Mediterranean diet and multiple health outcomes: an umbrella review of meta-analyses of observational studies and randomised

Mediterranean diet and multiple health outcomes: an umbrella review of meta-analyses of observational studies and randomized trials

Monica DINU, MSc[1]

Giuditta PAGLIAI, MSc[1]

Alessandro CASINI, MD[1,2]

Francesco SOFI, MD, PhD[1-3]

[1] Department of Experimental and Clinical Medicine, University of Florence, Italy; [2] Unit of Clinical Nutrition, University Hospital of Careggi, Florence, Italy; [3] Don Carlo Gnocchi Foundation Italy, Onlus IRCCS, Florence, Italy

Corresponding author:

Monica DINU, MSc
Department of Experimental and Clinical Medicine
University of Florence
Largo Brambilla, 3 50134 Florence
Tel: +39 055 7949420; Fax: +39 055 7949418; e-mail: mdinu@unifi.it

Running title: Mediterranean diet and health outcomes

Word count: 3906

Word count of abstract: 243

Number of tables: 2

Number of figures: 4

Number of references: 47

Abstract

Research has shown that a greater adherence to the Mediterranean diet is associated with a reduced risk of major chronic disease. However, the existing literature leads to debate for different issues, such as the measurement of the adherence to the Mediterranean diet, the use of a wide variety of dietary indices with various food components and the large heterogeneity across the studies. In order to summarize the evidence and evaluate the validity of the association between the adherence to the Mediterranean diet and multiple health outcomes, an umbrella review of the evidence across meta-analyses of observational studies and randomized clinical trials (RCTs) was performed. Thirteen meta-analyses of observational studies and 16 meta-analyses of RCTs investigating the association between the adherence to the Mediterranean diet and 37 different health outcomes, for a total population of over than 12,800,000 subjects, were identified. A robust evidence, supported by a p value < 0.001, a large simple size, and not a considerable heterogeneity between studies, for a greater adherence to the Mediterranean diet and a reduced the risk of overall mortality, cardiovascular diseases, coronary heart disease, myocardial infarction, overall cancer incidence, neurodegenerative diseases and diabetes was found. For most of the site-specific cancers, as well as for inflammatory and metabolic parameters, the evidence was only suggestive or weak and further studies are needed to draw firmer conclusions. No evidence, on the other hand, was reported for bladder, endometrial and ovarian cancers, as well as for LDL-cholesterol levels.

Key words: Mediterranean diet; Umbrella review; Meta-analyses; Outcomes

1. Introduction

The Mediterranean diet is a model of eating based on the traditional foods and drinks of the countries surrounding the Mediterranean Sea. Over the last few decades, it has been promoted worldwide as one of the healthiest dietary pattern and has been reported to be consistently beneficial with respect to chronic diseases and longevity. (1) There are individual foods and components within the Mediterranean Diet which are particularly beneficial to health (e.g. extra virgin olive oil), but overall it is the combination of foods which is linked to improved health. (2) This awareness shifted the research's focus from the analysis of individual nutrients to the evaluation of the whole diet and the interaction between its components.

Numerous different dietary indices estimating the adherence to the Mediterranean diet have been operationalised so far, finding that an increasing adherence to this diet is associated with a healthier life. In particular, recent meta-analyses demonstrated that a 2-point increase in adherence score determines a significant reduction of overall mortality, and a reduced risk of cardiovascular disease, cancer and neurodegenerative diseases. (3)

However, the existing literature is somewhat confusing and leads to debate for different issues such as the measurement of the adherence to the Mediterranean diet, the use of a wide variety of dietary indices with various food components and the large heterogeneity across the studies. In particular, 22 indexes quantifying the compliance to the Mediterranean diet have been described. (4). Several different methods such as the comparison between the highest and the lowest tertile, quintile or adherence category of the Mediterranean score used in each study, or continuous variables (1-point or 2-point increase in adherence score) have been used to pool data obtained with different indexes in meta-analyses.

Umbrella reviews or overviews of existing systematic reviews and/or meta-analyses are relatively new study designs that help providing a comprehensive and systematic examination of the scientific literature available for a specific research topic. (5) To the best of our knowledge, no attempts of reviewing the existing literature through an umbrella review in this issue has been conducted. Umbrella

review offers the possibility to understand the strength of evidence and extent of potential biases in the association between the adherence to the Mediterranean diet and different health outcomes.

Hence, aim of the present study was to summarise the available evidence on the existing meta-analyses on the Mediterranean diet and different health outcomes, and to provide an overview of the validity of the studied associations, by evaluating also possible hints of biases.

2. Methods

2.1. Search strategy

According to the Joanna Briggs Institute Umbrella Review Methodology (6) two reviewers (MD, FS) conducted a systematic literature search in Medline (1950 through February 2017), Embase (1980 through February 2017), Scopus (through February 2017), Cochrane database of systematic reviews, and Google Scholar (up to February 2017). Additional studies were searched by checking references of the identified articles. The following key words, used in combination as MeSH terms and text words were used: "diet", "Mediterranean" and their variants, which were used in combination with words relating to health status "plasma lipids", "cholesterol", "triglycerides", "glycaemia", "hematic parameters", "cancer", "circulatory diseases", "cardiovascular disease", "ischemic heart disease", "cerebrovascular disease", "mortality", "health effects", "health status", and their variants. The most updated or complete publication was used when more than an article was present for a single study. In addition, separate meta-analyses on multiple outcomes presented in a single article were assessed separately. Missing data or additional information were requested from the corresponding authors of the articles.

2.2. Eligibility criteria

Studies were included if they met the following criteria, established by using the PICOS strategy (Supplementary Table 1):

- Study design: systematic reviews including meta-analyses (quantitative analysis) of observational studies (prospective cohort studies, cross-sectional studies and case-control studies) or meta-analyses of randomized clinical trials (RCTs)
- Study population: >18 years
- Outcomes: health outcomes (e.g. overall mortality, cardiovascular diseases, cancer, cognitive disorders, metabolic disorders), modifications of metabolic risk parameters (e.g. anthropometric measurements, blood pressure, flow-mediated dilation, lipid profile and glycaemic profile) or modifications of inflammatory parameters (e.g. pro-inflammatory cytokines).

We excluded meta-analyses that did not present study specific data [effect size and 95% confidence intervals (CI)]. The decision to include studies was made on the basis of the study title, study abstract, and full-text screening.

2.3. Data extraction

Literature search and data extraction were conducted independently by two authors (MD, FS), with disagreements resolved by consensus with a third reviewer (GP). As the mixture of studies with different study design may increase heterogeneity, wherever possible we considered summary results separately in meta-analyses of prospective cohort studies, cross-sectional studies, case-control studies, and RCTs. The following data were extracted from each eligible meta-analysis and organized using a standard form: first author, year of publication, outcome examined, number of included studies, study design, type of comparison, number of events and population (in meta-analyses of cross-sectional and prospective cohort studies), number of cases and controls (in meta-analyses of case-control studies), number of subjects assigned to the intervention and the control groups (in meta-analyses of RCTs), maximally adjusted effect size measurements (i.e., relative risk/hazard ratio, odds ratio, mean difference) along with the corresponding 95% CI and quality of the included studies in each meta-analysis (when a qualitative assessment was performed). When the data were provided in mg/dL, they were transformed into mmol/L for consistency of results. Outcomes were categorized into 6 categories: overall mortality,

cardiovascular outcomes, cancer outcomes, cognitive disorders, metabolic disorders and inflammatory parameters.

2.4. Statistical analysis

The summary effect size and its confidence intervals (CIs) by 95% were estimated using both fixed-effects and random-effects models for each meta-analysis, by using Review Manager (RevMan, version 5.3 for Macintosh; The Cochrane Collaboration, Copenhagen, Denmark). For the summary random-effects, we estimated the 95% prediction interval (PI), which further accounts the degree of between-study heterogeneity and gives a range for which we are 95% confident that the effect in a new study examining the same association lies within. (7) Statistical heterogeneity between studies was evaluated using the I^2 statistic. (8) Where I^2 exceeded 50% or 75%, the heterogeneity was considered substantial or considerable, respectively.

In order to detect any evidence for small-study effects, we performed the Egger's regression asymmetry test (9) and we calculated the standard error (SE) of the effect size (under random effects) for the largest study of each meta-analysis. The largest study was defined on the basis of the smallest SE. If the p-value for Egger's test was <0.10 and the largest study had smaller effect size compared to the summary effect size (more conservative) both criteria for existence of small-study effects were fulfilled. (10)

Finally, according to previous umbrella reviews (11,12), we categorized the observed associations as convincing or not, by using the following criteria: significance at $p \leq 0.05$ and $p \leq 0.001$, which is considered to be a more appropriate threshold of statistical significance to reduce the number of false-positive findings (13); inclusion of over than 500 or 1,000 cases for binary outcomes (more than 2,500 or 5,000 total participants if the metric was continuous); absence of considerable heterogeneity ($I^2 <$ 75%); 95% PI excluding the null value and absence of small-study effects. Specifically, we identified 5 categories:

- *Convincing evidence:* significance threshold reached at $p \leq 0.001$ for both random- and fixed-effects calculation; >1,000 cases (or >5,000 total participants if the metric was continuous); not large heterogeneity between studies (I^2<50%); 95% PI excluding the null value; no evidence of small-study effects (if it could be tested)

- *Highly suggestive evidence:* significance threshold reached at $p \leq 0.001$ for both random- and fixed-effects calculation; >1,000 cases (or >5,000 total participants if the metric was continuous); not considerable heterogeneity between studies (I^2=50-75%)

- *Suggestive evidence:* significance threshold reached at $p \leq 0.001$ for random-effect calculation; 500-1,000 cases (or 2,500-5,000 total participants if the metric was continuous)

- *Weak evidence:* significance threshold reached at $p \leq 0.05$ for random-effects calculation

- *No-evidence:* significance threshold not reached ($p > 0.05$)

In addition, two reviewers (MD, FS) independently evaluated methodologic quality of the included meta-analyses using the modified version of the Assessment of Multiple Systematic Reviews (AMSTAR) questionnaire, developed to specifically address quality of meta-analyses on the Mediterranean diet - the $AMSTAR_{MedSD}$. (14) The $AMSTAR_{MedSD}$ contains a total of 14 questions, with a maximum score of 21. The scale's individual items describing individual methodologic aspects related to quality and rater's agreement, are described by Huedo-Medina. (14)

The concordance between the direction, the magnitude (overlapping CIs) and the statistical significance was examined when multiple meta-analyses of observational studies were present for the same outcome, while the concordance regarding the direction and the statistical significance was examined for multiple meta-analysis of RCTs. Statistical analysis was performed using the statistical package PASW 20.0 for Macintosh (SPSS, Inc.).

3. Results

Overall, 1,231 articles were identified, out of which 1,135 were excluded after a screening of titles and abstracts (including duplicates). Of the 96 remaining articles, 71 were excluded after full-text

187 screening for different reasons (Figure 1). The 25 remnant articles reported data from 140 different meta-
188 analyses.
189
190 ***3.1. Meta-analyses of observational studies***
191 Thirteen meta-analyses of observational studies (3, 15-26) reported the possible association
192 between the adherence to the Mediterranean diet and 35 different outcomes, for a total of 12,625,301
193 subjects. Study characteristics are summarized in Table 1. Overall, cohort prospective studies were
194 analysed in 12 different meta-analyses, case-control studies in 4, and cross-sectional studies in 5. Eleven
195 meta-analyses (16-26) compared high versus low adherence to the Mediterranean diet, 2 meta-analyses
196 (3, 15) evaluated health effects associated with a 2-point increase in the adherence score to the
197 Mediterranean diet, whereas 1 meta-analysis (22) evaluated health effects associated with a 1-point
198 increase in the adherence score.
199 By grouping the outcomes into the proposed categories, the included meta-analyses of
200 observational studies resulted as follows: overall mortality (n=1), cardiovascular outcomes (n=12), cancer
201 outcomes (n=26), cognitive disorders (n=14), and metabolic disorders (n=15). The median number of
202 included studies in each meta-analysis was 4 (range: 1-16), while the median number of cases was 1,752
203 (range: 111-82,198), and the median number of population/controls was 15,595 (range: 296-2,720,221).
204 For some specific outcomes (gastric cancer, liver cancer and oesophageal cancer), the selected meta-
205 analyses reported only 1 cohort study and only 1 case-control study.
206 Over than one meta-analysis was available for 21 different outcomes. As regards the concordance
207 between the magnitude, statistical significance of the effect and direction, agreement was present for
208 CVD incidence/mortality, overall cancer, colorectal cancer, neurodegenerative diseases, and diabetes.
209 Meta-analyses examining stroke, head/neck cancer, esophageal cancer, gastric cancer, breast cancer, liver
210 cancer, endometrial cancer, cognitive impairment, depression and metabolic syndrome reported
211 disagreement in terms of the statistical significance of the effect and/or in the magnitude, but not in the
212 direction of the effect, being all positively related to the protection for a greater adherence to the

Mediterranean diet. Finally, opposite results were found for dementia and prostate cancer, and non-comparable results were reported for waist circumference, triglycerides, HDL-cholesterol and glucose.

The forest plot with the summary effect for each health outcome evaluated in meta-analyses of observational studies is depicted in Figure 2. Whether for an outcome overlapping meta-analyses with the same study design existed, we retained the meta-analysis with the largest number of studies. Furthermore, whether the overlapping meta-analyses had the same number of studies, we reported the most recent.

3.2. Meta-analyses of randomised controlled studies (RCTs)

Sixteen different meta-analyses of RCTs (15, 16, 18, 26-38) analysed the effects of a dietary intervention with the Mediterranean diet on 26 outcomes (Table 2), grouped as follows: overall mortality (n=1), cardiovascular outcomes (n=26), metabolic disorders (n=41), and inflammatory parameters (n=3). The total number of subjects in the included RCTs was 202,148. The median number of the included studies in each meta-analysis was 6 (range: 1-39), and the median number of participants was 1,571 (101-25,370). Two meta-analyses of only 1 RCT included heart failure and diabetes, respectively, as clinical outcome.

Over than 1 meta-analysis was present for 15 different outcomes. For body weight, waist circumference, body mass index, total cholesterol, glucose, and C-reactive protein agreement existed across the meta-analyses for the statistical significance of the effect and the direction. On the other hand, meta-analyses examining CVD mortality, stroke, systolic blood pressure, diastolic blood pressure, triglycerides, HDL-cholesterol, insulin, and HbAc1 reported disagreements in terms of the significance of the effect, but not for the direction. As regarding LDL-cholesterol levels, no evidences were obtained in the 3 different meta-analyses.

The forest plot with the summary effects for each health outcome explored in RCTs is depicted in Figure 3.

3.3 Evaluation of bias, heterogeneity, and quality

The evaluation of the level of significance for both random- and fixed-effect calculations, the sample size, the heterogeneity, the 95% PI, and the presence of small study effects is reported in Supplementary Tables 2 and 3, for meta-analyses of observational studies and RCTs respectively. With regard to the bias assessment performed in order to detect evidences for small study effects, results are presented in Supplementary Tables 4 and 5.

On the basis of the $AMSTAR_{MedSD}$ assessment, meta-analyses achieved a medium-to-high quality score (mean ± SD: 16.36 ± 2.36). As reported in Supplementary Table 6, 11 meta-analyses totalled >80% of the highest achievable score (>16 points out of 21), and the remaining 14 meta-analyses totalled between 50% and 80% of the highest score (between 11 and 16 points). All the meta-analyses (100%) provided an 'a priori' design and performed a comprehensive literature search (22% at least searched electronic databases and 88% supplemented those with other sources such as reference list from other articles), and most of meta-analyses (84%) reported that there was duplicate study selection. Almost all the meta-analyses (96%) made it possible to replicate the literature search, but only 40% permitted the inclusion of grey literature. The list of included studies was provided in 92% of meta-analyses, 96% included characteristics of included studies, and 72% assessed and documented scientific quality of the included studies. In addition, the Newcastle Ottawa Scale (NOS) was used in 9 meta-analyses of observational studies (Supplementary Table 7). Five meta-analyses (3, 18, 25, 28, 31) performed a quality assessment using criteria set by the authors, 6 (20, 27, 29, 33, 37, 38) assessed the potential existence of bias using the Cochrane risk of bias tool, and 1 (35) used the Jadad score. Despite this, only 10% of meta-analyses reported how results might depend on study quality. All the meta-analyses used appropriate methods to combine study findings, whereas the likelihood of publication bias was assessed in 80% of meta-analyses.

3.4. Strength of evidence

Figure 4 shows the strength of the evidence estimated on the basis of the following criteria: level of significance for both random- and fixed-effect calculations, sample size, heterogeneity, 95% PI, and the presence of small study effects.

A positive effect of a greater adherence to the Mediterranean diet was found to be present in the convincing/highly suggestive categories for 12 different health outcomes (overall mortality, cardiovascular disease, coronary heart disease, myocardial infarction, overall cancer incidence/mortality, overall cancer incidence, breast cancer, neurodegenerative disease, cognitive impairment, Alzheimer's diseases, dementia and diabetes). Among these, overall mortality, cardiovascular disease, coronary heart disease, myocardial infarction and diabetes were examined by both meta-analyses of observational studies and RCTs, the latter showing no evidence (except for diabetes). For all the other outcomes, including overall cancer mortality, colorectal, gastric, pancreatic, liver and respiratory cancers, depression, as well as anthropometrical, metabolic and inflammatory risk parameters, the grade of evidence resulted suggestive or weak. As regarding stroke, systolic, diastolic blood pressure, and metabolic parameters, we observed mixed results, depending on the design of the included studies.

Finally, no association between the adherence to the Mediterranean diet and bladder, endometrial, and ovarian cancers in meta-analyses of observational studies was found. Similarly, there was no evidence for heart failure, major cardiovascular events and LDL-cholesterol in meta-analyses of RCTs.

4. Discussion

The present is the first umbrella review estimating the association between the adherence to the Mediterranean diet and 37 different health outcomes including overall mortality, cardiovascular outcomes, cancer outcomes, cognitive disorders, metabolic disorders, as well as inflammatory parameters. The overall analysis comprised 13 meta-analyses of observational studies and 16 meta-analyses of RCTs, for a total population of over than 12,800,000 subjects. Most summary estimates supported the notion that a greater adherence to the Mediterranean diet determines a reduction of the risk of chronic diseases and overall mortality. Furthermore, meta-analyses of RCTs demonstrated that subjects allocated to a

Mediterranean diet had, as compared with subjects following a control diet, better anthropometrical, metabolic and inflammatory risk parameters.

The largest proportion of the included meta-analyses examined metabolic disorders and cardiovascular outcomes. We observed a robust evidence, supported by a p value ≤ 0.001, large simple size, and not a considerable heterogeneity between studies for cardiovascular disease, coronary heart disease, and myocardial infarction, evaluated through meta-analyses of both observational studies and RCTs. The beneficial effects of the Mediterranean diet against these outcomes has usually been attributed to its influence on traditional atherosclerotic risk factors. (39-41) Accordingly, our analysis found suggestive evidence supporting the greater effectiveness of the Mediterranean diet in reducing weight, BMI and waist circumference, lowering total cholesterol levels, and increasing HDL-cholesterol levels, when compared to control diets. Conversely, no association was reported for LDL-cholesterol levels. Among metabolic disorders, our paper indicates that the association between the Mediterranean diet and reduced risk of diabetes was the most robust, whereas evidence for a protective effect against the metabolic syndrome was weaker. In addition, meta-analyses of RCTs provided suggestive evidence for a better glycaemic control, associated with reduced insulin resistance, in subjects following a Mediterranean diet in comparison to a control diet.

Actually, some authors have suggested that anti-inflammatory effects in the vascular wall may be another important mechanism that helps explaining the link between the Mediterranean diet and cardiovascular disease. (42) In addition, recent findings from the PREDIMED Study suggested that the reduction in serum nitric oxide and endothelin-1 as well as endothelin-1 receptors gene expression explain, at least partially, the effect of a Mediterranean diet high in olive oil or nuts on lowering blood pressure. (43) Few meta-analyses evaluated inflammatory parameters (28, 35), but all confirm an inverse relationship between a higher score of diet, CRP and IL-6, even if the grade of evidence is weak, partly due to a low statistical power. As regarding stroke, systolic and diastolic blood pressure, all meta-analyses of cross-sectional studies presented no evidences, in contrast to meta-analyses of prospective cohort

315 studies. This finding might be explained by intrinsic limitations of cross-sectional studies, that failed to
316 assess causal relationship between measures. (44)

317 As regarding cancer outcomes, selected meta-analyses suggested that adopting the Mediterranean
318 diet may help prevent cancer, although the current evidence is highly suggestive only for overall cancer,
319 and in particular for overall cancer incidence. A possible explanation of these results could be that
320 incidence and mortality are two different outcomes, with cancer mortality being mainly affected by the
321 treatment approaches. The analysis of specific localizations of cancer provided a small number of studies,
322 showing a suggestive or weak association for colorectal, liver, and pancreatic cancer. Conversely, meta-
323 analyses evaluating bladder, endometrial and ovarian cancer, provided null results. As far as the other
324 cancer sites such as breast, gastric, prostate, esophageal, respiratory and head/neck cancer are considered,
325 results resulted to be controversial. The low number of studies that analyzed this issue, and the low
326 sample size, as well as the limited cases (≤ 500) identified in some meta-analyses, may have limited
327 statistical power to detect an association. Moreover, the few existing studies have different study design,
328 so the comparison between studies is difficult. For example, as regarding breast cancer, the meta-analysis
329 of case-control studies (19), including approximately 15,000 subjects, showed a reduction in risk, whereas
330 the 2 meta-analyses of cohort studies (19, 20), including almost 1,500,000 subjects, reported no evidences.
331 The possible interpretation of this discrepancy could rely on the inherent limitations of self-reported
332 dietary data and report bias. Indeed, data originating from case-control studies result less robust because
333 of the likelihood of dietary report bias in subjects asked to report their dietary habits retrospectively after
334 a diagnosis of disease. Conversely, cohort studies generally assess dietary patterns before the onset of
335 diseases, being more likely to provide insight concerning the relationship between dietary exposures and
336 disease outcomes. (45) It is nevertheless important to know the role of dietary factors within the disease
337 process, in order to determine the relevant time-period of dietary assessment in cohort studies of chronic
338 diseases. (46)

339 The adherence to the Mediterranean diet was also correlated to cognitive functions. To date, there
340 are meta-analyses (3, 21, 23) providing convincing evidence in favour of a positive relationship with

neurodegenerative diseases, in particular with Alzheimer's disease and dementia, although, again, the meta-analysis of cross-sectional studies provided no evidence. (17) As previously discussed (47), standardization of tools used to assess cognitive function, is needed for evaluating the effectiveness of the Mediterranean diet for the prevention of cognitive impairment.

The methodologic quality of the meta-analyses and systematic reviews on the Mediterranean diet has been previously evaluated by Huedo-Medina and colleagues. (14) They applied the $AMSTAR_{MedSD}$ quality scale on 24 studies examining the association between the Mediterranean diet and cardiovascular disease outcomes, by identifying the studies that did not fully comply with contemporary methodologic quality standards. Our application of the $AMSTAR_{MedSD}$ tool obtained better results since all the investigated meta-analyses achieved a medium-to-high quality score, so suggesting that current meta-analyses evaluating the effects of the Mediterranean diet on health status partially or almost fully comply with methodologic quality standards. This difference could be explained by the fact that we included only meta-analyses, with respect to the reviews included by Huedo-Medina et al., that tended to achieve higher scores. (14)

The present umbrella review has several limitations that should be considered. First of all, very few studies exist for several outcomes like specific localizations of cancer or inflammatory parameters, making difficult to reach a definitive conclusion. Further and better designed studies are needed to confirm the present findings. Second, several primary studies achieved a low quality score when authors performed a quality assessment. Since the quality of meta-analyses is related to the quality of included studies, the results regarding the poorly covered outcomes need to be interpreted with caution. Third, a large part of evidence from RCTs is weak or suggestive, pointing out the need of further and better designed trials. Forth, the interpretation of tests for statistical bias offers suggestion of bias, but not definitive proofs.

In conclusion, this umbrella review provides a comprehensive resume of the published meta-analyses in relation to the Mediterranean diet and health outcomes, and maps the status of evidence. To date, the scientific literature has identified robust evidence for overall mortality, cardiovascular diseases,

overall cancer incidence, neurodegenerative diseases and diabetes. The relationship between the Mediterranean diet and other outcomes could be genuine, but there is still limited evidence for them. The large heterogeneity of dietary assessment methods and inadequacies relating to the study design, necessitate recommendations for future interventions to be sufficiently powered to detect clinical outcomes. Further studies adopting more uniform methodology and analyses, and detailed reporting of population, intervention, comparison and outcome data, would allow the quantification of the association of the Mediterranean diet adherence with health outcomes and quality of life.

Contributors: FS had the original idea for the study and designed the study. MD, GP and FS did the analysis. MD and FS wrote the first draft of the manuscript. All authors contributed to writing and reviewing the manuscript. AC and FS had final responsibility for the decision to submit the paper for publication.

Funding: No specific funding

Competing interest: The authors declare to have no conflict of interest

393 **References**

394 1) García-Fernández E, Rico-Cabanas L, Rosgaard N, Estruch R, Bach-Faig A. Mediterranean diet and
395 cardiodiabesity: a review. Nutrients 2014; 6: 3474-3500.
396
397 2) Vivancos M, Moreno JJ. Effect of resveratrol, tyrosol and beta-sitosterol on oxidised low-density
398 lipoprotein-stimulated oxidative stress, arachidonic acid release and prostaglandin E2 synthesis by RAW
399 264.7 macrophages. Br J Nutr 2008; 99: 1199-1207.
400
401 3) Sofi F, Macchi C, Abbate R, Gensini GF, Casini A. Mediterranean diet and health status: an updated
402 meta-analysis and a proposal for a literature-based adherence score. Public Health Nutr 2014; 17: 2769-
403 2782.
404
405 4) Hernández-Ruiz A, García-Villanova B, Guerra Hernández EJ, Amiano P, Azpiri M, Molina-Montes
406 E. Description of indexes based on the adherence to the Mediterranean dietary pattern: a review. Nutr
407 hosp 2015; 32: 1872-1884.
408
409 5) Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic
410 reviews: methodological development, conduct and reporting of an umbrella review approach. Int J Evid
411 Based Health 2015; 13: 132-140.
412
413 6) http://joannabriggs.org/assets/docs/sumari/ReviewersManual-Methodology-
414 JBI_Umbrella%20Reviews-2014.pdf
415
416 7) Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ 2011; 342: d549.
417

418 8) Cochran WG. The combination of estimates from different experiments. Biometrics 1954; 10: 101-
419 129.
420
421 9) Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical
422 test. BMJ 1997; 315: 629-634.
423
424 10) Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J et al. Recommendations for examining
425 and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ 2011; 343:
426 d4002.
427
428 11) Bellou V, Belbasis L, Tzoulaki I, Evangelou E, Ioannidis JP. Environmental risk factors and
429 Parkinson's disease: An umbrella review of meta-analyses. Parkinsonism Relat Disord 2016; 23: 1-9.
430
431 12) Belbasis L, Bellou V, Evangelou E, Ioannidis JP, Tzoulaki I. Environmental risk factors and multiple
432 sclerosis: an umbrella review of systematic reviews and meta-analyses. Lancet Neurol 2015; 14: 263-273.
433
434 13) Johnson VE. Revised standards for statistical evidence. Proc Natl Acad Sci USA 2013; 110: 19313–
435 19317.
436
437 14) Huedo-Medina TB, Garcia M, Bihuniak JD, Kenny A, Kerstetter J. Methodologic quality of meta-
438 analyses and systematic reviews on the Mediterranean diet and cardiovascular disease outcomes: a review.
439 Am J Clin Nutr 2016; 103: 841-850.
440
441 15) Martinez-Gonzalez MA, Bes-Rastrollo M. Dietary patterns, Mediterranean diet, and cardiovascular
442 disease. Curr Opin Lipidol 2014; 25: 20-26.
443

16) Grosso G, Marventano S, Yang J, Micek A, Pajak A, Scalfi L et al. A Comprehensive Meta-analysis on Evidence of Mediterranean Diet and Cardiovascular Disease: Are Individual Components Equal? Crit Rev Food Sci Nutr 2015; DOI: 10.1080/10408398.2015.1107021.

17) 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: 580-591.

18) Kastorini CM, Milionis HJ, Esposito K, Giugliano D, Goudevenos JA, Panagiotakos DB. The effect of Mediterranean diet on metabolic syndrome and its components: a meta-analysis of 50 studies and 534,906 individuals. J Am Coll Cardiol 2011; 57: 1299-1313.

19) Schwingshackl L, Hoffmann G. Adherence to Mediterranean diet and risk of cancer: an updated systematic review and meta-analysis of observational studies. Cancer Med 2015; 4: 1933-1947.

20) Bloomfield HE, Koeller E, Greer N, MacDonald R, Kane R, Wilt TJ. Effects on Health Outcomes of a Mediterranean Diet With No Restriction on Fat Intake: A Systematic Review and Meta-analysis. Ann Intern Med 2016; 165: 491-500.

21) Wu L, Sun D. Adherence to Mediterranean diet and risk of developing cognitive disorders: An updated systematic review and meta-analysis of prospective cohort studies. Sci Rep 2017; 7: 41317.

22) Singh B, Parsaik AK, Mielke MM, Erwin PJ, Knopman DS, Petersen RC et al. Association of mediterranean diet with mild cognitive impairment and Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis 2014; 39: 271-282.

470 23) Cao L, Tan L, Wang HF, Jiang T, Zhu XC, Lu H et al. Dietary Patterns and Risk of Dementia: a
471 Systematic Review and Meta-Analysis of Cohort Studies. Mol Neurobiol 2016; 53: 6144-6154.
472
473 24) Godos J, Zappalà G, Bernardini S, Giambini I, Bes-Rastrollo M, Martinez-Gonzalez M. Adherence
474 to the Mediterranean diet is inversely associated with metabolic syndrome occurrence: a meta-analysis of
475 observational studies. Int J Food Sci Nutr 2017; 68: 138-148.
476
477 25) Koloverou E, Esposito K, Giugliano D, Panagiotakos D. The effect of Mediterranean diet on the
478 development of type 2 diabetes mellitus: a meta-analysis of 10 prospective studies and 136,846
479 participants. Metabolism 2014; 63: 903-911.
480
481 26) Schwingshackl L, Missbach B, König J, Hoffmann G. Adherence to a Mediterranean diet and risk of
482 diabetes: a systematic review and meta-analysis. Public Health Nutr 2015; 18: 1292-1299.
483
484 27) Liyanage T, Ninomiya T, Wang A, Neal B, Jun M, Wong MG et al. Effects of the Mediterranean Diet
485 on Cardiovascular Outcomes-A Systematic Review and Meta-Analysis. PLoS One 2016; 11: e0159252.
486
487 28) Nordmann AJ, Suter-Zimmermann K, Bucher HC, Shai I, Tuttle KR, Estruch R et al. Meta-analysis
488 comparing Mediterranean to low-fat diets for modification of cardiovascular risk factors. Am J Med 2011;
489 124: 841-851.
490
491 29) Rees K, Hartley L, Flowers N, Clarke A, Hooper L, Thorogood M et al. 'Mediterranean' dietary
492 pattern for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2013; 8:
493 CD009825.
494

30) Huo R, Du T, Xu Y, Xu W, Chen X, Sun K et al. Effects of Mediterranean-style diet on glycemic control, weight loss and cardiovascular risk factors among type 2 diabetes individuals: a meta-analysis. Eur J Clin Nutr 2015; 69: 1200-1208.

31) Nissensohn M, Román-Viñas B, Sánchez-Villegas A, Piscopo S, Serra-Majem L. The Effect of the Mediterranean Diet on Hypertension: A Systematic Review and Meta-Analysis. J Nutr Educ Behav 2016; 48: 42-53.

32) Garcia M, Bihuniak JD, Shook J, Kenny A, Kerstetter J, Huedo-Medina TB. The Effect of the Traditional Mediterranean-Style Diet on Metabolic Risk Factors: A Meta-Analysis. Nutrients 2016; 8.

33) Gay HC, Rao SG, Vaccarino V, Ali MK. Effects of Different Dietary Interventions on Blood Pressure: Systematic Review and Meta-Analysis of Randomized Controlled Trials. Hypertension 2016; 67: 733-739.

34) Ndanuko RN, Tapsell LC, Charlton KE, Neale EP, Batterham MJ. Dietary Patterns and Blood Pressure in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Adv Nutr 2016; 7: 76-89.

35) Schwingshackl L, Hoffmann G. Mediterranean dietary pattern, inflammation and endothelial function: a systematic review and meta-analysis of intervention trials. Nutr Metab Cardiovasc Dis 2014; 24: 929-939.

36) Esposito K, Kastorini CM, Panagiotakos DB, Giugliano D. Mediterranean diet and weight loss: meta-analysis of randomized controlled trials. Metab Syndr Relat Disord 2011; 9: 1-12.

37) Ajala O, English P, Pinkney J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. Am J Clin Nutr 2013; 97: 505-516.

38) Esposito K, Maiorino MI, Bellastella G, Chiodini P, Panagiotakos D, Giugliano D. A journey into a Mediterranean diet and type 2 diabetes: a systematic review with meta-analyses. BMJ Open. 2015; 5: e008222.

39) Gajendragadkar PR, Hubsch A, Mäki-Petäjä KM, Serg M, Wilkinson IB, Cheriyan J. Effects of oral lycopene supplementation on vascular function in patients with cardiovascular disease and healthy volunteers: a randomised controlled trial. PLoS One 2014; 9: e99070.

40) Casas R, Sacanella E, Urpí-Sardà M, Chiva-Blanch G, Ros E, Martínez-González MA et al. The effects of the mediterranean diet on biomarkers of vascular wall inflammation and plaque vulnerability in subjects with high risk for cardiovascular disease. A randomized trial. PLoS One 2014; 9: e100084.

41) Storniolo CE, Roselló-Catafau J, Pintó X, Mitjavila MT, Moreno JJ. Polyphenol fraction of extra virgin olive oil protects against endothelial dysfunction induced by high glucose and free fatty acids through modulation of nitric oxide and endothelin-1. Redox Biol 2014; 2: 971-977.

42) Estruch R. Anti-inflammatory effects of the Mediterranean diet: the experience of the PREDIMED study. Proc Nutr Soc 2010; 69: 333-340.

43) Storniolo CE, Casillas R, Bulló M, Castañer O, Ros E, Sáez GT et al. A Mediterranean diet supplemented with extra virgin olive oil or nuts improves endothelial markers involved in blood pressure control in hypertensive women. Eur J Nutr 2017; 56: 89-97.

44) Sedgwick P. Cross sectional studies: advantages and disadvantages. BMJ 2014; 348: g2276.

45) Mann CJ. Observational research methods. Research design II: cohort, cross sectional, and case-control studies. Emerg Med J 2003; 20: 54-60.

46) Flegal KM. Evaluating epidemiologic evidence of the effects of food and nutrient exposures. Am J Clin Nutr 1999; 69: 1339S-1344S.

47) Cherbuin N, Anstey KJ. The Mediterranean diet is not related to cognitive change in a large prospective investigation: the PATH Through Life study. Am J Geriatr Psychiatry 2012; 20: 635-639.

575 **Legend to figures**

576

577 **Figure 1.** Flow diagram of the study selection process

578

579 **Figure 2.** Forest plot of all non-overlapping meta-analyses of observational studies reporting adherence
580 to Mediterranean diet in relation to different health outcomes

581

582 **Figure 3.** Forest plot of all non-overlapping meta-analyses of RCTs reporting Mediterranean diet versus
583 other diets intervention in relation to different health outcomes

584

585 **Figure 4.** Summary of the strength of evidence for the evaluated health outcomes. Numbers indicate the
586 number of meta-analyses with convincing, highly suggestive, suggestive, weak or no evidence for each
587 outcome

588

589

590

Table 1. Characteristics and quantitative synthesis of meta-analyses of observational studies reporting adherence to Mediterranean diet in relation to different clinical outcomes

Outcomes	Reference	n of studies/ study design	Comparison	Effect size	n	N	Summary relative risk (95% CI)		fixed p value	random p value	PI (95%)	I^2	Strength of evidence
							Fixed effects	Random Effects					
OVERALL MORTALITY													
Overall mortality	Sofi 2014[3]	15 cohort	2-point increase	RR	49 860	771 211	0.92 (0.91; 0.93)	0.91 (0.89; 0.93)	<0.0001	<0.0001	(0.89; 0.93)	47%	Highly suggestive
CARDIOVASCULAR OUTCOMES													
CVD inc/mort	Sofi 2014[3]	16 cohort	2-point increase	RR	16 566	775 081	0.91 (0.89; 0.93)	0.90 (0.87; 0.92)	<0.0001	<0.0001	(0.87; 0.93)	38%	**Convincing**
CVD inc/mort	M-Gonzalez 2014[15]	13 cohort	2-point increase	RR	18 589	676 331	0.94 (0.93; 0.96)	0.90 (0.86; 0.94)	<0.0001	<0.0001	(0.86; 0.94)	78%	Suggestive
CVD incidence	Grosso 2015[16]	13 cohort	high vs low	RR	13 434	275 162	0.75 (0.70; 0.80)	0.67 (0.58; 0.77)	<0.0001	<0.0001	(0.42; 1.06)	69%	Highly suggestive
CVD mortality	Grosso 2015[16]	13 cohort	high vs low	RR	9 563	778 510	0.86 (0.83; 0.90)	0.75 (0.68; 0.83)	<0.0001	<0.0001	(0.54; 1.04)	75%	Highly suggestive
CHD incidence	Grosso 2015[16]	4 cohort	high vs low	RR	2 943	153 502	0.74 (0.65; 0.83)	0.72 (0.60; 0.86)	<0.0001	0.0003	(0.40; 1.29)	43%	Highly suggestive
MI incidence	Grosso 2015[16]	3 cohort	high vs low	RR	1 364	44 428	0.67 (0.54; 0.83)	0.67 (0.54; 0.83)	0.0003	0.0003	(0.17; 2.71)	0%	Highly suggestive
Stroke	Psaltopoulou 2013[17]	4 cohort	high vs low	RR	2 560	152 843	0.84 (0.74; 0.95)	0.84 (0.74; 0.95)	0.007	0.007	(0.68; 1.03)	0%	Weak
Stroke	Psaltopoulou 2013[17]	2 case-contr	high vs low	RR	297	296	0.23 (0.15; 0.35)	0.20 (0.10; 0.41)	<0.0001	<0.0001	(0.09; 0.46)	0%	Weak
Stroke	Psaltopoulou 2013[17]	2 cross-sect	high vs low	RR	950	10 847	0.83 (0.67; 1.02)	0.83 (0.66; 1.06)	0.08	0.13	(0.51; 1.37)	13%	No evidence
Stroke	Grosso 2015[16]	5 cohort	high vs low	RR	2 444	159 995	0.81 (0.70; 0.93)	0.76 (0.60; 0.96)	0.003	0.02	(0.36; 1.59)	52%	Weak
Systolic BP (mmHg)	Kastorini 2011[18]	4 cross-sect	high vs low	MD	-	14 734 °	-2.83 (-3.00; -2.65)	-1.81 (-4.83; 1.21)	<0.0001	0.24	(-16.15; 11.43)	97%	No evidence
Diastolic BP (mmHg)	Kastorini 2011[18]	4 cross-sect	high vs low	MD	-	14 734 °	-6.28 (-6.45; 6.11)	-2.36 (-6.12; 1.40)	<0.0001	0.22	(-12.08; 8.46)	99%	No evidence
CANCER OUTCOMES													
Cancer inc/mort	Sofi 2014[3]	13 cohort	2-point increase	RR	82 198	2 720 221	0.96 (0.95; 0.97)	0.95 (0.93; 0.97)	<0.0001	<0.0001	(0.93; 0.97)	65%	Highly suggestive
Cancer inc/mort	Schwingshackl 2015[19]	11 cohort	high vs low	RR	46 715	956 821	0.87 (0.86; 0.89)	0.87 (0.81; 0.93)	<0.0001	<0.0001	(0.69; 1.09)	84%	Suggestive
Cancer mortality	Bloomfield 2016[20]	13 cohort	high vs low	RR	49 819	591 002	0.88 (0.86; 0.90)	0.86 (0.82; 0.91)	<0.0001	<0.0001	(0.69; 1.07)	77%	Suggestive
Cancer incidence	Bloomfield 2016[20]	3 cohort	high vs low	RR	48 683	534 058	0.96 (0.95; 0.97)	0.96 (0.95; 0.97)	<0.0001	<0.0001	(0.94; 0.98)	0%	**Convincing**
Colorectal cancer	Schwingshackl 2015[19]	3 cohort	high vs low	RR	8 935	1 013 583	0.84 (0.78; 0.90)	0.84 (0.75; 0.94)	<0.0001	0.002	(0.51; 1.38)	56%	Weak
Colorectal cancer	Schwingshackl 2015[19]	4 case-contr	high vs low	RR	4 744	36 099	0.87 (0.83; 0.90)	0.79 (0.67; 0.93)	<0.0001	0.004	(0.45; 1.38)	65%	Weak
Colorectal cancer	Bloomfield 2016[20]	9 cohort	high vs low	RR	12 819	1 415 995	0.93 (0.90; 0.97)	0.91 (0.84; 0.98)	0.002	0.02	0.72; 1.15)	63%	Weak
Breast cancer	Schwingshackl 2015[19]	4 cohort	high vs low	RR	15 832	489 109	0.98 (0.90; 1.07)	0.99 (0.89; 1.12)	0.64	0.93	(0.77; 1.29)	33%	No evidence
Breast cancer	Schwingshackl 2015[19]	8 case-contr	high vs low	RR	6 867	8 694	0.90 (0.85; 0.95)	0.90 (0.85; 0.95)	<0.0001	0.0001	(0.84; 0.96)	0%	**Convincing**
Breast cancer	Bloomfield 2016[20]	13 cohort	high vs low	RR	33 111	988 736	0.99 (0.95; 1.02)	0.96 (0.90; 1.03)	0.47	0.18	(0.76; 1.21)	53%	No evidence
Prostate cancer	Schwingshackl 2015[19]	3 cohort	high vs low	RR	29 806	366 037	0.96 (0.92; 1.00)	0.96 (0.92; 1.00)	0.03	0.04	(0.73; 1.25)	0%	Weak
Prostate cancer	Schwingshackl 2015[19]	1 case-contr	high vs low	RR	1 482	1 108	1.03 (0.81; 1.31)	1.03 (0.81; 1.31)	0.81	0.81	NE	NE	No evidence
Gastric cancer	Schwingshackl 2015[19]	2 cohort	high vs low	RR	1 382	980 012	0.82 (0.66; 1.01)	0.82 (0.61; 1.10)	0.06	0.18	(0.04; 15.06)	49%	No evidence
Gastric cancer	Schwingshackl 2015[19]	1 case-contr	high vs low	RR	999	2 628	0.57 (0.45; 0.72)	0.57 (0.45; 0.72)	<0.0001	<0.0001	NE	NE	Suggestive
Pancreatic cancer	Schwingshackl 2015[19]	1 case-contr	high vs low	RR	688	2 204	0.48 (0.35; 0.66)	0.48 (0.35; 0.66)	<0.0001	<0.0001	NE	NE	Suggestive
Liver cancer	Schwingshackl 2015[19]	1 case-contr	high vs low	RR	518	772	0.51 (0.34; 0.77)	0.51 (0.34; 0.77)	0.001	0.001	NE	NE	Weak
Liver cancer	Schwingshackl 2015[19]	1 cohort	high vs low	RR	509	494 942	0.62 (0.47; 0.82)	0.62 (0.47; 0.82)	0.0007	0.0007	NE	NE	Suggestive
Esophageal cancer	Schwingshackl 2015[19]	1 cohort	high vs low	RR	488	494 968	0.80 (0.60; 1.07)	0.68 (0.34; 1.36)	0.13	0.27	NE	71%	No evidence

Esophageal cancer	Schwingshackl 2015[19]	1 case-contr	high vs low	RR	304	743	0.26 (0.13; 0.52)	0.26 (0.13; 0.52)	0.0001	0.0001	NE	NE	Weak
Respiratory cancer	Schwingshackl 2015[19]	1 cohort	high vs low	RR	124	4 336	0.10 (0.01; 0.77)	0.10 (0.01; 0.77)	0.03	0.03	NE	NE	Weak
Head/neck cancer	Schwingshackl 2015[19]	3 case-contr	high vs low	RR	2 065	4 851	0.32 (0.26; 0.40)	0.32 (0.19; 0.55)	<0.0001	<0.001	(0.03; 2.95)	83%	Suggestive
Head/neck cancer	Schwingshackl 2015[19]	1 cohort	high vs low	RR	1 868	494 967	0.61 (0.33; 1.14)	0.61 (0.33; 1.14)	0.12	0.12	NE	NE	No evidence
Bladder cancer	Schwingshackl 2015[19]	1 cohort	high vs low	RR	1 425	477 312	0.84 (0.69; 1.02)	0.84 (0.69; 1.02)	0.08	0.08	NE	NE	No evidence
Endometrial cancer	Schwingshackl 2015[19]	1 cohort	high vs low	RR	1 392	84 415	0.98 (0.82; 1.17)	0.98 (0.82; 1.17)	0.82	0.82	NE	NE	No evidence
Endometrial cancer	Schwingshackl 2015[19]	2 case-contr	high vs low	RR	2 058	4 001	0.50 (0.41; 0.62)	0.61 (0.29; 1.29)	<0.0001	0.20	NE	89%	No evidence
Ovarian cancer	Schwingshackl 2015[19]	1 case-contr	high vs low	RR	696	82 948	0.91 (0.71; 1.17)	0.91 (0.71; 1.17)	0.46	0.46	NE	NE	No evidence
COGNITIVE DISORDERS													
Neurodeg. diseases	Sofi 2014[3]	5 cohort	2-point increase	RR	1 074	136 235	0.87 (0.81; 0.94)	0.87 (0.81; 0.94)	0.0005	0.0005	(0.77; 0.98)	0%	**Convincing**
Neurodeg. diseases	Wu 2017[21]	9 cohort	high vs low	RR	3 627	34 168	0.81 (0.74; 0.89)	0.79 (0.70; 0.90)	<0.0001	0.0003	(0.60; 1.04)	22%	Highly suggestive
Cognit. impairment	Psaltopoulou 2013[17]	4 cohort	high vs low	RR	819	5 916	0.72 (0.58; 0.88)	0.72 (0.58; 0.88)	0.001	0.001	(0.45; 1.13)	0%	Suggestive
Cognit. impairment	Singh 2014[22]	5 cohort	high vs low	HR	825	6 652	0.67 (0.55; 0.81)	0.67 (0.55; 0.81)	<0.0001	<0.0001	(0.49; 0.91)	0%	Suggestive
Cognit. impairment	Singh 2014[22]	5 cohort	1-point increase	HR	709^	6 878	0.92 (0.88; 0.97)	0.92 (0.88; 0.97)	0.0008	0.0008	(0.85; 1.00)	0%	Suggestive
Cognit. impairment	Psaltopoulou 2013[17]	1 case-contr	high vs low	RR	282	1 880	0.31 (0.16; 0.59)	0.31 (0.16; 0.59)	0.004	0.004	NE	NE	Weak
Cognit. impairment	Psaltopoulou 2013[17]	3 cross-sect	high vs low	RR	459	3 345	0.72 (0.58; 0.90)	0.52 (0.22; 1.22)	0.003	0.13	(0.01; 22.20)	88%	No evidence
Cognit. impairment	Wu 2017[21]	5 cohort	high vs low	RR	2 328	27 567	0.83 (0.75; 0.93)	0.83 (0.75; 0.93)	0.001	0.001	(0.66; 1.05)	0%	Highly suggestive
Alzheimer's disease	Wu 2017[21]	5 cohort	high vs low	RR	637	6 111	0.60 (0.48; 0.77)	0.60 (0.48; 0.77)	<0.0001	<0.0001	(0.44; 0.82)	0%	**Convincing**
Dementia	Cao 2015[23]	5 cohort	high vs low	RR	1 081	8 174	0.69 (0.57; 0.84)	0.69 (0.57; 0.84)	0.0002	0.0002	(0.51; 0.95)	0%	**Convincing**
Dementia	Wu 2017[21]	3 cohort	high vs low	RR	662	8 873	1.07 (0.81; 1.42)	1.07 (0.81; 1.42)	0.63	0.63	(0.58; 1.97)	0%	No evidence
Depression	Psaltopoulou 2013[17]	1 cohort	high vs low	RR	480	10 094	0.58 (0.44; 0.77)	0.58 (0.44; 0.77)	0.002	0.002	NE	NE	Weak
Depression	Psaltopoulou 2013[17]	1 case-contr	high vs low	RR	111	345	0.21 (0.09; 0.48)	0.21 (0.09; 0.48)	0.0002	0.0002	NE	NE	Weak
Depression	Psaltopoulou 2013[17]	7 cross-sect	high vs low	RR	1 718	7 406	0.80 (0.69; 0.93)	0.80 (0.69; 0.93)	0.004	0.004	(0.67; 0.96)	0%	Weak
METABOLIC DISORDERS													
WC (cm)	Kastorini 2011[18]	4 cross-sect	high vs low	MD	-	500 958 °	-1.34 (-1.42; -1.26)	-5.78 (-7.26; -4.31)	<0.0001	<0.0001	(-11.04; -0.52)	99%	Suggestive
WC (cm)	Godos 2017[24]	4 cross-sect	high vs low	RR	-	11 868 °	0.83 (0.74; 0.93)	0.82 (0.70; 0.96)	0.002	0.01	(0.54; 1.23)	22%	Weak
HDL-C (mmol/L)	Kastorini 2011[18]	6 cross-sect	high vs low	MD	-	9 831 °	0.06 (0.05; 0.06)	0.06 (0.03; 0.09)	<0.0001	<0.0001	(-2.43; 2.55)	87%	Suggestive
HDL-C (mmol/L)	Godos 2017[24]	4 cross-sect	high vs low	RR	-	11 868 °	0.92 (0.82; 1.02)	0.87 (0.77; 1.00)	0.10	0.04	(0.73; 1.04)	0%	Weak
TG (mmol/L)	Kastorini 2011[18]	6 cross-sect	high vs low	MD	-	9 831 °	-0.16 (-0.18; -0.14)	-0.11 (-0.18; -0.04)	<0.0001	<0.0001	(-15.06; 14.84)	82%	Suggestive
TG (mmol/L)	Godos 2017[24]	4 cross-sect	high vs low	RR	-	11 868 °	0.88 (0.78; 0.98)	0.84 (0.70; 1.01)	0.02	0.06	(0.49; 1.44)	44%	No evidence
Glucose (mmol/L)	Kastorini 2011[18]	6 cross-sect	high vs low	MD	-	9 269 °	-0.32 (-0.34; -0.31)	-0.22 (-0.32; -0.11)	<0.0001	0.0009	(-7.01; 6.57)	89%	Suggestive
Glucose (mmol/L)	Godos 2017[24]	4 cross-sect	high vs low	RR	-	11 868 °	1.03 (0.88; 1.21)	1.03 (0.87; 1.22)	0.73	0.72	(0.78; 1.35)	5%	No evidence
HOMA-Index	Kastorini 2011[18]	3 cross-sect	high vs low	MD	-	4 804 °	-0.41 (-0.43; -0.39)	-0.86 (-1.13; -0.59)	<0.0001	<0.0001	(-3.60; 3.08)	99%	Weak
Diabetes	Koloverou 2014[25]	10 cohort	high vs low	RR	19 663	136 846	0.84 (0.79; 0.89)	0.83 (0.74; 0.93)	<0.0001	0.002	(0.58; 1.18)	58%	Weak
Diabetes	Schwingshackl 2014[26]	8 cohort	high vs low	RR	19 463	111 269	0.83 (0.78; 0.89)	0.83 (0.74; 0.92)	<0.0001	0.0006	(0.62; 1.09)	56%	Highly suggestive
MetS	Kastorini 2011[18]	2 cohort	high vs low	RR	NA	4 495	0.80 (0.62; 1.03)	0.46 (0.11; 1.92)	0.08	0.30	NE	83%	No evidence

MetS	Kastorini 2011[18]	4 cross-sect	high vs low	OR	NA	4 500	0.88 (0.77; 1.00)	0.85 (0.61; 1.19)	0.06	0.34	(0.87; 25.09)	79%	No evidence
MetS	Godos 2017[24]	8 case-contr	high vs low	RR	4 590	17 390	0.98 (0.94; 1.01)	0.84 (0.73; 0.97)	0.18	0.02	(0.54; 1.31)	71%	Weak
MetS	Godos 2017[24]	4 cohort	high vs low	RR	1 752	16 457	0.74 (0.63; 0.88)	0.73 (0.54; 0.98)	0.0005	0.001	(0.29; 1.83)	74%	Suggestive

CVD = cardiovascular disease; CHD = coronary heart disease; MI = myocardial infarction; BP = blood pressure; CI = cognitive impairment; WC = waist circumference; HDL-C = high density lipoprotein cholesterol; TG = triglycerides; MetS = Metabolic Syndrome; RR = relative risk, MD = mean difference; OR = odds ratio; HR = hazard ratio; NA = not available; NE = not estimable because less than 3 studies were available for each meta-analysis
° number of total participants; ^ data from 1 study (Cherbuin 2011) was not available
To convert mmol/L cholesterol to mg/dL, multiply mmol/L by 38.67. To convert mmol/L triglycerides to mg/dL, multiply mmol/L by 88.57. To convert mg/dL blood glucose to mmol/L, multiply mmol/L by 18.

Supplementary Table 1. PICOS criteria used in the present umbrella review

Parameter	Description
Population	Inclusion: adults (>18 years) Exclusion: children and pregnant women
Intervention/correlate	Inclusion: Mediterranean diet Exclusion: other diets
Comparison	Observational studies: high adherence versus low adherence to the Mediterranean diet Randomized clinical trials: Mediterranean diet versus other diets
Outcome	Inclusion: health outcomes (e.g. overall mortality, cardiovascular diseases, cancer, cognitive disorders, diabetes, metabolic syndrome), modifications of metabolic risk parameters (e.g. anthropometric measurements, blood pressure, flow-mediated dilation, lipid profile and glycemic profile) or modifications of inflammatory parameters (e.g. pro-inflammatory cytokines) Exclusion: not health-related outcomes
Study design	Inclusion: systematic reviews including meta-analyses (quantitative analysis) of prospective studies, cross-sectional studies, case-control studies, or randomized clinical trials Exclusion: studies not published as peer-reviewed meta-analyses in international scientific journals, systematic reviews without quantitative analysis

Supplementary Table 2. Assessment across the meta-analyses of observational studies reporting adherence to the Mediterranean diet in relation to different health outcomes

Outcomes	Reference	Study design	Significance threshold reached (random effects)	Significance threshold reached (fixed effects)	Sample size	Estimate of heterogeneity	95% prediction interval	† Small study effects
OVERALL MORTALITY								
Overall mortality	Sofi 2014[3]	cohort	<0.001	<0.001	>1000	Not large	Excluding the null value	Yes
CARDIOVASCULAR OUTCOMES								
CVD incidence/mortality	Sofi 2014[3]	cohort	<0.001	<0.001	>1000	Not large	Excluding the null value	No[a]
CVD incidence/mortality	M-Gonzalez 2014[15]	cohort	<0.001	<0.001	>1000	Considerable	Excluding the null value	Yes
CVD incidence	Grosso 2015[16]	cohort	<0.001	<0.001	>1000	Substantial	Including the null value	Yes
CVD mortality	Grosso 2015[16]	cohort	<0.001	<0.001	>1000	Substantial	Including the null value	Yes
CHD incidence	Grosso 2015[16]	cohort	<0.001	<0.001	>1000	Not large	Including the null value	No
MI incidence	Grosso 2015[16]	cohort	<0.001	<0.001	>1000	Not large	Including the null value	No
Stroke	Psaltopoulou 2013[17]	cohort	<0.05	<0.05	>1000	Not large	Including the null value	No
Stroke	Psaltopoulou 2013[17]	case control	<0.001	<0.001	<500	Not large	Excluding the null value	NA
Stroke	Psaltopoulou 2013[17]	cross sectional	>0.05	>0.05	>500	Not large	Including the null value	No
Stroke	Grosso 2015[16]	cohort	<0.05	<0.05	>1000	Substantial	Including the null value	No
Systolic BP (mmHg)	Kastorini 2011[18]	cross sectional	>0.05	<0.001	>5000	Considerable	Including the null value	NA
Diastolic BP (mmHg)	Kastorini 2011[18]	cross sectional	>0.05	<0.001	>5000	Considerable	Including the null value	NA
CANCER OUTCOMES								
Cancer incidence/mortality	Sofi 2014[3]	cohort	<0.001	<0.001	>1000	Substantial	Excluding the null value	No
Cancer incidence/mortality	Schwingshackl 2015[19]	cohort	<0.001	<0.001	>1000	Considerable	Including the null value	No
Cancer mortality	Bloomfield 2016[20]	cohort	<0.001	<0.001	>1000	Considerable	Including the null value	No
Cancer incidence	Bloomfield 2016[20]	cohort	<0.001	<0.001	>1000	Not large	Excluding the null value	No
Colorectal cancer	Schwingshackl 2015[19]	cohort	<0.05	<0.001	>1000	Substantial	Including the null value	No
Colorectal cancer	Schwingshackl 2015[19]	case control	<0.05	<0.001	>1000	Substantial	Including the null value	No
Colorectal cancer	Bloomfield 2016[20]	cohort	<0.05	<0.05	>1000	Substantial	Including the null value	No
Breast cancer	Schwingshackl 2015[19]	cohort	>0.05	>0.05	>1000	Not large	Including the null value	No
Breast cancer	Schwingshackl 2015[19]	case control	<0.001	<0.001	>1000	Not large	Excluding the null value	No
Breast cancer	Bloomfield 2016[20]	cohort	>0.05	>0.05	>1000	Substantial	Including the null value	No
Prostate cancer	Schwingshackl 2015[19]	cohort	<0.05	<0.05	>1000	Not large	Including the null value	No
Prostate cancer	Schwingshackl 2015[19]	case-control	>0.05	>0.05	>1000	NA	NA	NA
Gastric cancer	Schwingshackl 2015[19]	cohort	>0.05	>0.05	>1000	Not large	Including the null value	No
Gastric cancer	Schwingshackl 2015[19]	case control	<0.001	<0.001	>500	NA	NA	NA
Pancreatic cancer	Schwingshackl 2015[19]	case control	<0.001	<0.001	>500	NA	NA	NA
Liver cancer	Schwingshackl 2015[19]	case control	<0.05	<0.05	>500	NA	NA	NA
Liver cancer	Schwingshackl 2015[19]	cohort	<0.001	<0.001	>500	NA	NA	NA
Esophageal cancer	Schwingshackl 2015[19]	cohort	>0.05	>0.05	<500	NA	NA	NA
Esophageal cancer	Schwingshackl 2015[19]	case control	<0.001	<0.001	<500	NA	NA	NA
Respiratory cancer	Schwingshackl 2015[19]	cohort	<0.05	<0.05	<500	NA	NA	NA
Head/neck cancer	Schwingshackl 2015[19]	case control	<0.001	<0.001	>1000	Considerable	Including the null value	No
Head/neck cancer	Schwingshackl 2015[19]	cohort	>0.05	>0.05	>1000	NA	NA	NA
Bladder cancer	Schwingshackl 2015[19]	cohort	>0.05	>0.05	>1000	NA	NA	NA
Endometrial cancer	Schwingshackl 2015[19]	cohort	>0.05	<0.05	>1000	NA	NA	NA
Endometrial cancer	Schwingshackl 2015[19]	case control	>0.05	<0.001	>1000	Considerable	NA	NA
Ovarian cancer	Schwingshackl 2015[19]	case control	>0.05	>0.05	>500	NA	NA	NA
COGNITIVE DISORDERS								

Neurodegenerative diseases	Sofi 2014[3]	cohort	<0.001	<0.001	>1000	Not large	Excluding the null value	No
Neurodegenerative diseases	Wu 2017[21]	cohort	<0.001	<0.001	>5000	Not large	Including the null value	No
Cognitive impairment	Psaltopoulou 2013[17]	cohort	<0.001	<0.001	>500	Not large	Including the null value	No
Cognitive impairment	Singh 2014[22]	cohort	<0.001	<0.001	>500	Not large	Excluding the null value	No
Cognitive impairment	Singh 2014[22]	cohort	<0.001	<0.001	>500	Not large	Excluding the null value	No
Cognitive impairment	Psaltopoulou 2013[17]	case control	<0.05	<0.05	<500	NA	NA	NA
Cognitive impairment	Psaltopoulou 2013[17]	cross sectional	>0.05	<0.05	<500	Considerable	Including the null value	No
Cognitive impairment	Wu 2017[21]	cohort	<0.001	<0.001	>5000	Not large	Including the null value	No[a]
Alzheimer's disease	Wu 2017[21]	cohort	<0.001	<0.001	>5000	Not large	Excluding the null value	No
Dementia	Cao 2015[23]	cohort	<0.001	<0.001	>1000	Not large	Excluding the null value	No
Dementia	Wu 2017[21]	cohort	>0.05	>0.05	>5000	Not large	Including the null value	No
Depression	Psaltopoulou 2013[17]	cohort	<0.05	<0.05	<500	NA	NA	NA
Depression	Psaltopoulou 2013[17]	case control	<0.001	<0.001	<500	NA	NA	NA
Depression	Psaltopoulou 2013[17]	cross-sectional	<0.05	<0.05	>1000	Not large	Excluding the null value	No
METABOLIC DISORDERS								
WC (cm)	Kastorini 2011[18]	cross sectional	<0.001	<0.001	>5000	Considerable	Excluding the null value	NA
WC (cm)	Godos 2017[24]	cross sectional	<0.05	<0.05	>5000	Not large	Including the null value	No
HDL-C (mmol/L)	Kastorini 2011[18]	cross sectional	<0.001	<0.001	>5000	Considerable	Including the null value	NA
HDL-C (mmol/L)	Godos 2017[24]	cross sectional	<0.05	>0.05	>5000	Not large	Including the null value	No
TG (mmol/L)	Kastorini 2011[18]	cross sectional	<0.001	<0.001	>5000	Considerable	Including the null value	NA
TG (mmol/L)	Godos 2017[24]	cross sectional	>0.05	<0.05	>5000	Not large	Including the null value	No
Glucose (mmol/L)	Kastorini 2011[18]	cross sectional	<0.001	<0.001	>5000	Considerable	Including the null value	NA
Glucose (mmol/L)	Godos 2017[24]	cross sectional	>0.05	>0.05	>5000	Not large	Including the null value	No
HOMA-Index	Kastorini 2011[18]	cross sectional	<0.001	<0.001	>2500	Considerable	Including the null value	NA
Diabetes	Koloverou 2014[25]	cohort	<0.05	<0.001	>1000	Substantial	Including the null value	No
Diabetes	Schwingshackl 2014[26]	cohort	<0.001	<0.001	>1000	Substantial	Including the null value	No[a]
MetS	Kastorini 2011[18]	cohort	>0.05	>0.05	>2500	Considerable	NA	NA
MetS	Kastorini 2011[18]	cross sectional	>0.05	>0.05	>2500	Considerable	Including the null value	NA
MetS	Godos 2017[24]	cohort	<0.05	>0.05	>5000	Substantial	Including the null value	No
MetS	Godos 2017[24]	cross sectional	<0.001	<0.001	>5000	Substantial	Including the null value	Yes

CVD = cardiovascular disease; CHD = coronary heart disease; MI = myocardial infarction; BP = blood pressure; HDL-C = high density lipoprotein cholesterol; TG = triglycerides; MetS = Metabolic Syndrome; NA = not available

† The presence of small study effects and/or excess significance test was not assessed in meta-analyses where data were reported as WMD

[a] The Egger test was statistically significant ($p<0.10$) but the largest study had larger effect size compared to the summary effect size under random effects, denoting the absence of small-study effects

Supplementary Table 3. Assessment across the meta-analyses of randomised controlled studies evaluating Mediterranean diet intervention versus other diets intervention in relation different health outcomes

Outcomes	Reference	Significance threshold reached (random effects)	Significance threshold reached (fixed effects)	Sample size	Estimate of heterogeneity	95% prediction interval	† Small study effects/excess significance bias
OVERALL MORTALITY							
Overall mortality	Liyanage 2016[27]	>0.05	>0.05	>5000	Substantial	Including the null value	No[a]
CARDIOVASCULAR OUTCOMES							
CVD incidence/mortality	M-Gonzalez 2014[15]	<0.05	<0.001	>5000	Substantial	NA	NA
CVD mortality	Grosso 2015[16]	<0.05	<0.05	>5000	Not large	Including the null value	No[a]
CVD mortality	Liyanage 2016[27]	>0.05	>0.05	>5000	Considerable	Including the null value	No[a]
CHD incidence	Liyanage 2016[27]	>0.05	>0.05	>5000	Considerable	NA	NA
Stroke	Grosso 2015[16]	<0.05	<0.05	>5000	Not large	NA	NA
Stroke	Liyanage 2016[27]	>0.05	<0.05	>5000	Not large	NA	NA
MI incidence	Grosso 2015[16]	<0.001	<0.001	>5000	Not large	Including the null value	No[a]
Heart failure	Liyanage 2016[27]	>0.05	>0.05	<2500	NE	NA	NA
MACE	Liyanage 2016[27]	>0.05	<0.001	>5000	Considerable	NA	NA
Systolic BP (mmHg)	Nordmann 2011[28]	<0.001	<0.001	>2500	Considerable	Including the null value	NA
Systolic BP (mmHg)	Kastorini 2011[18]	<0.001	<0.001	>2500	Not large	Including the null value	No
Systolic BP (mmHg)	Rees 2013[29]	<0.05	<0.001	>5000	Considerable	Including the null value	NA
Systolic BP (mmHg)	Huo 2014[30] ‡	NA	NA	NA	Not large	NA	NA
Systolic BP (mmHg)	Nissensohn 2015[27]	<0.05	<0.001	>5000	Considerable	Including the null value	NA
Systolic BP (mmHg)	Garcia 2016[24]	>0.05	<0.001	>5000	Substantial	Including the null value	NA
Systolic BP (mmHg)	Gay 2016[33]	<0.001	<0.001	>2500	Considerable	Including the null value	NA
Systolic BP (mmHg)	Ndanuko 2016[26]	<0.001	<0.001	<2500	Not large	Excluding the null value	NA
Diastolic BP (mmHg)	Nordmann 2011[28]	<0.001	<0.001	>2500	Substantial	Including the null value	NA
Diastolic BP (mmHg)	Kastorini 2011[18]	<0.001	<0.001	>2500	Not large	Excluding the null value	No
Diastolic BP (mmHg)	Rees 2013[29]	<0.001	<0.001	>5000	Substantial	Including the null value	NA
Diastolic BP (mmHg)	Huo 2014[30] ‡	NA	NA	NA	Not large	NA	NA
Diastolic BP (mmHg)	Nissensohn 2015[31]	<0.05	>0.05	>5000	Substantial	Including the null value	NA
Diastolic BP (mmHg)	Gay 2016[33]	<0.001	<0.001	>5000	Substantial	Including the null value	NA
Diastolic BP (mmHg)	Garcia 2016[32]	<0.05	<0.001	>2500	Considerable	Excluding the null value	No
Diastolic BP (mmHg)	Ndanuko 2016[34]	<0.001	<0.001	<2500	Not large	Excluding the null value	NA
FMD (%)	Schwingshackl 2014[35]	<0.05	<0.05	<2500	Not large	NA	NA
METABOLIC DISORDERS							
Weight (kg)	Esposito 2011[36] ‡	<0.001	NA	>2500	Considerable	NA	NA
Weight (kg)	Nordmann 2011[28]	<0.001	<0.001	>2500	Considerable	Including the null value	NA
Weight (kg)	Huo 2014[30]	<0.05	<0.05	<2500	Not large	Excluding the null value	No
BMI (kg/m^2)	Nordmann 2011[28]	<0.001	<0.001	>2500	Considerable	Including the null value	NA
BMI (kg/m^2)	Esposito 2011[36] ‡	<0.001	NA	>2500	Considerable	NA	NA
BMI (kg/m^2)	Huo 2014[30] ‡	<0.001	<0.001	<2500	Not large	Excluding the null value	No
WC (cm)	Nordmann 2011[28]	<0.001	<0.001	>2500	Considerable	Including the null value	NA
WC (cm)	Kastorini 2011[18]	<0.05	<0.05	<2500	Not large	Including the null value	No
WC (cm)	Huo 2014[30] ‡	NA	NA	<2500	Not large	NA	NA
WC (cm)	Garcia 2016[32]	<0.001	<0.001	>2500	Considerable	Including the null value	No
TC (mmol/L)	Nordmann 2011[28]	<0.001	<0.001	>2500	Substantial	Including the null value	NA

TC (mmol/L)	Rees 2013[29]	<0.05	<0.001	>2500	Substantial	Including the null value	NA
TC (mmol/L)	Huo 2014[30]	<0.001	<0.001	<2500	Not large	Excluding the null value	Yes
LDL-C (mmol/L)	Nordmann 2011[28]	>0.05	0.05	<2500	Not large	Including the null value	NA
LDL-C (mmol/L)	Rees 2013[29]	>0.05	<0.05	>2500	Not large	Including the null value	NA
LDL-C (mmol/L)	Huo 2014[30]	>0.05	>0.05	<2500	Not large	Including the null value	No
HDL-C (mmol/L)	Nordmann 2011[28]	>0.05	<0.001	>2500	Considerable	Including the null value	NA
HDL-C (mmol/L)	Kastorini 2011[18]	<0.001	<0.001	>2500	Substantial	Including the null value	No[a]
HDL-C (mmol/L)	Rees 2013[29]	>0.05	<0.001	>2500	Considerable	Including the null value	NA
HDL-C (mmol/L)	Huo 2014[30]	<0.05	<0.001	<2500	Substantial	Excluding the null value	No
HDL-C (mmol/L)	Garcia 2016[32]	>0.05	<0.001	<2500	Considerable	Including the null value	No
TG (mmol/L)	Kastorini 2011[18]	<0.05	<0.001	>2500	Substantial	Including the null value	No
TG (mmol/L)	Rees 2013[29]	>0.05	<0.001	>2500	Considerable	Including the null value	NA
TG (mmol/L)	Huo 2014[30]	<0.05	<0.001	<2500	Substantial	Including the null value	No
TG (mmol/L)	Garcia 2016[32]	<0.001	<0.001	<2500	Considerable	Including the null value	Yes
Glucose (mmol/L)	Nordmann 2011[28]	<0.05	<0.001	>2500	Considerable	Including the null value	NA
Glucose (mmol/L)	Kastorini 2011[18]	<0.001	<0.001	<2500	Substantial	Including the null value	No
Glucose (mmol/L)	Huo 2014[30]	<0.05	<0.001	<2500	Substantial	Including the null value	No
Glucose (mmol/L)	Garcia 2016[32]	<0.001	<0.001	>2500	Considerable	Including the null value	No
HOMA-Index	Kastorini 2011[18]	<0.001	<0.001	<2500	Considerable	Including the null value	NA
HOMA-Index	Huo 2014[30] ‡	NA	NA	NA	Not large	NA	NA
Insulin (μU/mL)	Nordmann 2011[28]	<0.001	<0.001	<2500	Considerable	Including the null value	No
Insulin (μU/mL)	Huo 2014[30]	<0.001	<0.001	<2500	Not large	Excluding the null value	NA
HbA_{c1}	Huo 2014[30]	<0.001	<0.001	<2500	Substantial	Including the null value	NA
HbA_{c1}	Ajala 2013[37]	>0.05	<0.001	<2500	Considerable	Including the null value	NA
HbA_{c1}	Esposito 2015[38]	<0.001	<0.001	<2500	Not large	Including the null value	NA
Diabetes	Schwingshackl 2014[26]	<0.05	<0.05	>2500	NE	NA	NA
MetS	Kastorini 2011[18]	<0.05	<0.001	<2500	Substantial	NA	NA
MetS remission	Esposito 2015[38]	<0.05	<0.001	>2500	Substantial	NA	NA
Adiponectin (μg/mL)	Schwingshackl 2014[35]	<0.05	<0.001	<2500	Considerable	NA	NA
ICAM-1 (ng/mL)	Schwingshackl 2014[35]	<0.05	<0.001	<2500	Not large	NA	NA
INFLAMMATORY PARAMETERS							
CRP (mg/L)	Nordmann 2011[28]	<0.001	<0.001	<2500	Considerable	Including the null value	NA
CRP (mg/L)	Schwingshackl 2014[35]	<0.001	<0.001	<2500	Considerable	Including the null value	NA
IL-6 (pg/mL)	Schwingshackl 2014[35]	<0.05	<0.001	<2500	Considerable	Including the null value	NA

CVD = cardiovascular disease; MI = myocardial infarction; BP = blood pressure; FMD = flow mediated dilation; BMI = body mass index; WC = waist circumference; TC = total cholesterol; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; TG = triglycerides; HbA_{1c} = haemoglobin A_{1c}; MetS = Metabolic Syndrome; ICAM-1 = intercellular adhesion molecule 1; CRP = C-reactive protein; IL-6 = interleukin-6; NA = not available

† The presence of small study effects and/or excess significance test was not assessed in meta-analyses where data were reported as WMD

[a] The Egger test was statistically significant ($p<0.10$) but the largest study had larger effect size compared to the summary effect size under random effects, denoting the absence of small-study effects

Supplementary Table 4. Bias assessment of meta-analyses of observational studies reporting high versus low adherence to Mediterranean diet in relation to different health outcomes

Outcome	Reference	Study design	Largest study (95% CI)	SE	† Egger test p-value
Overall mortality	Sofi 2014[3]	cohort	0.93 (0.91; 0.94)	0.01	<0.01
CVD incidence/mortality	Sofi 2014[3]	cohort	0.95 (0.91; 0.99)	0.02	<0.01
CVD incidence/mortality	M-Gonzalez 2014[15]	cohort	1.00 (0.98; 1.03)	0.01	<0.01
CVD incidence	Grosso 2015[16]	cohort	0.84 (0.75; 0.94)	0.06	<0.01
CVD mortality	Grosso 2015[16]	cohort	0.99 (0.93; 1.05)	0.03	<0.01
CHD incidence	Grosso 2015[16]	cohort	0.78 (0.65; 0.94)	0.09	0.35
MI incidence	Grosso 2015[16]	cohort	0.70 (0.53; 0.92)	0.14	0.34
Stroke	Psaltopoulou 2013[17]	cohort	0.87 (0.74; 1.03)	0.08	0.65
Stroke	Psaltopoulou 2013[17]	case-control	0.25 (0.15; 0.92)	0.26	NE
Stroke	Psaltopoulou 2013[17]	cross-sectional	0.70 (0.65; 1.06)	0.16	NE
Stroke	Grosso 2015[16]	cohort	0.90 (0.75; 1.08)	0.09	0.35
Systolic BP (mmHg)	Kastorini 2011[18]	cross-sectional	-3.00 (-3.18; -2.82)	0.09	0.62
Diastolic BP (mmHg)	Kastorini 2011[18]	cross-sectional	-7.00 (-7.18; -6.82)	0.09	0.19
Cancer incidence/mortality	Sofi 2014[3]	cohort	0.96 (0.95; 0.97)	0.01	0.10
Cancer incidence/mortality	Schwingshackl 2015[19]	cohort	0.80 (0.77; 0.83)	0.02	0.78
Cancer mortality	Bloomfield 2016[20]	cohort	0.95 (0.91; 0.99)	0.02	0.45
Cancer incidence	Bloomfield 2016[20]	cohort	0.96 (0.95; 0.97)	0.01	0.25
Colorectal cancer	Schwingshackl 2015[19]	cohort	0.89 (0.80; 0.99)	0.05	0.95
Colorectal cancer	Schwingshackl 2015[19]	case-control	0.88 (0.84; 0.92)	0.02	0.10
Colorectal cancer	Bloomfield 2016[20]	cohort	1.03 (0.93; 1.14)	0.05	0.19
Breast cancer	Schwingshackl 2015[19]	cohort	0.98 (0.86; 1.11)	0.07	0.29
Breast cancer	Schwingshackl 2015[19]	case-control	0.91 (0.86; 0.96)	0.03	0.28
Breast cancer	Bloomfield 2016[20]	cohort	0.94 (0.88; 1.00)	0.03	0.10
Prostate cancer	Schwingshackl 2015[19]	cohort	0.95 (0.92; 1.00)	0.03	NE
Gastric cancer	Schwingshackl 2015[19]	cohort	0.67 (0.47; 0.96)	0.18	NE
Esophageal cancer	Schwingshackl 2015[19]	cohort	0.91 (0.66; 1.25)	0.16	NE
Head/neck cancer	Schwingshackl 2015[19]	case-control	0.59 (0.39; 0.89)	0.21	0.13
Endometrial cancer	Schwingshackl 2015[19]	case-control	0.43 (0.34; 0.54)	0.12	NE
Neurodegenerative disease	Sofi 2014[3]	cohort	0.93 (0.80; 1.08)	0.08	0.47
Neurodegenerative diseases	Wu 2017[21]	cohort	0.87 (0.76; 1.00)	0.07	0.33
Cognitive impairment	Psaltopoulou 2013[17]	cohort	0.71 (0.52; 1.00)	0.17	0.21
Cognitive impairment	Singh 2014[22]	cohort	0.72 (0.52; 1.00)	0.17	0.98
Cognitive impairment	Singh 2014[22]	cohort	0.92 (0.85; 0.99)	0.04	0.13
Cognitive impairment	Psaltopoulou 2013[17]	cross-sectional	1.00 (0.77; 1.29)	0.13	0.62
Cognitive impairment	Wu 2017[21]	cohort	0.87 (0.76; 1.00)	0.07	0.05
Alzheimer's disease	Wu 2017[21]	cohort	0.60 (0.42; 0.86)	0.18	0.29
Dementia	Cao 2015[23]	cohort	0.72 (0.52; 1.00)	0.17	0.60
Dementia	Wu 2017[21]	cohort	1.13 (0.79; 1.62)	0.18	0.52

Depression	Psaltopoulou 2013[17]	cross-sectional	0.84 (0.68; 1.03)	0.11	0.71
Diabetes	Koloverou 2014[25]	cohort	0.88 (0.79; 0.97)	0.05	0.13
Diabetes	Schwingshackl 2014[35]	cohort	0.88 (0.79; 0.98)	0.06	0.09
MetS	Godos 2017[24]	cohort	0.96 (0.71; 1.30)	0.15	0.32
MetS	Godos 2017[24]	case-control	1.01 (0.97; 1.05)	0.02	0.04
WC (cm)	Godos 2017[24]	cross-sectional	0.76 (0.64; 0.90)	0.09	0.64
HDL-C (mmol/L)	Godos 2017[24]	cross-sectional	0.84 (0.69; 1.02)	0.10	0.15
TG (mmol/L)	Godos 2017[24]	cross-sectional	0.99 (0.83; 1.18)	0.09	0.15
Glucose (mmol/L)	Godos 2017[24]	cross-sectional	1.01 (0.77; 1.32)	0.14	0.34

CVD = cardiovascular disease; MI = myocardial infarction; BP = blood pressure; WC = waist circumference; HDL-C = high density lipoprotein cholesterol; TG = triglycerides; MetS = Metabolic Syndrome; NE = not estimable because less than 3 studies were available for each meta-analysis

† The Egger test was not performed in meta-analyses where data were reported as WMD

To convert mmol/L cholesterol to mg/dL, multiply mmol/L by 38.67. To convert mmol/L triglycerides to mg/dL, multiply mmol/L by 88.57. To convert mg/dL blood glucose to mmol/L, multiply mmol/L by 18

Supplementary Table 5. Bias assessment of meta-analyses of randomised control studies evaluating Mediterranean diet intervention versus other diets intervention in relation different health outcomes

Outcome	**Reference**	**Largest study (95% CI)**	**SE**	**Egger test p-value †**
Overall mortality	Liyanage 2016[27]	1.01 (0.81; 1.25)	0.11	0.20
CVD incidence/mortality	M-Gonzales 2014[15]	0.71 (0.56; 0.90)	0.19	NE
CVD mortality	Grosso 2015[16]	0.83 (0.54; 1.28)	2.00	0.04
CVD mortality	Liyanage 2016[27]	1.22 (0.90; 1.65)	0.16	<0.01
CHD incidence	Liyanage 2016[27]	0.88 (0.59; 1.30)	0.20	NE
Stroke	Grosso 2015[16]	0.61 (0.44; 0.85)	0.17	NE
Stroke	Liyanage 2016[27]	0.68 (0.49; 0.96)	0.17	NE
MI incidence	Grosso 2015[16]	0.77 (0.52; 1.14)	0.20	0.09
Heart failure	Liyanage 2016[27]	0.25 (0.05; 1.17)	0.82	NE
MACE	Liyanage 2016[27]	0.81 (0.64; 1.02)	0.12	NE
Systolic BP (mmHg)	Garcia 2016[32]	-1.00 (-1.06; -0.94)	0.03	0.14
Diastolic BP (mmHg)	Garcia 2016[32]	-0.51 (-0.67; -0.34)	0.08	0.83
WC (cm)	Garcia 2016[32]	-0.69 (-0.87; -0.52)	0.09	0.85
HDL-C (mmol/L)	Garcia 2016[32]	-0.05 (-0.28; 0.18)	0.12	0.71
TG (mmol/L)	Garcia 2016[32]	-0.07 (0.27; 0.13)	0.10	0.09
Glucose (mmol/L)	Garcia 2016[32]	-0.40 (-0.45; -0.34)	0.03	0.52
MetS remission	Esposito 2015[38]	1.32 (1.12; 1.55)	0.08	NE

CVD = cardiovascular disease; MI = myocardial infarction; BP = blood pressure; ; FMD = flow mediated dilation; BMI = body mass index; MACE = major cardiovascular events; WC = waist circumference; TC = total cholesterol; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; TG = triglycerides; HbA_{1c} = haemoglobin A_{1c}; MetS = Metabolic Syndrome; ICAM-1 = intercellular adhesion molecule 1; CRP = C-reactive protein; IL-6 = interleukin-6; NE = not estimable because less than three studies were available for each meta-analysis

† The Egger test was not performed in meta-analyses where data were reported as WMD

To convert mmol/L cholesterol to mg/dL, multiply mmol/L by 38.67. To convert mmol/L triglycerides to mg/dL, multiply mmol/L by 88.57. To convert mg/dL blood glucose to mmol/L, multiply mmol/L by 18.

Supplementary Table 6. Item-by-item methodological quality of meta-analyses examining Mediterranean diet and health outcomes

	AMSTAR$_{MedSD}$ Items														
	A priori design		*Literature search and Duplicate effort*					*Coding of studies*		*Analysis and Interpretation*					**Total score**
Meta-analyses	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Q10**	**Q11**	**Q12**	**Q13**	**Q14**	
Esposito 2011[36]	1	1	1	2	1	1	1	1	2	0	2	1	1	1	16
Kastorini 2011[18]	1	1	1	2	1	0	1	1	2	1	3	1	1	1	17
Nordmann 2011[28]	1	1	1	2	1	0	1	1	1	0	3	1	1	1	15
Ajala 2013[37]	1	1	0	2	0	0	2	1	2	0	3	1	0	1	14
Psaltopoulou 2013[17]	1	1	1	2	2	1	1	1	2	0	3	2	1	1	19
Rees 2013[29]	1	1	1	2	2	1	2	1	2	0	3	2	1	1	20
Huo 2014[30]	1	1	1	2	1	0	1	1	2	0	3	1	1	1	16
Koloverou 2014[25]	1	1	1	2	1	0	1	1	1	0	3	2	1	1	16
M-Gonzalez 2014[15]	1	1	0	1	1	1	0	0	0	0	3	1	1	1	11
Schwingshackl 2014[26]	1	1	1	2	1	0	1	1	2	0	3	2	1	1	17
Schwingshackl 2014[35]	1	1	1	1	1	0	1	1	2	0	3	2	1	1	16
Singh 2014[22]	1	1	2	2	2	1	2	1	2	0	3	1	1	1	20
Sofi 2014[3]	1	1	1	2	1	1	0	1	0	0	3	1	1	1	14
Cao 2015[23]	1	1	1	2	1	0	1	1	0	0	3	1	1	1	14
Esposito 2015[38]	1	1	2	2	1	0	1	1	2	0	3	1	1	1	17
Grosso 2015[16]	1	1	1	2	1	0	1	1	2	0	3	1	1	1	16
Nissensohn 2015[27]	1	1	1	2	1	1	1	1	2	0	3	2	1	1	18
Schwingshackl 2015[19]	1	1	1	2	1	1	1	1	2	0	3	2	1	1	18
Bloomfield 2016[20]	1	1	0	2	2	0	1	1	2	0	3	1	0	1	15
Garcia 2016[32]	1	1	1	2	2	1	2	1	2	0	3	2	1	1	20
Gay 2016[33]	1	1	1	2	1	0	1	1	2	0	3	2	0	1	16
Liyanage 2016[27]	1	1	1	2	2	0	2	1	2	1	3	1	0	1	18
Ndanuko 2016[34]	1	1	0	1	1	0	1	1	1	0	3	1	0	1	12
Godos 2017[24]	1	1	1	2	1	0	1	1	1	0	3	1	1	1	15
Wu 2017[21]	1	1	1	2	2	1	2	1	2	0	3	1	1	1	19
Completely satisfactory (%)	100%	100%	76%	88%	28%	40%	24%	96%	72%	8%	96%	36%	80%	100%	
Not completely satisfactory (%)	NA	NA	8%	12%	68%	NA	68%	NA	16%	NA	4%	64%	NA	NA	
Unsatisfactory (%)	0	0	16%	0	4%	60%	8%	4%	12%	92%	0	0	20%	0	

Q1 = Was an 'a priori' design provided? (0 – 1); Q2 = Were population variables defined and considered in the methods? (0 – 1); Q3 = Was there duplicate study selection and data extraction? (0 – 2); Q4 = Was a comprehensive literature search performed? (0 – 2); Q5 = Is it possible to replicate the search? (0 – 2); Q6 = Did the inclusion criteria permit grey literature? (0 – 1); Q7 = Was a list of studies (included and excluded) provided? (0 – 2); Q8 = Were the characteristics of the included studies provided? (0 – 1); Q9 = Was the scientific quality of the included studies assessed and documented? (0 – 2); Q10 = Did results depend on study quality, either overall, or in interaction with moderators? (0 – 1); Q11 = Were the methods used to combine the findings of studies appropriate? (0 – 3); Q12 = Was the effect size index chosen justified, statistically? (0 – 2); Q13 = Was the likelihood of publication bias assessed? (0 – 1); Q14 = Was the conflict of interest included? (0 – 1)
2 (or 3 for those with 3 category option) = Completely satisfied, 1 (or 2 for those with 3 category option) = Partially satisfied; 0 = Not satisfied; NA = Not applicable
Satisfactory percentages are based out of the total meta-analyses for which the dimension was judged applicable

Supplementary Table 7. Meta-analyses assessed the quality of the primary observational studies using the Newcastle Ottawa Scale (NOS)

Reference	Outcome	Type of studies	High quality (NOS score = 9)	Moderate quality (NOS score = 7 or 8)	Low quality (NOS score < 7)
Stroke	Psaltopoulou 2013[17]	cohort	1	3	0
Stroke	Psaltopoulou 2013[17]	case-control	0	1	1
Stroke *	Psaltopoulou 2013[17]	cross-sectional	0	2	3
Stroke	Grosso 2015[16]	cohort	0	5	0
CVD incidence	Grosso 2015[16]	cohort	0	11	2
CVD mortality	Grosso 2015[16]	cohort	0	10	3
CHD incidence	Grosso 2015[16]	cohort	0	3	1
MI incidence	Grosso 2015[16]	cohort	0	3	0
Overall cancer	Schwingshackl 2015[19]	cohort	2	7	1
Colorectal cancer	Schwingshackl 2015[19]	cohort	0	3	0
Colorectal cancer	Schwingshackl 2015[19]	cross-sectional	0	2	2
Breast cancer	Schwingshackl 2015[19]	cohort	0	4	0
Breast cancer	Schwingshackl 2015[19]	cross-sectional	0	4	4
Prostate cancer	Schwingshackl 2015[19]	cohort	1	1	1
Prostate cancer	Schwingshackl 2015[19]	cross-sectional	0	1	0
Gastric cancer	Schwingshackl 2015[19]	cohort	1	1	0
Gastric cancer	Schwingshackl 2015[19]	cross-sectional	0	0	1
Esophageal cancer	Schwingshackl 2015[19]	cohort	1	0	0
Esophageal cancer	Schwingshackl 2015[19]	cross-sectional	0	0	1
Endometrial cancer	Schwingshackl 2015[19]	cohort	0	1	0
Endometrial cancer	Schwingshackl 2015[19]	cross-sectional	0	0	1
Ovarian cancer	Schwingshackl 2015[19]	cross-sectional	0	1	0
Respiratory cancer	Schwingshackl 2015[19]	cohort	0	0	1
Bladder cancer	Schwingshackl 2015[19]	cohort	0	1	0
Pancreatic cancer	Schwingshackl 2015[19]	cross-sectional	0	0	1
Liver cancer	Schwingshackl 2015[19]	cohort	1	0	0
Liver cancer	Schwingshackl 2015[19]	cross-sectional	0	0	1
Head/neck cancer	Schwingshackl 2015[19]	cohort	1	0	0
Head/neck cancer	Schwingshackl 2015[19]	cross-sectional	0	0	4
Neurodegenerative disease	Wu 2017[21]	cohort	2	11	0
Cognitive impairment	Psaltopoulou 2013[17]	cohort	1	3	0
Cognitive impairment	Psaltopoulou 2013[17]	cross-sectional	0	1	0
Cognitive impairment *	Psaltopoulou 2013[17]	cross-sectional	0	2	2
Cognitive impairment	Singh 2014[22]	cohort	1	4	0
Cognitive impairment °	Singh 2014[22]	cohort	1	4	0
Cognitive impairment	Wu 2017[21]	cohort	1	4	0
Alzheimer's disease	Wu 2017[21]	cohort	0	5	0
Dementia	Wu 2017[21]	cohort	1	2	0

Depression	Psaltopoulou 2013[17]	cohort	0	0	1
Depression	Psaltopoulou 2013[17]	cross-sectional	0	0	1
Depression *	Psaltopoulou 2013[17]	cross-sectional	0	5	2
Diabetes	Schwingshackl 2014[35]	cohort	2	5	0
Systolic BP	Nissensohn 2016[31]	RCTs	0	1	5
Diastolic BP	Nissensohn 2016[31]	RCTs	0	1	5

*These papers used as a threshold for high quality a NOS score = 6
° 1-point increase in adherence to the Mediterranean Diet
RCT = randomized controlled trials. Data not reported in the study by Godos et al, 2017[24]

Table 2. Characteristics and quantitative synthesis of meta-analyses of randomised control studies (RCTs) reporting Mediterranean diet versus other diets intervention in relation to different clinical outcomes

Outcomes	Reference	n of studies	Effect size	n Mediterranean diet	n control diet	Summary relative risk (95% CI)		fixed p value	random p value	PI (95%)	I^2	Strength of evidence
						Fixed effects	Random Effects					
OVERALL MORTALITY												
Overall mortality	Liyanage 2016[27]	3	RR	6 630	4 041	1.05 (0.90; 1.22)	0.93 (0.65; 1.33)	0.57	0.70	(0.44; 2.52)	66%	No evidence
CARDIOVASCULAR OUTCOMES												
CVD inc/mort	M-Gonzalez 2014[15]	2	RR	5 133	7 761	0.64 (0.53; 0.79)	0.62 (0.45; 0.86)	0.0001	0.004	NE	54%	Weak
CVD mortality	Grosso 2015[16]	4	RR	7 418	4 875	0.65 (0.48; 0.89)	0.59 (0.38; 0.93)	0.007	0.02	(0.12; 3.02)	46%	Weak
CVD mortality	Liyanage 2016[27]	3	RR	6 106	3 517	0.99 (0.78; 1.26)	0.79 (0.42; 1.50)	0.95	0.47	(0.12; 7.96)	78%	No evidence
CHD incidence	Liyanage 2016[27]	2	RR	5 299	2 753	0.73 (0.51; 1.05)	0.56 (0.20; 1.61)	0.09	0.28	NE	76%	No evidence
Stroke	Grosso 2015[16]	2	RR	6 617	4 071	0.64 (0.47; 0.87)	0.64 (0.47; 0.86)	0.004	0.004	NE	0%	Weak
Stroke	Liyanage 2016[27]	2	RR	5 299	2 753	0.66 (0.48; 0.92)	0.64 (0.34; 1.20)	0.01	0.16	NE	6%	No evidence
MI incidence	Grosso 2015[16]	3	RR	7 116	4572	0.61 (0.46; 0.79)	0.60 (0.44; 0.82)	0.0003	0.001	(0.04; 9.06)	26%	Highly suggestive
Heart failure	Liyanage 2016[27]	1	RR	302	303	0.25 (0.05; 1.17)	0.25 (0.05; 1.17)	0.08	0.08	NE	NE	No evidence
MACE	Liyanage 2016[27]	2	RR	5 299	2 753	0.69 (0.55; 0.86)	0.45 (0.13; 1.57)	0.0009	0.21	NE	94%	No evidence
Systolic BP (mmHg)	Nordmann 2011[28]	6	WMD	1 641	1 009	-2.18 (-2.55; -1.80	-1.70 (-3.35; -0.05)	<0.0001	<0.0001	(-6.97; 3.57)	89%	Suggestive
Systolic BP (mmHg)	Kastorini 2011[18]	14	MD	1 632	1 436	-1.79 (-2.25; -1.32)	-2.35 (-3.51; -1.18)	<0.0001	0.0001	(-5.71; 1.01)	15%	Suggestive
Systolic BP (mmHg)	Rees 2013[29]	5	MD	14 357	25 370	-1.51 (-1.78; -1.24)	-2.61 (-4.54; -0.69)	<0.0001	0.008	(-8.75; 3.53)	94%	Weak
Systolic BP (mmHg)	Huo 2014[30] ‡	6	WMD	NA	NA	NA	-1.45 (-1.97; -0.94)	NA	NA	NA	0%	NA
Systolic BP (mmHg)	Nissensohn 2015[27]	6	WMD	5 226	5 111	-0.74 (-1.19; -0.30)	-1.44 (-2.88; 0.01)	0.001	0.05	(-5.52; 2.64)	87%	Weak
Systolic BP (mmHg)	Garcia 2016[24]	25	SMD	NA	3 262 °	-0.76 (-0.81; -0.72)	-0.67 (-0.87; -0.47)	<0.0001	<0.0001	(-1.64; 0.30)	93%	Suggestive
Systolic BP (mmHg)	Gay 2016[33]	4	WMD	5 148	5 013	-1.99 (-2.35; -1.64)	-1.17 (-2.81; 0.46)	<0.0001	0.16	(-8.76; 4.52)	93%	No evidence
Systolic BP (mmHg)	Ndanuko 2016[26]	3	WMD	310	225	-3.02 (-3.47; -2.58)	-3.02 (-3.47; -2.58)	<0.0001	<0.0001	(-5.94; -0.10)	0%	Weak
Diastolic BP (mmHg)	Nordmann 2011[28]	6	WMD	1 641	1 009	-1.77 (-2.02; -1.52)	-1.47 (-2.14; -0.80)	<0.0001	0.0001	(-3.26; 0.32)	60%	Suggestive
Diastolic BP (mmHg)	Kastorini 2011[18]	14	MD	1 632	1 436	-1.51 (-1.87; -1.15)	-1.58 (-2.02; -1.13)	<0.0001	<0.0001	(-2.15; -1.01)	2%	Suggestive
Diastolic BP (mmHg)	Rees 2013[29]	5	MD	17 356	25 366	-1.07 (-1.23; -0.92)	-1.69 (-2.79; -0.59)	<0.0001	0.003	(-5.09; 1.71)	93%	Suggestive
Diastolic BP (mmHg)	Huo 2014[30] ‡	3	WMD	NA	NA	NA	-1.41 (-1.84; -0.97)	NA	NA	NA	0%	NA
Diastolic BP (mmHg)	Nissensohn 2015[31]	6	WMD	5 226	5 111	-0.21 (-0.48; 0.07)	-0.70 (-1.34; -0.07)	0.14	0.03	(-2.19; 0.79)	63%	Weak
Diastolic BP (mmHg)	Gay 2016[33]	4	WMD	5 148	5 013	-1.61 (-1.84; -1.39)	-1.44 (-2.11; -0.76)	<0.0001	<0.0001	(-6.75; 1.53)	82%	Suggestive
Diastolic BP (mmHg)	Garcia 2016[32]	25	SMD	NA	3 262 °	-0.98 (-1.05; -0.92)	-0.94 (-1.55; -0.34)	<0.0001	0.002	(-2.62; 0.74)	99%	Weak
Diastolic BP (mmHg)	Ndanuko 2016[34]	3	WMD	310	225	-1.99 (-2.28; -1.71)	-1.99 (-2.28; -1.71)	<0.0001	<0.0001	(-3.87; -0.11)	0%	Weak
FMD (%)	Schwingshackl 2014[35]	2	WMD	109	101	1.71 (0.56; 2.87)	1.86 (0.23; 3.48)	0.004	0.02	NE	43%	Weak
METABOLIC DISORDERS												
Weight (kg)	Esposito 2011[36] ‡	15	MD	1 937	1 588	NA	-1.75 (-2.86; -0.64)	NA	<0.001	NA	95%	Weak
Weight (kg)	Nordmann 2011[28]	6	WMD	1 641	1 009	-1.92 (-2.12; -1.71)	-2.24 (-3.86; -0.86)	<0.0001	<0.0001	(-7.89; 3.41)	97%	Suggestive
Weight (kg)	Huo 2014[30]	6	MD	492	365	-0.29 (-0.55; -0.04)	-0.29 (-0.55; -0.04)	0.02	0.02	(0.59; 0.01)	0%	Weak

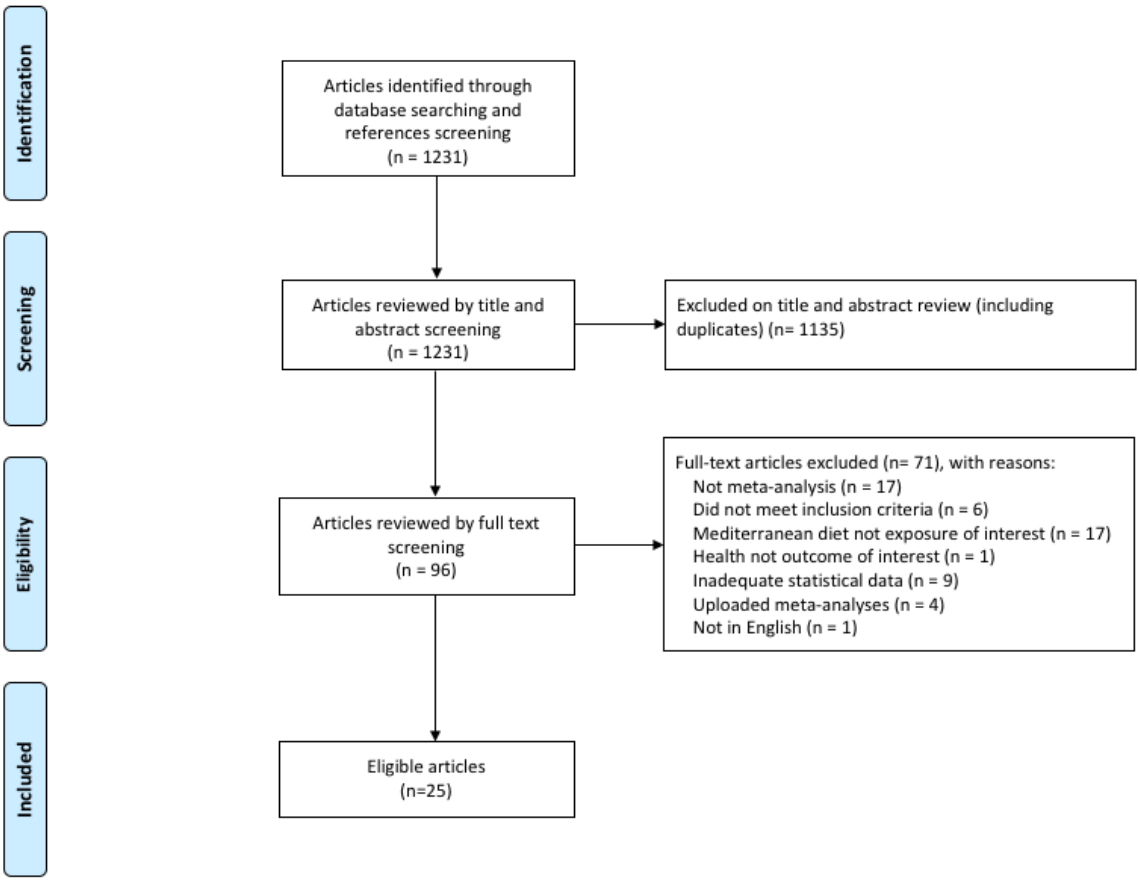
BMI (kg/m²)	Nordmann 2011[28]	6	WMD	1 641	1 009	-0.61 (-0.69; -0.53)	-0.56 (-1.01; -0.11)	<0.0001	<0.0001	(-2.04; 0.92)	94%	Weak
BMI (kg/m²)	Esposito 2011[36] ‡	12	MD	1 590	1 571	NA	-0.57 (-0.93; -0.21)	NA	<0.001	NA	92%	Suggestive
BMI (kg/m²)	Huo 2014[30] ‡	6	MD	520	500	-0.29 (-0.45; -0.13)	-0.29 (-0.46; -0.12)	0.0005	0.0005	(-0.49; -0.09)	0%	Weak
WC (cm)	Nordmann 2011[28]	5	WMD	1 581	949	-1.93 (-2.03; -1.83)	-0.89 (-1.97; 0.18)	<0.0001	<0.0001	(-4.77; 2.99)	92%	Suggestive
WC (cm)	Kastorini 2011[18]	11	MD	997	669	-0.42 (-0.83; -0.01)	-0.42 (-0.82; -0.02)	0.04	0.04	(-0.86; 0.02)	0%	Weak
WC (cm)	Huo 2014[30] ‡	3	WMD	NA	416 °	NA	-0.41 (-0.89; 0.08)	NA	NA	NA	0%	NA
WC (cm)	Garcia 2016[32]	39	SMD	NA	2 508 °	-0.45 (-0.49; -0.41)	-0.51 (-0.65; -0.36)	<0.0001	<0.0001	(-1.36; 0.34)	90%	Suggestive
TC (mmol/L)	Nordmann 2011[28]	6	WMD	1 641	1 009	-0.21 (-0.24; -0.19)	-0.19 (-0.27; -0.11)	<0.0001	<0.0001	(-8.05; 7.67)	72%	Suggestive
TC (mmol/L)	Rees 2013[29]	8	MD	2 089	2 063	-0.20 (-0.23; -0.17)	-0.16 (-0.26; -0.06)	<0.0001	0.003	(-0.43; 0.11)	74%	Weak
TC (mmol/L)	Huo 2014[30]	6	MD	492	365	-0.14 (-0.19; -0.09)	-0.14 (-0.19; -0.09)	<0.0001	<0.0001	(-0.20; -0.08)	0%	Weak
LDL-C (mmol/L)	Nordmann 2011[28]	3	WMD	1 388	752	-0.07 (-0.13; 0.01)	-0.09 (-0.19; 0.02)	0.05	0.10	(-24.78; 24.60)	23%	No evidence
LDL-C (mmol/L)	Rees 2013[29]	6	MD	1 629	1 598	-0.07 (0.13; -0.01)	-0.07 (-0.18; 0.03)	0.02	0.15	(-0.23; 0.09)	22%	No evidence
LDL-C (mmol/L)	Huo 2014[30]	6	MD	384	258	-0.11 (-0.23; 0.02)	-0.11 (-0.24; 0.01)	0.09	0.09	(-0.29; 0.07)	0%	No evidence
HDL-C (mmol/L)	Nordmann 2011[28]	6	WMD	1 641	1 009	-0.01 (-0.02; -0.01)	0.02 (-0.05; 0.10)	<0.0001	0.52	(-9.11; 9.15)	99%	No evidence
HDL-C (mmol/L)	Kastorini 2011[18]	29	MD	2 202	1 903	0.05 (0.04; 0.06)	0.03 (0.01; 0.05)	<0.0001	0.0004	(-3.37; 3.43)	64%	Suggestive
HDL-C (mmol/L)	Rees 2013[29]	7	MD	1 719	1 688	0.05 (0.04; 0.06)	0.01 (-0.04; 0.06)	<0.0001	0.70	(-0.05; 0.07)	84%	No evidence
HDL-C (mmol/L)	Huo 2014[30]	6	MD	492	365	0.07 (0.05; 0.08)	0.06 (0.02; 0.10)	<0.0001	0.005	(0.01; 0.11)	54%	Weak
HDL-C (mmol/L)	Garcia 2016[32]	26	SMD	NA	1 612 °	0.18 (0.11; 0.24)	0.21 (-0.03; 0.44)	<0.0001	0.09	(-1.02; 1.44)	91%	No evidence
TG (mmol/L)	Kastorini 2011[18]	29	MD	2 202	1 903	-0.09 (-0.11; 0.06)	-0.07 (-0.12; -0.02)	<0.0001	0.004	(-18.04; 17.90)	55%	Weak
TG (mmol/L)	Rees 2013[29]	6	MD	1 659	1 659	-0.17 (-0.19; -0.16)	0.00 (-0.15; 0.16)	<0.0001	0.95	(-0.53; 0.53)	94%	No evidence
TG (mmol/L)	Huo 2014[30]	6	MD	492	365	-0.23 (-0.29; -0.17)	-0.29 (-0.47; -0.10)	<0.0001	0.003	(-0.73; 0.15)	59%	Weak
TG (mmol/L)	Garcia 2016[32]	25	SMD	NA	1 758 °	-0.34 (-0.40; -0.28)	-0.45 (-0.66; -0.25)	<0.0001	0.0001	(-1.47; 0.57)	90%	Weak
Glucose (mmol/L)	Nordmann 2011[28]	6	WMD	1 641	1 009	-0.12 (-0.14; -0.10)	-0.21 (-0.39; -0.03)	<0.0001	0.02	(-9.57; 9.15)	97%	Weak
Glucose (mmol/L)	Kastorini 2011[18]	17	MD	1 357	1 139	-0.18 (-0.24; -0.13)	-0.22 (-0.32; -0.11)	0.0001	0.0001	(-7.77; 7.33)	72%	Weak
Glucose (mmol/L)	Huo 2014[30]	6	MD	260	342	-0.84 (-1.05; -0.63)	-0.72 (-1.24; -0.21)	<0.0001	0.006	(-2.01; 0.57)	66%	Weak
Glucose (mmol/L)	Garcia 2016[32]	23	SMD	NA	2 975 °	-0.37 (-0.41; -0.33)	-0.37 (-0.41; -0.33)	<0.0001	<0.0001	(-1.30; 0.56)	92%	Suggestive
HOMA-Index	Kastorini 2011[18]	10	MD	1 031	711	-0.54 (-0.62; -0.47)	-0.45 (-0.74; -0.16)	<0.0001	<0.0001	(-1.60; 0.70)	90%	Weak
HOMA-Index	Huo 2014[30] ‡	6	WMD	NA	NA	NA	-0.55 (-1.53; 0.42)	NA	NA	NA	46%	NA
Insulin (μU/mL)	Nordmann 2011[28]	5	WMD	418	411	-0.27 (-0.40; -0.15)	-1.06 (-2.94; 0.81)	<0.0001	0.27	(-7.61; 5.49)	98%	Weak
Insulin (μU/mL)	Huo 2014[30]	5	MD	238	319	-0.55 (-0.81; -0.29)	-0.55 (-0.81; -0.29)	0.0001	0.0001	(-0.92; -0.18)	0%	Suggestive
HbA_{1c}	Huo 2014[30]	9	MD	568	521	-0.49 (-0.55; -0.42)	-0.30 (-0.46; -0.14)	<0.0001	0.0003	(-0.73; 0.13)	67%	Weak
HbA_{1c}	Ajala 2013[37]	3	WMD	308	280	-0.41 (-0.58; -0.24)	-0.28 (-0.71; 0.15)	<0.0001	0.21	(-5.49; 4.93)	82%	No evidence
HbA_{1c}	Esposito 2015[38]	3	MD	395	278	-0.47 (-0.56; -0.38)	-0.47 (-0.56; -0.38)	<0.0001	<0.0001	(-1.05; 0.11)	4%	Weak
Diabetes	Schwingshackl 2014[26]	1	RR	NA	3541	0.70 (0.54; 0.91)	0.70 (0.54; 0.91)	0.007	0.007	NE	NE	Weak
MetS	Kastorini 2011[18]	2	RR	902	482	0.45 (0.32; 0.64)	0.42 (0.21; 0.85)	<0.0001	0.02	NE	74%	Weak
MetS remission	Esposito 2015[38]	2	MD	2 388	1 184	1.43 (1.25; 1.64)	1.49 (1.14; 1.94)	<0.0001	0.004	NE	71%	Weak

Adiponectin (µg/mL)	Schwingshackl 2014[35]	2	WMD	156	130	1.73 (1.06; 2.40)	1.69 (0.27; 3.11)	<0.0001	0.02	NE	78%	Weak
ICAM-1 (ng/mL)	Schwingshackl 2014[35]	2	WMD	389	197	-25.4 (-38.3; -12.5)	-23.7 (-41.2; -6.22)	0.00001	0.008	NE	34%	Weak
INFLAMMATORY PARAMETERS												
CRP (mg/L)	Nordmann 2011[28]	5	WMD	1 533	902	-1.03 (-1.13; -0.94)	-0.97 (-1.49; -0.46)	<0.0001	0.0002	(-2.71; 0.77)	82%	Weak
CRP (mg/L)	Schwingshackl 2014[35]	14	WMD	1 120	822	-0.97 (-1.06; -0.88)	-0.98 (-1.48; -0.49)	<0.0001	<0.0001	(-2.70; 0.74)	91%	Weak
IL-6 (pg/mL)	Schwingshackl 2014[35]	6	WMD	646	431	-0.55 (-0.62; -0.49)	-0.42 (-0.73; -0.11)	<0.0001	0.008	(-1.40; 0.56)	81%	Weak

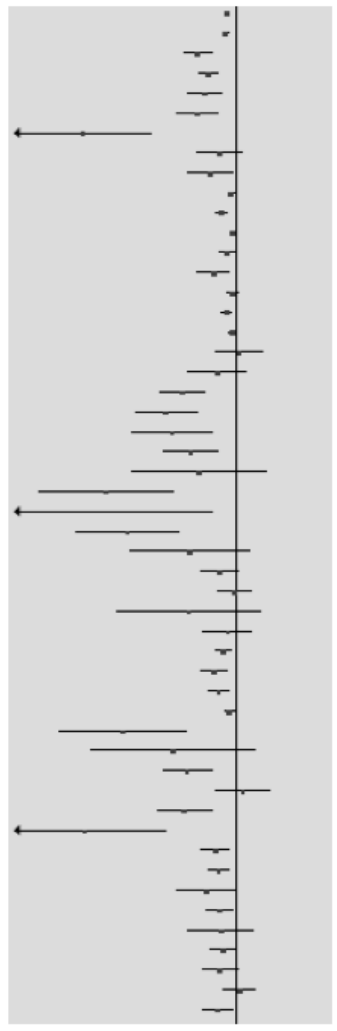
CVD = cardiovascular disease; MI = myocardial infarction; MACE = major cardiovascular events; BP = blood pressure; FMD = flow mediated dilation; BMI = body mass index; WC = waist circumference; TC = total cholesterol; LDL-C = low density lipoprotein cholesterol; HDL-C = high density lipoprotein cholesterol; TG = triglycerides; HbA_{1c} = haemoglobin A_{1c}; MetS = Metabolic Syndrome; ICAM-1 = intercellular adhesion molecule 1; CRP = C-reactive protein; IL-6 = interleukin-6; RR = relative risk, MD = mean difference; WMD = weighted mean difference; SMD = standardized mean difference; NA = not available; NE = not estimable because less than 3 studies were available for each meta-analysis; ° number of total participants

‡ The meta-analysis did not provide adequate data to estimate the summary effect size; we report the random-effects summary effect size as presented by the authors of the original meta-analysis

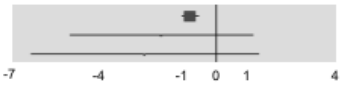
To convert mmol/L cholesterol to mg/dL, multiply mmol/L by 38.67. To convert mmol/L triglycerides to mg/dL, multiply mmol/L by 88.57. To convert mg/dL blood glucose to mmol/L, multiply mmol/L by 18.


Identification
Screening
Eligibility
Included
Articles identified through database searching and references screening (n = 1231)
Articles reviewed by title and abstract screening (n = 1231)
Excluded on title and abstract review (including duplicates) (n= 1135)
Articles reviewed by full text screening (n = 96)
Full-text articles excluded (n= 71), with reasons:
Not meta-analysis (n = 17)
Did not meet inclusion criteria (n = 6)
Mediterranean diet not exposure of interest (n = 17)
Health not outcome of interest (n = 1)
Inadequate statistical data (n = 9)
Uploaded meta-analyses (n = 4)
Not in English (n = 1)
Eligible articles (n=25)

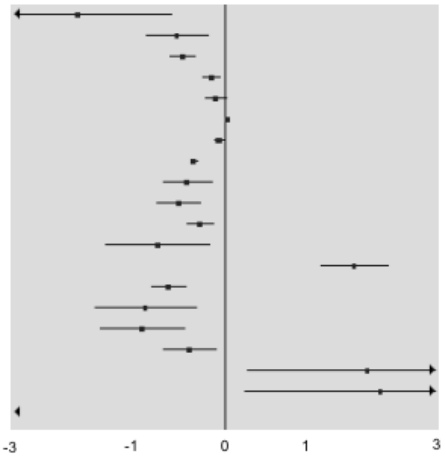
Outcome	n of studies	Study design	n of events (cases) / total (controls)	Comparison	Relative risk (95% CI)
Overall mortality [3]	15	cohort	49 860 / 771 211	2 point increase	0.91 (0.89, 0.93)
CVD incidence/mortality [3]	17	cohort	16 566 / 775 081	2 point increase	0.89 (0.87, 0.92)
CVD incidence [16]	13	cohort	13 434 / 275 162	high vs low	0.67 (0.58, 0.77)
CVD mortality [16]	13	cohort	9 563 / 778 510	high vs low	0.75 (0.68, 0.83)
CHD incidence [16]	4	cohort	2 943 / 153 502	high vs low	0.72 (0.60, 0.86)
MI incidence [16]	3	cohort	1 364 / 44 428	high vs low	0.67 (0.54, 0.83)
Stroke [18]	2	case-control	297 / 296	high vs low	0.20 (0.10, 0.41)
Stroke [18]	2	cross-sectional	950 / 10 847	high vs low	0.84 (0.66, 1.06)
Stroke [18]	5	cohort	2 444 / 159 995	high vs low	0.76 (0.60, 0.96)
Cancer incidence/mortality [3]	10	cohort	82 198 / 2 720 221	2 point increase	0.95 (0.93, 0.97)
Cancer mortality [20]	13	cohort	49 819 / 591 002	high vs low	0.86 (0.82; 0.91)
Cancer incidence [20]	3	cohort	48 683 / 534 058	high vs low	0.96 (0.95; 0.97)
Colorectal cancer [20]	9	cohort	12 819 / 1 415 995	high vs low	0.91 (0.84; 0.98)
Colorectal cancer [19]	4	case-control	4 744 / 36 099	high vs low	0.79 (0.67, 0.93)
Breast cancer [20]	13	cohort	33 111 / 988 736	high vs low	0.96 (0.90; 1.03)
Breast cancer [19]	8	case-control	6 867 / 8 694	high vs low	0.90 (0.85, 0.95)
Prostate cancer [19]	2	cohort	29 806 / 366 037	high vs low	0.96 (0.92, 1.00)
Prostate cancer [19]	1	case-control	1 482 / 1 108	high vs low	1.03 (0.81, 1.31)
Gastric cancer [19]	1	cohort	1 382 / 980 012	high vs low	0.82 (0.61, 1.10)
Gastric cancer [19]	1	case-control	999 / 2 628	high vs low	0.57 (0.45, 0.72)
Pancreatic cancer [19]	1	case-control	688 / 2 204	high vs low	0.48 (0.35, 0.66)
Liver cancer [19]	1	case-control	518 / 772	high vs low	0.51 (0.34, 0.77)
Liver cancer [19]	1	cohort	509 / 494 942	high vs low	0.62 (0.47, 0.82)
Esophageal cancer [19]	1	cohort	488 / 494 968	high vs low	0.68 (0.34, 1.36)
Esophageal cancer [19]	1	case-control	304 / 743	high vs low	0.26 (0.13, 0.52)
Respiratory cancer [19]	1	cohort	124 / 4 336	high vs low	0.09 (0.01, 0.77)
Head/neck cancer [19]	4	case-control	2 065 / 4 851	high vs low	0.32 (0.19, 0.55)
Head/neck cancer [19]	1	cohort	1 868 / 49 4967	high vs low	0.61 (0.33, 1.14)
Bladder cancer [19]	1	cohort	1 425 / 477 312	high vs low	0.84 (0.69, 1.02)
Endometrial cancer [19]	1	cohort	1 392 / 84 415	high vs low	0.98 (0.82, 1.17)
Endometrial cancer [19]	2	case-control	2 058 / 4 001	high vs low	0.61 (0.29, 1.29)
Ovarian cancer [19]	1	case-control	696 / 82 948	high vs low	0.91 (0.71, 1.17)
Neurodegenerative diseases [3]	5	cohort	1 074 / 136 235	2 point increase	0.79 (0.70, 0.90)
Neurodegenerative diseases [21]	9	cohort	3 627 / 34 168	high vs low	0.87 (0.81, 0.94)
Cognitive impairment [21]	9	cohort	2 328 / 27 567	high vs low	0.83 (0.75, 0.93)
Cognitive impairment [22]	5	cohort	709 / 6 878	1 point increase	0.92 (0.88, 0.97)
Cognitive impairment [17]	1	case-control	282 / 1 880	high vs low	0.31 (0.16, 0.59)
Cognitive impairment [17]	3	cross-sectional	459 / 3 345	high vs low	0.52 (0.22, 1.22)
Alzheimer's disease [21]	5	cohort	637 / 6 111	high vs low	0.60 (0.48, 0.77)
Dementia [21]	3	cohort	662 / 8 873	high vs low	1.07 (0.81, 1.42)
Depression [17]	1	cohort	480 / 10 094	high vs low	0.58 (0.44, 0.77)
Depression [17]	1	case-control	111 / 345	high vs low	0.21 (0.09, 0.48)
Depression [17]	7	cross-sectional	1 718 / 7 406	high vs low	0.80 (0.69, 0.93)
Diabetes [25]	10	cohort	19 663 / 136 846	high vs low	0.83 (0.74, 0.93)
MetS [24]	4	cohort	1 752 / 16 457	high vs low	0.73 (0.54, 0.98)
MetS [24]	8	case-control	4 590 / 17 390	high vs low	0.84 (0.73, 0.97)
MetS [18]	4	cross-sectional	NA / 4 500	high vs low	0.85 (0.61, 1.19)
HDL-cholesterol [24]	4	cross-sectional	NA / 11 868	high vs low	0.87 (0.77, 1.00)
Triglycerides [24]	4	cross-sectional	NA / 11 868	high vs low	0.84 (0.70, 1.01)
Glucose [24]	4	cross-sectional	NA / 11 868	high vs low	1.03 (0.87, 1.22)
Waist circumference [24]	4	cross-sectional	NA / 11 868	high vs low	0.82 (0.70, 0.96)



Outcome	n of studies	Study design	n of events (cases) / total (controls)	Comparison	Mean Difference (95% CI)
HOMA-Index [18]	3	cross-sectional	NA / 4 804	high vs low	-0.86 (-1.13, -0.59)
Systolic pressure [18]	4	cross-sectional	NA / 14 734	high vs low	-1.81 (-4.83, 1.21)
Diastolic pressure [18]	4	cross-sectional	NA / 14 734	high vs low	-2.36 (-6.12, 1.40)



Outcome	n of studies	n of subjects (Mediterranean diet)	n of subjects (other diets)	Mean Difference (95% CI)
Weight [36]	15	1 937	1 588	-1.75 (-2.86, -0.64)
BMI [36]	12	1 590	1 571	-0.57 (-0.93, -0.21)
Waist circumference [32]	39	NA	2 580*	-0.51 (-0.65, -0.36)
Total cholesterol [29]	8	2 089	2 063	-0.16 (-0.26, -0.06)
LDL cholesterol [30]	6	384	258	-0.11 (-0.24, 0.02)
HDL cholesterol [18]	29	2 202	1 903	0.03 (0.01, 0.05)
Triglycerides [18]	29	2 202	1 903	-0.07 (-0.12, -0.02)
Glucose [32]	23	NA	2 975*	-0.37 (-0.41, -0.33)
HOMA-Index [18]	10	1 031	711	-0.45 (-0.74, -0.16)
Insulin [30]	5	238	319	-0.55 (-0.81, -0.29)
HbAc1 [30]	9	568	521	-0.30 (-0.46, -0.14)
MetS [18]	2	902	482	-0.80 (-1.42, -0.18)
MetS remission [38]	2	2 388	1 184	1.49 (1.14, 1.94)
Systolic BP [32]	25	NA	3 262*	-0.67 (-0.87, -0.47)
Diastolic BP [32]	25	NA	3 262*	-0.94 (-1.55, -0.34)
CRP [35]	14	1 120	822	-0.98 (-1.48, -0.49)
IL-6 [35]	6	646	431	-0.42 (-0.73, -0.11)
Adiponectin [35]	2	156	130	1.69 (0.27, 3.11)
FMD [35]	2	109	101	1.86 (0.23, 3.48)
ICAM-1 [35]	2	389	197	-23.7 (-41.2, -6.22)



				Relative risk (95% CI)
Overall mortality [27]	3	6 630	4 041	0.93 (0.65, 1.33)
CVD incidence/mortality [15]	2	5 133	7 761	0.62 (0.45, 0.86)
CVD mortality [16]	4	7 418	4 875	0.59 (0.38, 0.93)
CHD incidence [27]	2	5 299	2 753	0.56 (0.20, 1.61)
Stroke [27]	2	6 617	4 071	0.64 (0.47, 0.86)
Heart failure [27]	1	302	303	0.25 (0.05, 1.17)
MACE [27]	2	5 299	2 753	0.45 (0.13, 1.57)
MI incidence [16]	3	7 116	4 572	0.60 (0.44, 0.82)
Diabetes [26]	1	NA	3 541	0.70 (0.54, 0.91)