
- Abstracts of meeting presentations
- Non-human studies
- Cross-sectional or case-control studies
- Studies that did not specifically considered the adherence to the MedDiet on cardiovascular incidence or mortality from cardiovascular disease, or for which estimates for MedDiet associations were not available
- Studies of other exposures or studies reporting outcomes of other diseases
- Studies that have studied the adherence to the MedDiet using factor analysis

DATA EXTRACTION

Two independent reviewers initially will conduct the search strategy on primary titles and abstracts to select potential articles. Next, one of the reviewers will assess in detail the selected full-text article and will decide their eligibility according to the inclusion/exclusion criteria and will extract the data of interest for the cumulative meta-analysis after discussion and consensus.

**Study details:** authors, study design, sample size and sample characteristics, dietary assessment method, average duration of follow-up, number of non-fatal and fatal events and results and covariates in fully adjusted model.

**Analyses plan**

- Relative risks and 95% confidence intervals will be considered as the magnitude of association for all studies, and the odds ratios or hazard ratios will be considered equivalent to relative risks.
- Those articles reporting both risk of mortality from or incidence of cardiovascular disease will be treated as two separate reports.
- Because it is possible that different cut-off points for adherence to the MedDiet categories will be present in different articles, we will compute a relative risk with 95% confidence interval for an increase of two points in adherence to the MedDiet score for each report.
- Papers published by the same research group and studying similar factors in the same cohort will be checked for potential duplicate data. When it occurs, the most recent set will be used for meta-analysis, but excluding the incident events or cases of mortality reported in previous research.

**Management and Coordination**
- MAM-G will develop the initial plan, study design, and will be responsible for data collection, data extraction, and data initial interpretation.
- MAM-G will be responsible for statistical analysis.
- MAM-G and IZ will be responsible for data interpretation, critical revision of intellectual content, and approval of the version to be published.

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