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

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2	of meta-analyses of observational studies and randomized trials
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14 15 16 17 18 19 20 21 22 23	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 <b>Running title</b> : Mediterranean diet and health outcomes
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#### 35 Abstract

36 Research has shown that a greater adherence to the Mediterranean diet is associated with a reduced risk 37 of major chronic disease. However, the existing literature leads to debate for different issues, such as the 38 measurement of the adherence to the Mediterranean diet, the use of a wide variety of dietary indices with 39 various food components and the large heterogeneity across the studies. In order to summarize the 40 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 41 42 studies and randomized clinical trials (RCTs) was performed. Thirteen meta-analyses of observational 43 studies and 16 meta-analyses of RCTs investigating the association between the adherence to the 44 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 45 46 a considerable heterogeneity between studies, for a greater adherence to the Mediterranean diet and a 47 reduced the risk of overall mortality, cardiovascular diseases, coronary heart disease, myocardial 48 infarction, overall cancer incidence, neurodegenerative diseases and diabetes was found. For most of the 49 site-specific cancers, as well as for inflammatory and metabolic parameters, the evidence was only 50 suggestive or weak and further studies are needed to draw firmer conclusions. No evidence, on the other 51 hand, was reported for bladder, endometrial and ovarian cancers, as well as for LDL-cholesterol levels.

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

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#### 61 **1. Introduction**

62 The Mediterranean diet is a model of eating based on the traditional foods and drinks of the 63 countries surrounding the Mediterranean Sea. Over the last few decades, it has been promoted worldwide 64 as one of the healthiest dietary pattern and has been reported to be consistently beneficial with respect 65 to chronic diseases and longevity. (1) There are individual foods and components within the 66 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 67 focus from the analysis of individual nutrients to the evaluation of the whole diet and the interaction 68 69 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 theassociation 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 metaanalyses 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.

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### 92 2. Methods

#### 93 2.1. Search strategy

94 According to the Joanna Briggs Institute Umbrella Review Methodology (6) two reviewers (MD, 95 FS) conducted a systematic literature search in Medline (1950 through February 2017), Embase (1980 96 through February 2017), Scopus (through February 2017), Cochrane database of systematic reviews, and 97 Google Scholar (up to February 2017). Additional studies were searched by checking references of the 98 identified articles. The following key words, used in combination as MeSH terms and text words were 99 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", 100 101 "circulatory diseases", "cardiovascular disease", "ischemic heart disease", "cerebrovascular disease", "mortality", "health effects", "health status", and their variants. The most updated or complete 102 publication was used when more than an article was present for a single study. In addition, separate meta-103 104 analyses on multiple outcomes presented in a single article were assessed separately. Missing data or 105 additional information were requested from the corresponding authors of the articles.

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#### 107 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)

113 - 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.

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#### 122 2.3. Data extraction

123 Literature search and data extraction were conducted independently by two authors (MD, FS), 124 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 125 126 separately in meta-analyses of prospective cohort studies, cross-sectional studies, case-control studies, 127 and RCTs. The following data were extracted from each eligible meta-analysis and organized using a 128 standard form: first author, year of publication, outcome examined, number of included studies, study 129 design, type of comparison, number of events and population (in meta-analyses of cross-sectional and 130 prospective cohort studies), number of cases and controls (in meta-analyses of case-control studies), 131 number of subjects assigned to the intervention and the control groups (in meta-analyses of RCTs), 132 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 133 134 qualitative assessment was performed). When the data were provided in mg/dL, they were transformed 135 into mmol/L for consistency of results. Outcomes were categorized into 6 categories: overall mortality, 136 cardiovascular outcomes, cancer outcomes, cognitive disorders, metabolic disorders and inflammatory137 parameters.

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## 139 2.4. Statistical analysis

140 The summary effect size and its confidence intervals (CIs) by 95% were estimated using both 141 fixed-effects and random-effects models for each meta-analysis, by using Review Manager (RevMan, 142 version 5.3 for Macintosh; The Cochrane Collaboration, Copenhagen, Denmark). For the summary 143 random-effects, we estimated the 95% prediction interval (PI), which further accounts the degree of 144 between-study heterogeneity and gives a range for which we are 95% confident that the effect in a new 145 study examining the same association lies within. (7) Statistical heterogeneity between studies was evaluated using the I<sup>2</sup> statistic. (8) Where I<sup>2</sup> exceeded 50% or 75%, the heterogeneity was considered 146 147 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  $p \le 0.05$  and  $p \le 0.001$ , which is considered to be a more appropriate threshold of statistical significance to reduce the number of falsepositive 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:

- 165 *Highly suggestive evidence:* significance threshold reached at  $p \le 0.001$  for both random- and fixed-166 effects calculation; >1,000 cases (or >5,000 total participants if the metric was continuous); not 167 considerable heterogeneity between studies (I<sup>2</sup>=50-75%)
- 168 Suggestive evidence: significance threshold reached at  $p \le 0.001$  for random-effect calculation; 500-
- 169 1,000 cases (or 2,500-5,000 total participants if the metric was continuous)
- 170 Weak evidence: significance threshold reached at  $p \le 0.05$  for random-effects calculation
- 171 *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<sub>MedSD</sub>. (14) The AMSTAR<sub>MedSD</sub> 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.).
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#### 184 **3. Results**

185 Overall, 1,231 articles were identified, out of which 1,135 were excluded after a screening of titles
186 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.

By grouping the outcomes into the proposed categories, the included meta-analyses of observational studies resulted as follows: overall mortality (n=1), cardiovascular outcomes (n=12), cancer outcomes (n=26), cognitive disorders (n=14), and metabolic disorders (n=15). The median number of included studies in each meta-analysis was 4 (range: 1-16), while the median number of cases was 1,752 (range: 111-82,198), and the median number of population/controls was 15,595 (range: 296-2,720,221). For some specific outcomes (gastric cancer, liver cancer and oesophageal cancer), the selected metaanalyses reported only 1 cohort study and only 1 case-control study.

Over than one meta-analysis was available for 21 different outcomes. As regards the concordance between the magnitude, statistical significance of the effect and direction, agreement was present for CVD incidence/mortality, overall cancer, colorectal cancer, neurodegenerative diseases, and diabetes. Meta-analyses examining stroke, head/neck cancer, esophageal cancer, gastric cancer, breast cancer, liver cancer, endometrial cancer, cognitive impairment, depression and metabolic syndrome reported disagreement in terms of the statistical significance of the effect and/or in the magnitude, but not in the direction of the effect, being all positively related to the protection for a greater adherence to the

213 Mediterranean diet. Finally, opposite results were found for dementia and prostate cancer, and non-214 comparable results were reported for waist circumference, triglycerides, HDL-cholesterol and glucose.

215 The forest plot with the summary effect for each health outcome evaluated in meta-analyses of 216 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. 217 218 Furthermore, whether the overlapping meta-analyses had the same number of studies, we reported the 219 most recent.

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

222 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 223 (n=1), cardiovascular outcomes (n=26), metabolic disorders (n=41), and inflammatory parameters (n=3). 224 225 The total number of subjects in the included RCTs was 202,148. The median number of the included 226 studies in each meta-analysis was 6 (range: 1-39), and the median number of participants was 1,571 (101-227 25,370). Two meta-analyses of only 1 RCT included heart failure and diabetes, respectively, as clinical 228 outcome.

229 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 230 231 across the meta-analyses for the statistical significance of the effect and the direction. On the other hand, 232 meta-analyses examining CVD mortality, stroke, systolic blood pressure, diastolic blood pressure, 233 triglycerides, HDL-cholesterol, insulin, and HbAc1 reported disagreements in terms of the significance 234 of the effect, but not for the direction. As regarding LDL-cholesterol levels, no evidences were obtained 235 in the 3 different meta-analyses.

236 The forest plot with the summary effects for each health outcome explored in RCTs is depicted 237 in Figure 3.

#### 239 *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.

245 On the basis of the AMSTAR<sub>MedSD</sub> assessment, meta-analyses achieved a medium-to-high quality score (mean  $\pm$  SD: 16.36  $\pm$  2.36). As reported in Supplementary Table 6, 11 meta-analyses totalled >80% 246 247 of the highest achievable score (>16 points out of 21), and the remaining 14 meta-analyses totalled 248 between 50% and 80% of the highest score (between 11 and 16 points). All the meta-analyses (100%) 249 provided an 'a priori' design and performed a comprehensive literature search (22% at least searched 250 electronic databases and 88% supplemented those with other sources such as reference list from other 251 articles), and most of meta-analyses (84%) reported that there was duplicate study selection. Almost all 252 the meta-analyses (96%) made it possible to replicate the literature search, but only 40% permitted the 253 inclusion of grey literature. The list of included studies was provided in 92% of meta-analyses, 96% 254 included characteristics of included studies, and 72% assessed and documented scientific quality of the 255 included studies. In addition, the Newcastle Ottawa Scale (NOS) was used in 9 meta-analyses of 256 observational studies (Supplementary Table 7). Five meta-analyses (3, 18, 25, 28, 31) performed a quality 257 assessment using criteria set by the authors, 6 (20, 27, 29, 33, 37, 38) assessed the potential existence of 258 bias using the Cochrane risk of bias tool, and 1 (35) used the Jadad score. Despite this, only 10% of meta-259 analyses reported how results might depend on study quality. All the meta-analyses used appropriate 260 methods to combine study findings, whereas the likelihood of publication bias was assessed in 80% of 261 meta-analyses.

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# 263 *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.

267 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, 268 269 cardiovascular disease, coronary heart disease, myocardial infarction, overall cancer incidence/mortality, 270 overall cancer incidence, breast cancer, neurodegenerative disease, cognitive impairment, Alzheimer's 271 diseases, dementia and diabetes). Among these, overall mortality, cardiovascular disease, coronary heart 272 disease, myocardial infarction and diabetes were examined by both meta-analyses of observational studies 273 and RCTs, the latter showing no evidence (except for diabetes). For all the other outcomes, including 274 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 275 276 suggestive or weak. As regarding stroke, systolic, diastolic blood pressure, and metabolic parameters, we 277 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.

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#### 282 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 290 Mediterranean diet had, as compared with subjects following a control diet, better anthropometrical,291 metabolic and inflammatory risk parameters.

292 The largest proportion of the included meta-analyses examined metabolic disorders and 293 cardiovascular outcomes. We observed a robust evidence, supported by a p value  $\leq 0.001$ , large simple 294 size, and not a considerable heterogeneity between studies for cardiovascular disease, coronary heart 295 disease, and myocardial infarction, evaluated through meta-analyses of both observational studies and 296 RCTs. The beneficial effects of the Mediterranean diet against these outcomes has usually been attributed 297 to its influence on traditional atherosclerotic risk factors. (39-41) Accordingly, our analysis found 298 suggestive evidence supporting the greater effectiveness of the Mediterranean diet in reducing weight, 299 BMI and waist circumference, lowering total cholesterol levels, and increasing HDL-cholesterol levels, 300 when compared to control diets. Conversely, no association was reported for LDL-cholesterol levels. 301 Among metabolic disorders, our paper indicates that the association between the Mediterranean diet and 302 reduced risk of diabetes was the most robust, whereas evidence for a protective effect against the 303 metabolic syndrome was weaker. In addition, meta-analyses of RCTs provided suggestive evidence for a 304 better glycaemic control, associated with reduced insulin resistance, in subjects following a Mediterranean 305 diet in comparison to a control diet.

306 Actually, some authors have suggested that anti-inflammatory effects in the vascular wall may be 307 another important mechanism that helps explaining the link between the Mediterranean diet and 308 cardiovascular disease. (42) In addition, recent findings from the PREDIMED Study suggested that the 309 reduction in serum nitric oxide and endothelin-1 as well as endothelin-1 receptors gene expression 310 explain, at least partially, the effect of a Mediterranean diet high in olive oil or nuts on lowering blood 311 pressure. (43) Few meta-analyses evaluated inflammatory parameters (28, 35), but all confirm an inverse 312 relationship between a higher score of diet, CRP and IL-6, even if the grade of evidence is weak, partly 313 due to a low statistical power. As regarding stroke, systolic and diastolic blood pressure, all meta-analyses 314 of cross-sectional studies presented no evidences, in contrast to meta-analyses of prospective cohort studies. This finding might be explained by intrinsic limitations of cross-sectional studies, that failed to
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

341 neurodegenerative diseases, in particular with Alzheimer's disease and dementia, although, again, the 342 meta-analysis of cross-sectional studies provided no evidence. (17) As previously discussed (47), 343 standardization of tools used to assess cognitive function, is needed for evaluating the effectiveness of 344 the Mediterranean diet for the prevention of cognitive impairment.

345 The methodologic quality of the meta-analyses and systematic reviews on the Mediterranean diet 346 has been previously evaluated by Huedo-Medina and colleagues. (14) They applied the AMSTAR<sub>MedSD</sub> 347 quality scale on 24 studies examining the association between the Mediterranean diet and cardiovascular 348 disease outcomes, by identifying the studies that did not fully comply with contemporary methodologic 349 quality standards. Our application of the AMSTAR<sub>MedSD</sub> tool obtained better results since all the 350 investigated meta-analyses achieved a medium-to-high quality score, so suggesting that current meta-351 analyses evaluating the effects of the Mediterranean diet on health status partially or almost fully comply 352 with methodologic quality standards. This difference could be explained by the fact that we included only 353 meta-analyses, with respect to the reviews included by Huedo-Medina et al., that tended to achieve higher 354 scores. (14)

355 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, 356 357 making difficult to reach a definitive conclusion. Further and better designed studies are needed to 358 confirm the present findings. Second, several primary studies achieved a low quality score when authors 359 performed a quality assessment. Since the quality of meta-analyses is related to the quality of included 360 studies, the results regarding the poorly covered outcomes need to be interpreted with caution. Third, a 361 large part of evidence from RCTs is weak or suggestive, pointing out the need of further and better 362 designed trials. Forth, the interpretation of tests for statistical bias offers suggestion of bias, but not 363 definitive proofs.

In conclusion, this umbrella review provides a comprehensive resume of the published metaanalyses 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,

367	overall cancer incidence, neurodegenerative diseases and diabetes. The relationship between the
368	Mediterranean diet and other outcomes could be genuine, but there is still limited evidence for them. The
369	large heterogeneity of dietary assessment methods and inadequacies relating to the study design,
370	necessitate recommendations for future interventions to be sufficiently powered to detect clinical
371	outcomes. Further studies adopting more uniform methodology and analyses, and detailed reporting of
372	population, intervention, comparison and outcome data, would allow the quantification of the association
373	of the Mediterranean diet adherence with health outcomes and quality of life.
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575 Legend to lighter	575	Legend	to	figures
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577 Figure 1. Flow diagram of the study selection process

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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

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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

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

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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/	Comparison	Effect	n	Ν	Summary relati	ve risk (95% CI)	fixed	random	PI (95%)	$I^2$	Strength of
		study design		size			Fixed effects	Random Effects	p value	p value			evidence
OVERALL MORTA	LITY	-	-	-	-	-	-	-	-	-	-	-	-
Overall mortality	Sofi 2014 <sup>3</sup>	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
CARDIOVASCULA	R OUTCOMES												
CVD inc/mort	Sofi 2014 <sup>3</sup>	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 <sup>15</sup>	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 201516	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 201516	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 201516	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 201516	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 201317	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 201317	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 201317	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 201516	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 201118	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 201118	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 OUTCOM	IES												
Cancer inc/mort	Sofi 2014 <sup>3</sup>	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 201519	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 201620	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 201620	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 201519	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 201519	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 201620	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 201519	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 <sup>19</sup>	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 201620	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 201519	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 201519	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 201519	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 201519	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 201519	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 201519	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 201519	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 201519	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 201519	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 <sup>19</sup>	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 201519	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 <sup>19</sup>	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 201519	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 <sup>19</sup>	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 201519	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 <sup>19</sup>	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 DISO	RDERS												
Neurodeg. diseases	Sofi 2014 <sup>3</sup>	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 <sup>21</sup>	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 201317	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 201422	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 201422	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 201317	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 201317	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 <sup>21</sup>	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 <sup>21</sup>	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 <sup>23</sup>	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 <sup>21</sup>	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 201317	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 201317	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 201317	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 DISO	RDERS												
WC (cm)	Kastorini 2011 <sup>18</sup>	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 <sup>24</sup>	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 <sup>18</sup>	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 201724	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 201118	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 201724	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 201118	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 201724	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 201118	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 <sup>25</sup>	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 <sup>26</sup>	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 201118	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 201118	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 201724	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 <sup>24</sup>	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	Significance	Sample	Estimate of heterogeneity	95% prediction interval	† Small study
			(random effects)	(fixed effects)	size			enects
OVERALL MORTALITY			· /	, ,				
Overall mortality	Sofi 2014 <sup>3</sup>	cohort	< 0.001	< 0.001	>1000	Not large	Excluding the null value	Yes
CARDIOVASCULAR OUTCO	MES					<u> </u>	0	
CVD incidence/mortality	Sofi 2014 <sup>3</sup>	cohort	< 0.001	< 0.001	>1000	Not large	Excluding the null value	No <sup>a</sup>
CVD incidence/mortality	M-Gonzalez 2014 <sup>15</sup>	cohort	< 0.001	< 0.001	>1000	Considerable	Excluding the null value	Yes
CVD incidence	Grosso 201516	cohort	< 0.001	< 0.001	>1000	Substantial	Including the null value	Yes
CVD mortality	Grosso 201516	cohort	< 0.001	< 0.001	>1000	Substantial	Including the null value	Yes
CHD incidence	Grosso 2015 <sup>16</sup>	cohort	< 0.001	< 0.001	>1000	Not large	Including the null value	No
MI incidence	Grosso 201516	cohort	< 0.001	< 0.001	>1000	Not large	Including the null value	No
Stroke	Psaltopoulou 201317	cohort	< 0.05	< 0.05	>1000	Not large	Including the null value	No
Stroke	Psaltopoulou 201317	case control	< 0.001	< 0.001	<500	Not large	Excluding the null value	NA
Stroke	Psaltopoulou 201317	cross sectional	>0.05	>0.05	>500	Not large	Including the null value	No
Stroke	Grosso 2015 <sup>16</sup>	cohort	< 0.05	< 0.05	>1000	Substantial	Including the null value	No
Systolic BP (mmHg)	Kastorini 201118	cross sectional	>0.05	< 0.001	>5000	Considerable	Including the null value	NA
Diastolic BP (mmHg)	Kastorini 201118	cross sectional	>0.05	< 0.001	>5000	Considerable	Including the null value	NA
CANCER OUTCOMES								
Cancer incidence/mortality	Sofi 2014 <sup>3</sup>	cohort	< 0.001	< 0.001	>1000	Substantial	Excluding the null value	No
Cancer incidence/mortality	Schwingshackl 201519	cohort	< 0.001	< 0.001	>1000	Considerable	Including the null value	No
Cancer mortality	Bloomfield 2016 <sup>20</sup>	cohort	< 0.001	< 0.001	>1000	Considerable	Including the null value	No
Cancer incidence	Bloomfield 2016 <sup>20</sup>	cohort	< 0.001	< 0.001	>1000	Not large	Excluding the null value	No
Colorectal cancer	Schwingshackl 201519	cohort	< 0.05	< 0.001	>1000	Substantial	Including the null value	No
Colorectal cancer	Schwingshackl 201519	case control	< 0.05	< 0.001	>1000	Substantial	Including the null value	No
Colorectal cancer	Bloomfield 2016 <sup>20</sup>	cohort	< 0.05	< 0.05	>1000	Substantial	Including the null value	No
Breast cancer	Schwingshackl 2015 <sup>19</sup>	cohort	>0.05	>0.05	>1000	Not large	Including the null value	No
Breast cancer	Schwingshackl 2015 <sup>19</sup>	case control	< 0.001	< 0.001	>1000	Not large	Excluding the null value	No
Breast cancer	Bloomfield 2016 <sup>20</sup>	cohort	>0.05	>0.05	>1000	Substantial	Including the null value	No
Prostate cancer	Schwingshackl 2015 <sup>19</sup>	cohort	< 0.05	< 0.05	>1000	Not large	Including the null value	No
Prostate cancer	Schwingshackl 2015 <sup>19</sup>	case-control	>0.05	>0.05	>1000	NA	NA	NA
Gastric cancer	Schwingshackl 2015 <sup>19</sup>	cohort	>0.05	>0.05	>1000	Not large	Including the null value	No
Gastric cancer	Schwingshackl 2015 <sup>19</sup>	case control	< 0.001	< 0.001	>500	NA	NA	NA
Pancreatic cancer	Schwingshackl 2015 <sup>19</sup>	case control	< 0.001	< 0.001	>500	NA	NA	NA
Liver cancer	Schwingshackl 2015 <sup>19</sup>	case control	< 0.05	< 0.05	>500	NA	NA	NA
Liver cancer	Schwingshackl 2015 <sup>19</sup>	cohort	< 0.001	< 0.001	>500	NA	NA	NA
Esophageal cancer	Schwingshackl 2015 <sup>19</sup>	cohort	>0.05	>0.05	<500	NA	NA	NA
Esophageal cancer	Schwingshackl 2015 <sup>19</sup>	case control	< 0.001	< 0.001	<500	NA	NA	NA
Respiratory cancer	Schwingshackl 2015 <sup>19</sup>	cohort	< 0.05	< 0.05	<500	NA	NA	NA
Head/neck cancer	Schwingshackl 201519	case control	< 0.001	< 0.001	>1000	Considerable	Including the null value	No
Head/neck cancer	Schwingshackl 201519	cohort	>0.05	>0.05	>1000	NA	NA	NA
Bladder cancer	Schwingshackl 201519	cohort	>0.05	>0.05	>1000	NA	NA	NA
Endometrial cancer	Schwingshackl 201519	cohort	>0.05	< 0.05	>1000	NA	NA	NA
Endometrial cancer	Schwingshackl 201519	case control	>0.05	< 0.001	>1000	Considerable	NA	NA
Ovarian cancer	Schwingshackl 201519	case control	>0.05	>0.05	>500	NA	NA	NA
COGNITIVE DISORDERS								

Neurodegenerative diseases	Sofi 2014 <sup>3</sup>	cohort	< 0.001	< 0.001	>1000	Not large	Excluding the null value	No
Neurodegenerative diseases	Wu 2017 <sup>21</sup>	cohort	< 0.001	< 0.001	>5000	Not large	Including the null value	No
Cognitive impairment	Psaltopoulou 201317	cohort	< 0.001	< 0.001	>500	Not large	Including the null value	No
Cognitive impairment	Singh 2014 <sup>22</sup>	cohort	< 0.001	< 0.001	>500	Not large	Excluding the null value	No
Cognitive impairment	Singh 2014 <sup>22</sup>	cohort	< 0.001	< 0.001	>500	Not large	Excluding the null value	No
Cognitive impairment	Psaltopoulou 201317	case control	< 0.05	< 0.05	<500	NA	NA	NA
Cognitive impairment	Psaltopoulou 201317	cross sectional	>0.05	< 0.05	<500	Considerable	Including the null value	No
Cognitive impairment	Wu 2017 <sup>21</sup>	cohort	< 0.001	< 0.001	>5000	Not large	Including the null value	No <sup>a</sup>
Alzheimer's disease	Wu 2017 <sup>21</sup>	cohort	< 0.001	< 0.001	>5000	Not large	Excluding the null value	No
Dementia	Cao 2015 <sup>23</sup>	cohort	< 0.001	< 0.001	>1000	Not large	Excluding the null value	No
Dementia	Wu 2017 <sup>21</sup>	cohort	>0.05	>0.05	>5000	Not large	Including the null value	No
Depression	Psaltopoulou 201317	cohort	< 0.05	< 0.05	<500	NA	NA	NA
Depression	Psaltopoulou 201317	case control	< 0.001	< 0.001	<500	NA	NA	NA
Depression	Psaltopoulou 201317	cross-sectional	< 0.05	< 0.05	>1000	Not large	Excluding the null value	No
METABOLIC DISORDERS								
WC (cm)	Kastorini 201118	cross sectional	< 0.001	< 0.001	>5000	Considerable	Excluding the null value	NA
WC (cm)	Godos 2017 <sup>24</sup>	cross sectional	< 0.05	< 0.05	>5000	Not large	Including the null value	No
HDL-C (mmol/L)	Kastorini 201118	cross sectional	< 0.001	< 0.001	>5000	Considerable	Including the null value	NA
HDL-C (mmol/L)	Godos 2017 <sup>24</sup>	cross sectional	< 0.05	>0.05	>5000	Not large	Including the null value	No
TG (mmol/L)	Kastorini 201118	cross sectional	< 0.001	< 0.001	>5000	Considerable	Including the null value	NA
TG (mmol/L)	Godos 2017 <sup>24</sup>	cross sectional	>0.05	< 0.05	>5000	Not large	Including the null value	No
Glucose (mmol/L)	Kastorini 201118	cross sectional	< 0.001	< 0.001	>5000	Considerable	Including the null value	NA
Glucose (mmol/L)	Godos 2017 <sup>24</sup>	cross sectional	>0.05	>0.05	>5000	Not large	Including the null value	No
HOMA-Index	Kastorini 201118	cross sectional	< 0.001	< 0.001	>2500	Considerable	Including the null value	NA
Diabetes	Koloverou 2014 <sup>25</sup>	cohort	< 0.05	< 0.001	>1000	Substantial	Including the null value	No
Diabetes	Schwingshackl 2014 <sup>26</sup>	cohort	< 0.001	< 0.001	>1000	Substantial	Including the null value	No <sup>a</sup>
MetS	Kastorini 201118	cohort	>0.05	>0.05	>2500	Considerable	NA	NA
MetS	Kastorini 201118	cross sectional	>0.05	>0.05	>2500	Considerable	Including the null value	NA
MetS	Godos 201724	cohort	< 0.05	>0.05	>5000	Substantial	Including the null value	No
MetS	Godos 201724	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 <sup>a</sup> 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	Significance threshold	Sample size	Estimate of	95% prediction interval	† Small study
		threshold reached	reached		heterogeneity		effects/excess
OVERALL MORTALITY		(random effects)	(fixed effects)				significance bias
	L: 201 <i>(</i> 27	> 0.05	> 0.05	> 5000		T 1 1 .1 11 1	N. a
	Liyanage 201627	>0.05	>0.05	>5000	Substantial	Including the null value	INO <sup>a</sup>
CARDIOVASCULAR OUTCOMES	M.C. 1. 201415	<0.05	<0.001	> 5000		NT A	NT A
CVD incidence/mortality	M-Gonzalez 2014 <sup>13</sup>	< 0.05	<0.001	>5000	Substantial		INA N.
CVD mortality	Grosso 2015 <sup>10</sup>	< 0.05	< 0.05	>5000	Not large	Including the null value	No <sup>a</sup>
CVD mortality	Liyanage 201627	>0.05	>0.05	>5000	Considerable	Including the null value	No <sup>a</sup>
CHD incidence	Liyanage 2016 <sup>27</sup>	>0.05	>0.05	>5000	Considerable	NA	NA
Stroke	Grosso 2015 <sup>16</sup>	< 0.05	<0.05	>5000	Not large	NA	NA
Stroke	Liyanage 2016 <sup>27</sup>	>0.05	<0.05	>5000	Not large	NA	NA
MI incidence	Grosso 2015 <sup>16</sup>	< 0.001	<0.001	>5000	Not large	Including the null value	No <sup>a</sup>
Heart failure	Liyanage 2016 <sup>27</sup>	>0.05	>0.05	<2500	NE	NA	NA
MACE	Liyanage 2016 <sup>27</sup>	>0.05	<0.001	>5000	Considerable	NA	NA
Systolic BP (mmHg)	Nordmann 2011 <sup>28</sup>	< 0.001	<0.001	>2500	Considerable	Including the null value	NA
Systolic BP (mmHg)	Kastorini 2011 <sup>18</sup>	< 0.001	< 0.001	>2500	Not large	Including the null value	No
Systolic BP (mmHg)	Rees 2013 <sup>29</sup>	< 0.05	< 0.001	>5000	Considerable	Including the null value	NA
Systolic BP (mmHg)	Huo 2014 <sup>30</sup> ‡	NA	NA	NA	Not large	NA	NA
Systolic BP (mmHg)	Nissensohn 2015 <sup>27</sup>	< 0.05	< 0.001	>5000	Considerable	Including the null value	NA
Systolic BP (mmHg)	Garcia 2016 <sup>24</sup>	>0.05	< 0.001	>5000	Substantial	Including the null value	NA
Systolic BP (mmHg)	Gay 2016 <sup>33</sup>	< 0.001	< 0.001	>2500	Considerable	Including the null value	NA
Systolic BP (mmHg)	Ndanuko 2016 <sup>26</sup>	< 0.001	< 0.001	<2500	Not large	Excluding the null value	NA
Diastolic BP (mmHg)	Nordmann 2011 <sup>28</sup>	< 0.001	< 0.001	>2500	Substantial	Including the null value	NA
Diastolic BP (mmHg)	Kastorini 201118	< 0.001	< 0.001	>2500	Not large	Excluding the null value	No
Diastolic BP (mmHg)	Rees 2013 <sup>29</sup>	< 0.001	< 0.001	>5000	Substantial	Including the null value	NA
Diastolic BP (mmHg)	Huo 2014 <sup>30</sup> ‡	NA	NA	NA	Not large	NA	NA
Diastolic BP (mmHg)	Nissensohn 2015 <sup>31</sup>	< 0.05	>0.05	>5000	Substantial	Including the null value	NA
Diastolic BP (mmHg)	Gay 2016 <sup>33</sup>	< 0.001	< 0.001	>5000	Substantial	Including the null value	NA
Diastolic BP (mmHg)	Garcia 2016 <sup>32</sup>	< 0.05	< 0.001	>2500	Considerable	Excluding the null value	No
Diastolic BP (mmHg)	Ndanuko 2016 <sup>34</sup>	< 0.001	< 0.001	<2500	Not large	Excluding the null value	NA
FMD (%)	Schwingshackl 201435	< 0.05	< 0.05	<2500	Not large	NA	NA
METABOLIC DISORDERS							
Weight (kg)	Esposito 2011 <sup>36</sup> ‡	< 0.001	NA	>2500	Considerable	NA	NA
Weight (kg)	Nordmann 2011 <sup>28</sup>	< 0.001	< 0.001	>2500	Considerable	Including the null value	NA
Weight (kg)	Huo 2014 <sup>30</sup>	< 0.05	< 0.05	<2500	Not large	Excluding the null value	No
BMI (kg/m <sup>2</sup> )	Nordmann 2011 <sup>28</sup>	< 0.001	< 0.001	>2500	Considerable	Including the null value	NA
BMI $(kg/m^2)$	Esposito 2011 <sup>36</sup> ‡	< 0.001	NA	>2500	Considerable	NA	NA
BMI $(kg/m^2)$	Huo 2014 <sup>30</sup> ‡	< 0.001	< 0.001	<2500	Not large	Excluding the null value	No
WC (cm)	Nordmann 2011 <sup>28</sup>	< 0.001	< 0.001	>2500	Considerable	Including the null value	NA
WC (cm)	Kastorini 201118	< 0.05	< 0.05	<2500	Not large	Including the null value	No
WC (cm)	Huo 2014 <sup>30</sup> ‡	NA	NA	<2500	Not large	NA	NA
WC (cm)	Garcia 2016 <sup>32</sup>	< 0.001	< 0.001	>2500	Considerable	Including the null value	No
TC (mmol/L)	Nordmann 2011 <sup>28</sup>	< 0.001	< 0.001	>2500	Substantial	Including the null value	NA

TC (mmol/L)	Rees 201329	< 0.05	< 0.001	>2500	Substantial	Including the null value	NA
TC (mmol/L)	Huo 2014 <sup>30</sup>	< 0.001	< 0.001	<2500	Not large	Excluding the null value	Yes
LDL-C (mmol/L)	Nordmann 2011 <sup>28</sup>	>0.05	0.05	<2500	Not large	Including the null value	NA
LDL-C (mmol/L)	Rees 2013 <sup>29</sup>	>0.05	< 0.05	>2500	Not large	Including the null value	NA
LDL-C (mmol/L)	Huo 2014 <sup>30</sup>	>0.05	>0.05	<2500	Not large	Including the null value	No
HDL-C (mmol/L)	Nordmann 2011 <sup>28</sup>	>0.05	< 0.001	>2500	Considerable	Including the null value	NA
HDL-C (mmol/L)	Kastorini 201118	< 0.001	< 0.001	>2500	Substantial	Including the null value	No <sup>a</sup>
HDL-C (mmol/L)	Rees 2013 <sup>29</sup>	>0.05	< 0.001	>2500	Considerable	Including the null value	NA
HDL-C (mmol/L)	Huo 2014 <sup>30</sup>	< 0.05	< 0.001	<2500	Substantial	Excluding the null value	No
HDL-C (mmol/L)	Garcia 2016 <sup>32</sup>	>0.05	< 0.001	<2500	Considerable	Including the null value	No
TG (mmol/L)	Kastorini 201118	< 0.05	< 0.001	>2500	Substantial	Including the null value	No
TG (mmol/L)	Rees 2013 <sup>29</sup>	>0.05	< 0.001	>2500	Considerable	Including the null value	NA
TG (mmol/L)	Huo 2014 <sup>30</sup>	< 0.05	< 0.001	<2500	Substantial	Including the null value	No
TG (mmol/L)	Garcia 2016 <sup>32</sup>	< 0.001	< 0.001	<2500	Considerable	Including the null value	Yes
Glucose (mmol/L)	Nordmann 2011 <sup>28</sup>	< 0.05	< 0.001	>2500	Considerable	Including the null value	NA
Glucose (mmol/L)	Kastorini 201118	< 0.001	< 0.001	<2500	Substantial	Including the null value	No
Glucose (mmol/L)	Huo 2014 <sup>30</sup>	< 0.05	< 0.001	<2500	Substantial	Including the null value	No
Glucose (mmol/L)	Garcia 2016 <sup>32</sup>	< 0.001	< 0.001	>2500	Considerable	Including the null value	No
HOMA-Index	Kastorini 201118	< 0.001	< 0.001	<2500	Considerable	Including the null value	NA
HOMA-Index	Huo 2014 <sup>30</sup> ‡	NA	NA	NA	Not large	NA	NA
Insulin (µU/mL)	Nordmann 2011 <sup>28</sup>	< 0.001	< 0.001	<2500	Considerable	Including the null value	No
Insulin (µU/mL)	Huo 2014 <sup>30</sup>	< 0.001	< 0.001	<2500	Not large	Excluding the null value	NA
HbA <sub>c1</sub>	Huo 2014 <sup>30</sup>	< 0.001	< 0.001	<2500	Substantial	Including the null value	NA
HbA <sub>c1</sub>	Ajala 2013 <sup>37</sup>	>0.05	< 0.001	<2500	Considerable	Including the null value	NA
HbA <sub>c1</sub>	Esposito 201538	< 0.001	< 0.001	<2500	Not large	Including the null value	NA
Diabetes	Schwingshackl 2014 <sup>26</sup>	< 0.05	< 0.05	>2500	NE	NA	NA
MetS	Kastorini 201118	< 0.05	< 0.001	<2500	Substantial	NA	NA
MetS remission	Esposito 2015 <sup>38</sup>	< 0.05	< 0.001	>2500	Substantial	NA	NA
Adiponectin (µg/mL)	Schwingshackl 201435	< 0.05	< 0.001	<2500	Considerable	NA	NA
ICAM-1 (ng/mL)	Schwingshackl 201435	< 0.05	< 0.001	<2500	Not large	NA	NA
INFLAMMATORY PARAMETERS							
CRP (mg/L)	Nordmann 2011 <sup>28</sup>	< 0.001	< 0.001	<2500	Considerable	Including the null value	NA
CRP (mg/L)	Schwingshackl 201435	< 0.001	< 0.001	<2500	Considerable	Including the null value	NA
IL-6 (pg/mL)	Schwingshackl 201435	< 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<sub>1c</sub> = haemoglobin A<sub>1c</sub>; 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

<sup>a</sup> 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	SE	† Egger test p-value
			(95% CI)		
Overall mortality	Sofi 2014 <sup>3</sup>	cohort	0.93 (0.91; 0.94)	0.01	< 0.01
CVD incidence/mortality	Sofi 2014 <sup>3</sup>	cohort	0.95 (0.91; 0.99)	0.02	< 0.01
CVD incidence/mortality	M-Gonzalez 2014 <sup>15</sup>	cohort	1.00 (0.98; 1.03)	0.01	< 0.01
CVD incidence	Grosso 2015 <sup>16</sup>	cohort	0.84 (0.75; 0.94)	0.06	< 0.01
CVD mortality	Grosso 2015 <sup>16</sup>	cohort	0.99 (0.93; 1.05)	0.03	< 0.01
CHD incidence	Grosso 2015 <sup>16</sup>	cohort	0.78 (0.65; 0.94)	0.09	0.35
MI incidence	Grosso 2015 <sup>16</sup>	cohort	0.70 (0.53; 0.92)	0.14	0.34
Stroke	Psaltopoulou 201317	cohort	0.87 (0.74; 1.03)	0.08	0.65
Stroke	Psaltopoulou 201317	case-control	0.25 (0.15; 0.92)	0.26	NE
Stroke	Psaltopoulou 201317	cross-sectional	0.70 (0.65; 1.06)	0.16	NE
Stroke	Grosso 2015 <sup>16</sup>	cohort	0.90 (0.75; 1.08)	0.09	0.35
Systolic BP (mmHg)	Kastorini 201118	cross-sectional	-3.00 (-3.18; -2.82)	0.09	0.62
Diastolic BP (mmHg)	Kastorini 201118	cross-sectional	-7.00 (-7.18; -6.82)	0.09	0.19
Cancer incidence/mortality	Sofi 2014 <sup>3</sup>	cohort	0.96 (0.95; 0.97)	0.01	0.10
Cancer incidence/mortality	Schwingshackl 201519	cohort	0.80 (0.77; 0.83)	0.02	0.78
Cancer mortality	Bloomfield 2016 <sup>20</sup>	cohort	0.95 (0.91; 0.99)	0.02	0.45
Cancer incidence	Bloomfield 2016 <sup>20</sup>	cohort	0.96 (0.95; 0.97)	0.01	0.25
Colorectal cancer	Schwingshackl 201519	cohort	0.89 (0.80; 0.99)	0.05	0.95
Colorectal cancer	Schwingshackl 201519	case-control	0.88 (0.84; 0.92)	0.02	0.10
Colorectal cancer	Bloomfield 2016 <sup>20</sup>	cohort	1.03 (0.93; 1.14)	0.05	0.19
Breast cancer	Schwingshackl 201519	cohort	0.98 (0.86; 1.11)	0.07	0.29
Breast cancer	Schwingshackl 201519	case-control	0.91 (0.86; 0.96)	0.03	0.28
Breast cancer	Bloomfield 2016 <sup>20</sup>	cohort	0.94 (0.88; 1.00)	0.03	0.10
Prostate cancer	Schwingshackl 201519	cohort	0.95 (0.92; 1.00)	0.03	NE
Gastric cancer	Schwingshackl 201519	cohort	0.67 (0.47; 0.96)	0.18	NE
Esophageal cancer	Schwingshackl 201519	cohort	0.91 (0.66; 1.25)	0.16	NE
Head/neck cancer	Schwingshackl 2015 <sup>19</sup>	case-control	0.59 (0.39; 0.89)	0.21	0.13
Endometrial cancer	Schwingshackl 201519	case-control	0.43 (0.34; 0.54)	0.12	NE
Neurodegenerative disease	Sofi 2014 <sup>3</sup>	cohort	0.93 (0.80; 1.08)	0.08	0.47
Neurodegenerative diseases	Wu 2017 <sup>21</sup>	cohort	0.87 (0.76; 1.00)	0.07	0.33
Cognitive impairment	Psaltopoulou 201317	cohort	0.71 (0.52; 1.00)	0.17	0.21
Cognitive impairment	Singh 2014 <sup>22</sup>	cohort	0.72 (0.52; 1.00)	0.17	0.98
Cognitive impairment	Singh 2014 <sup>22</sup>	cohort	0.92 (0.85; 0.99)	0.04	0.13
Cognitive impairment	Psaltopoulou 201317	cross-sectional	1.00 (0.77; 1.29)	0.13	0.62
Cognitive impairment	Wu 2017 <sup>21</sup>	cohort	0.87 (0.76; 1.00)	0.07	0.05
Alzheimer's disease	Wu 2017 <sup>21</sup>	cohort	0.60 (0.42; 0.86)	0.18	0.29
Dementia	Cao 2015 <sup>23</sup>	cohort	0.72 (0.52; 1.00)	0.17	0.60
Dementia	Wu 2017 <sup>21</sup>	cohort	1.13 (0.79; 1.62)	0.18	0.52

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Depression	Psaltopoulou 201317	cross-sectional	0.84 (0.68; 1.03)	0.11	0.71	
Diabetes	Koloverou 2014 <sup>25</sup>	cohort	0.88 (0.79; 0.97)	0.05	0.13	
Diabetes	Schwingshackl 201435	cohort	0.88 (0.79; 0.98)	0.06	0.09	
MetS	Godos 2017 <sup>24</sup>	cohort	0.96 (0.71; 1.30)	0.15	0.32	
MetS	Godos 2017 <sup>24</sup>	case-control	1.01 (0.97; 1.05)	0.02	0.04	
WC (cm)	Godos 2017 <sup>24</sup>	cross-sectional	0.76 (0.64; 0.90)	0.09	0.64	
HDL-C (mmol/L)	Godos 2017 <sup>24</sup>	cross-sectional	0.84 (0.69; 1.02)	0.10	0.15	
TG (mmol/L)	Godos 2017 <sup>24</sup>	cross-sectional	0.99 (0.83; 1.18)	0.09	0.15	
Glucose (mmol/L)	Godos 2017 <sup>24</sup>	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 38.57. To convert mg/dL blood glucose to mmol/L, multiply mmol/L by 18

Supplemen	ntary Table 5.	Bias assessment	of meta-analy	ses of rar	ndomise	l contro	l studi	es evalu	ating	Medite	rranean di	et inter	vention ve	ersus othe	er diet	s interv	ention i	n relatio	n differ	ent heal	th outcomes
11			1						0												

Outcome	Reference	Largest study	SE	Egger test
		(95% CI)		p-value †
Overall mortality	Liyanage 2016 <sup>27</sup>	1.01 (0.81; 1.25)	0.11	0.20
CVD incidence/mortality	M-Gonzales 2014 <sup>15</sup>	0.71 (0.56; 0.90)	0.19	NE
CVD mortality	Grosso 2015 <sup>16</sup>	0.83 (0.54; 1.28)	2.00	0.04
CVD mortality	Liyanage 2016 <sup>27</sup>	1.22 (0.90; 1.65)	0.16	< 0.01
CHD incidence	Liyanage 2016 <sup>27</sup>	0.88 (0.59; 1.30)	0.20	NE
Stroke	Grosso 2015 <sup>16</sup>	0.61 (0.44; 0.85)	0.17	NE
Stroke	Liyanage 2016 <sup>27</sup>	0.68 (0.49; 0.96)	0.17	NE
MI incidence	Grosso 2015 <sup>16</sup>	0.77 (0.52; 1.14)	0.20	0.09
Heart failure	Liyanage 2016 <sup>27</sup>	0.25 (0.05; 1.17)	0.82	NE
MACE	Liyanage 2016 <sup>27</sup>	0.81 (0.64; 1.02)	0.12	NE
Systolic BP (mmHg)	Garcia 2016 <sup>32</sup>	-1.00 (-1.06; -0.94)	0.03	0.14
Diastolic BP (mmHg)	Garcia 2016 <sup>32</sup>	-0.51 (-0.67; -0.34)	0.08	0.83
WC (cm)	Garcia 2016 <sup>32</sup>	-0.69 (-0.87; -0.52)	0.09	0.85
HDL-C (mmol/L)	Garcia 2016 <sup>32</sup>	-0.05 (-0.28; 0.18)	0.12	0.71
TG (mmol/L)	Garcia 2016 <sup>32</sup>	-0.07 (0.27; 0.13)	0.10	0.09
Glucose (mmol/L)	Garcia 2016 <sup>32</sup>	-0.40 (-0.45; -0.34)	0.03	0.52
MetS remission	Esposito 2015 <sup>38</sup>	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<sub>1c</sub> = haemoglobin A<sub>1c</sub>; 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 <sub>MedSD</sub> Items															
	A prior	ri design	Li	iterature sed	arch and D	Duplicate eff	ort	Coding	of studies		Analysis	s and Inter	pretation		Total
Meta-analyses	Q1	Q2	Q3	<b>Q</b> 4	Q5	<b>Q</b> 6	<b>Q</b> 7	<b>Q</b> 8	Q9	Q10	Q11	Q12	Q13	Q14	score
Esposito 2011 <sup>36</sup>	1	1	1	2	1	1	1	1	2	0	2	1	1	1	16
Kastorini 2011 <sup>18</sup>	1	1	1	2	1	0	1	1	2	1	3	1	1	1	17
Nordmann 2011 <sup>28</sup>	1	1	1	2	1	0	1	1	1	0	3	1	1	1	15
Ajala 2013 <sup>37</sup>	1	1	0	2	0	0	2	1	2	0	3	1	0	1	14
Psaltopoulou 2013 <sup>17</sup>	1	1	1	2	2	1	1	1	2	0	3	2	1	1	19
Rees 2013 <sup>29</sup>	1	1	1	2	2	1	2	1	2	0	3	2	1	1	20
Huo 2014 <sup>30</sup>	1	1	1	2	1	0	1	1	2	0	3	1	1	1	16
Koloverou 2014 <sup>25</sup>	1	1	1	2	1	0	1	1	1	0	3	2	1	1	16
M-Gonzalez 2014 <sup>15</sup>	1	1	0	1	1	1	0	0	0	0	3	1	1	1	11
Schwingshackl 2014 <sup>26</sup>	1	1	1	2	1	0	1	1	2	0	3	2	1	1	17
Schwingshackl 2014 <sup>35</sup>	1	1	1	1	1	0	1	1	2	0	3	2	1	1	16
Singh 2014 <sup>22</sup>	1	1	2	2	2	1	2	1	2	0	3	1	1	1	20
Sofi 2014 <sup>3</sup>	1	1	1	2	1	1	0	1	0	0	3	1	1	1	14
Cao 2015 <sup>23</sup>	1	1	1	2	1	0	1	1	0	0	3	1	1	1	14
Esposito 2015 <sup>38</sup>	1	1	2	2	1	0	1	1	2	0	3	1	1	1	17
Grosso 2015 <sup>16</sup>	1	1	1	2	1	0	1	1	2	0	3	1	1	1	16
Nissensohn 2015 <sup>27</sup>	1	1	1	2	1	1	1	1	2	0	3	2	1	1	18
Schwingshackl 2015 <sup>19</sup>	1	1	1	2	1	1	1	1	2	0	3	2	1	1	18
Bloomfield 2016 <sup>20</sup>	1	1	0	2	2	0	1	1	2	0	3	1	0	1	15
Garcia 2016 <sup>32</sup>	1	1	1	2	2	1	2	1	2	0	3	2	1	1	20
Gay 2016 <sup>33</sup>	1	1	1	2	1	0	1	1	2	0	3	2	0	1	16
Liyanage 2016 <sup>27</sup>	1	1	1	2	2	0	2	1	2	1	3	1	0	1	18
Ndanuko 2016 <sup>34</sup>	1	1	0	1	1	0	1	1	1	0	3	1	0	1	12
Godos 2017 <sup>24</sup>	1	1	1	2	1	0	1	1	1	0	3	1	1	1	15
Wu 2017 <sup>21</sup>	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 includedstudies 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

Reference	Outcome	Type of studies	High quality (NOS score = 9)	Moderate quality (NOS score = $7 \text{ or } 8$ )	Low quality (NOS score $\leq 7$ )
Stroke	Psaltopoulou 2013 <sup>17</sup>	cohort	1		
Stroke	Psaltopoulou 2013 <sup>17</sup>	case-control	0	1	1
Stroke *	Psaltopoulou 2013 <sup>17</sup>	cross-sectional	0	2	3
Stroke	Grosso 2015 <sup>16</sup>	cohort	0	- 5	0
CVD incidence	Grosso 2015 <sup>16</sup>	cohort	0	11	2
CVD mortality	Grosso 2015 <sup>16</sup>	cohort	0	10	- 3
CHD incidence	Grosso 2015 <sup>16</sup>	cohort	0	3	1
MI incidence	Grosso 2015 <sup>16</sup>	cohort	0	3	0
Overall cancer	Schwingshackl 2015 <sup>19</sup>	cohort	2	7	1
Colorectal cancer	Schwingshackl 2015 <sup>19</sup>	cohort	0	3	0
Colorectal cancer	Schwingshackl 2015 <sup>19</sup>	cross-sectional	0	2	2
Breast cancer	Schwingshackl 2015 <sup>19</sup>	cohort	0	4	0
Breast cancer	Schwingshackl 2015 <sup>19</sup>	cross-sectional	0	4	4
Prostate cancer	Schwingshackl 2015 <sup>19</sup>	cohort	1	1	1
Prostate cancer	Schwingshackl 2015 <sup>19</sup>	cross-sectional	0	1	0
Gastric cancer	Schwingshackl 2015 <sup>19</sup>	cohort	1	1	0
Gastric cancer	Schwingshackl 2015 <sup>19</sup>	cross-sectional	0	0	1
Esophageal cancer	Schwingshackl 2015 <sup>19</sup>	cohort	1	0	0
Esophageal cancer	Schwingshackl 2015 <sup>19</sup>	cross-sectional	0	0	1
Endometrial cancer	Schwingshackl 2015 <sup>19</sup>	cohort	0	1	0
Endometrial cancer	Schwingshackl 2015 <sup>19</sup>	cross-sectional	0	0	1
Ovarian cancer	Schwingshackl 2015 <sup>19</sup>	cross-sectional	0	1	0
Respiratory cancer	Schwingshackl 201519	cohort	0	0	1
Bladder cancer	Schwingshackl 201519	cohort	0	1	0
Pancreatic cancer	Schwingshackl 201519	cross-sectional	0	0	1
Liver cancer	Schwingshackl 201519	cohort	1	0	0
Liver cancer	Schwingshackl 201519	cross-sectional	0	0	1
Head/neck cancer	Schwingshackl 2015 <sup>19</sup>	cohort	1	0	0
Head/neck cancer	Schwingshackl 2015 <sup>19</sup>	cross-sectional	0	0	4
Neurodegenerative disease	Wu 2017 <sup>21</sup>	cohort	2	11	0
Cognitive impairment	Psaltopoulou 201317	cohort	1	3	0
Cognitive impairment	Psaltopoulou 2013 <sup>17</sup>	cross-sectional	0	1	0
Cognitive impairment *	Psaltopoulou 2013 <sup>17</sup>	cross-sectional	0	2	2
Cognitive impairment	Singh 2014 <sup>22</sup>	cohort	1	4	0
Cognitive impairment °	Singh 2014 <sup>22</sup>	cohort	1	4	0
Cognitive impairment	Wu 2017 <sup>21</sup>	cohort	1	4	0
Alzheimer's disease	Wu 2017 <sup>21</sup>	cohort	0	5	0
Dementia	Wu 2017 <sup>21</sup>	cohort	1	2	0

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

Depression	Psaltopoulou 2013 <sup>17</sup>	cohort	0	0	1
Depression	Psaltopoulou 2013 <sup>17</sup>	cross-sectional	0	0	1
Depression *	Psaltopoulou 2013 <sup>17</sup>	cross-sectional	0	5	2
Diabetes	Schwingshackl 2014 <sup>35</sup>	cohort	2	5	0
Systolic BP	Nissensohn 2016 <sup>31</sup>	RCTs	0	1	5
Diastolic BP	Nissensohn 2016 <sup>31</sup>	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<sup>24</sup>

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	Effect	n	n	Summary relati	ve risk (95% CI)	fixed	random	PI (95%)	$I^2$	Strength of
		of studies	size	Mediterranean diet	control diet	Fixed effects	Random Effects	p value	p value			evidence
OVERALL MORTAL	ITY											
Overall mortality	Liyanage 2016 <sup>27</sup>	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 <sup>15</sup>	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 201516	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 <sup>27</sup>	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 <sup>27</sup>	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 201516	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 <sup>27</sup>	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 201516	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 <sup>27</sup>	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 <sup>27</sup>	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 <sup>28</sup>	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 201118	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 <sup>29</sup>	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 <sup>30</sup> ‡	6	WMD	NA	NA	NA	-1.45 (-1.97; -0.94)	NA	NA	NA	0%	NA
Systolic BP (mmHg)	Nissensohn 201527	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 <sup>24</sup>	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 <sup>33</sup>	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 <sup>26</sup>	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 <sup>28</sup>	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 201118	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 <sup>29</sup>	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 <sup>30</sup> ‡	3	WMD	NA	NA	NA	-1.41 (-1.84; -0.97)	NA	NA	NA	0%	NA
Diastolic BP (mmHg)	Nissensohn 2015 <sup>31</sup>	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 <sup>33</sup>	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 <sup>32</sup>	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 <sup>34</sup>	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 201435	2	WMD	109	101	1.71 (0.56; 2.87)	1.86 (0.23; 3.48)	0.004	0.02	NE	43%	Weak
METABOLIC DISOR	RDERS											
Weight (kg)	Esposito 2011 <sup>36</sup> ‡	15	MD	1 937	1 588	NA	-1.75 (-2.86; -0.64)	NA	< 0.001	NA	95%	Weak
Weight (kg)	Nordmann 2011 <sup>28</sup>	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 <sup>30</sup>	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 <sup>28</sup>	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 <sup>36</sup> ‡	12	MD	1 590	1 571	NA	-0.57 (-0.93; -0.21)	NA	< 0.001	NA	92%	Suggestive
BMI (kg/m <sup>2</sup> )	Huo 2014 <sup>30</sup> ‡	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 <sup>28</sup>	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 201118	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 <sup>30</sup> ‡	3	WMD	NA	416 °	NA	-0.41 (-0.89; 0.08)	NA	NA	NA	0%	NA
WC (cm)	Garcia 2016 <sup>32</sup>	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 <sup>28</sup>	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 <sup>29</sup>	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 <sup>30</sup>	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 <sup>28</sup>	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 <sup>29</sup>	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 <sup>30</sup>	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 <sup>28</sup>	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 201118	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 <sup>29</sup>	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 <sup>30</sup>	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 <sup>32</sup>	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 201118	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 <sup>29</sup>	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 <sup>30</sup>	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 <sup>32</sup>	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 <sup>28</sup>	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 <sup>18</sup>	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 <sup>30</sup>	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 <sup>32</sup>	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 <sup>18</sup>	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 <sup>30</sup> ‡	6	WMD	NA	NA	NA	-0.55 (-1.53; 0.42)	NA	NA	NA	46%	NA
Insulin ( $\mu U/mL$ )	Nordmann 2011 <sup>28</sup>	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 <sup>30</sup>	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 <sup>30</sup>	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 <sub>1c</sub>	Ajala 2013 <sup>37</sup>	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 <sub>1c</sub>	Esposito 201538	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 <sup>26</sup>	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 201118	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 <sup>38</sup>	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 <sup>35</sup>	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 201435	2	WMD	389	197	-25.4 (-38.3; -12.5)	-23.7 (-41.2; -6.22)	0.00001	0.008	NE	34%	Weak
INFLAMMATORY PA	RAMETERS											
CRP (mg/L)	Nordmann 2011 <sup>28</sup>	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 201435	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 201435	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<sub>1c</sub> = haemoglobin A<sub>1c</sub>; 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 by 18.



Outcome	n of studies	Study design	n of events (cases) / total (controls)	Comparison	Relative risk (95% Cl)	Relative risk (95% Cl)
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	<u>← → − − − − − − − − − − − − − − − − − − </u>	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 <sup>3</sup>	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	999/2628	high vs low		0.57 (0.45, 0.72)
Pancreatic cancer 19	1	case-control	688/2204	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 1º	4	case-control	2 065 / 4 851	high vs low		0.32 (0.19, 0.55)
Plead/neck cancer 19	1	cohort	1 808 / 49 490 /	high vs low		0.61 (0.33, 1.14)
Endometrial concer 19	1	cohort	1 425 / 477 312	high vs low		0.84 (0.69, 1.02)
Endometrial cancer 19	1	conort	1 392 / 64 415	high vs low		0.98 (0.82, 1.17)
Overien cancer 19	2	case-control	2 000 / 4 001	high vs low		0.61 (0.29, 1.29)
Neurodegenerative diseases 3	5	case-control	1 074 / 136 235	2 point increase		0.91 (0.71, 1.17)
Neurodegenerative diseases 21	0	conort	3 627 / 34 168	2 point increase		0.79 (0.70, 0.90)
Cognitive impairment 21	å	conort	2 328 / 27 567	high vs low		0.83 (0.75, 0.03)
Cognitive impairment 22	5	conort	709/6878	1 noint increase	~	0.03 (0.75, 0.93)
Cognitive impairment 17	1	conort case_control	282 / 1 880	high vs low	ĭ	0.32 (0.86, 0.57)
Cognitive impairment <sup>17</sup>	3	cross-sectional	459 / 3 345	high vs low		0.57 (0.10, 0.33)
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)
					0.1 0.2 0.5 1 Mean Difference	2 Mean Difference
					(95% Cl)	(95% CI)
HOMA-Index <sup>18</sup>	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)
				-	7 -4 -1 0 1	4

Outcome	n of studies	n of subjects (Mediterranean diet)	n of subjects (other diets)	Mean Difference (95% CI)	Mean Difference (95% CI)
Weight <sup>36</sup> BMI <sup>36</sup> Waist circumference <sup>32</sup> Total cholesterol <sup>29</sup> LDL cholesterol <sup>30</sup> HDL cholesterol <sup>18</sup> Triglycerides <sup>18</sup> Glucose <sup>32</sup> HOMA-Index <sup>18</sup> Insulin <sup>30</sup> HbAc1 <sup>30</sup> MetS <sup>18</sup> MetS remission <sup>38</sup> Systolic BP <sup>32</sup> Diastolic BP <sup>32</sup> CRP <sup>35</sup> LL-6 <sup>35</sup> Adiponectin <sup>35</sup> FMD <sup>35</sup>	15 12 39 8 6 29 29 23 10 5 9 2 25 25 14 6 2 2 2	1 937 1 590 NA 2 089 384 2 202 2 202 NA 1 031 238 568 902 2 388 NA NA 1 120 646 156 109	1 588 1 571 2 580* 2 063 258 1 903 1 903 2 975* 711 319 521 482 1 184 3 262* 3 262* 822 431 130 101		$\begin{array}{c} -1.75 \left(-2.86, -0.64\right) \\ -0.57 \left(-0.93, -0.21\right) \\ -0.51 \left(-0.65, -0.36\right) \\ -0.16 \left(-0.26, -0.06\right) \\ -0.11 \left(-0.24, 0.02\right) \\ 0.03 \left(0.01, 0.05\right) \\ -0.07 \left(-0.12, -0.02\right) \\ -0.37 \left(-0.41, -0.33\right) \\ -0.45 \left(-0.74, -0.16\right) \\ -0.55 \left(-0.81, -0.29\right) \\ -0.30 \left(-0.46, -0.14\right) \\ -0.80 \left(-1.42, -0.18\right) \\ 1.49 \left(1.14, 1.94\right) \\ -0.67 \left(-0.87, -0.47\right) \\ -0.94 \left(-1.55, -0.34\right) \\ -0.98 \left(-1.48, -0.49\right) \\ -0.42 \left(-0.73, -0.11\right) \\ 1.69 \left(0.27, 3.11\right) \\ 1.86 \left(0.23, 3.48\right) \end{array}$
ICAM-1 35	2	389	197	·	-23.7 (-41.2, -6.22)
				Relative risk (95% CI)	Relative risk (95% Cl)
Overall mortality <sup>27</sup> CVD incidence/mortality <sup>15</sup> CVD mortality <sup>16</sup> CHD incidence <sup>27</sup> Stroke <sup>27</sup> Heart failure <sup>27</sup> MACE <sup>27</sup> MI incidence <sup>16</sup> Diabetes <sup>26</sup>	3 2 4 2 1 2 3 1	6 630 5 133 7 418 5 299 6 617 302 5 299 7 116 NA	4 041 7 761 4 875 2 753 4 071 303 2 753 4 572 3 541		0.93 (0.65, 1.33) 0.62 (0.45, 0.86) 0.59 (0.38, 0.93) 0.56 (0.20, 1.61) 0.64 (0.47, 0.86) 0.25 (0.05, 1.17) 0.45 (0.13, 1.57) 0.60 (0.44, 0.82) 0.70 (0.54, 0.91)

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Cardiovascular disease Coronary heart disease Myocardial infarction Stroke Heart failure Major cardiovascular events Cancer incidence/mortality Cancer mortality **Cancer incidence Colorectal cancer Breast cancer** Prostate cancer Gastric cancer Pancreatic cancer Liver cancer Oesophageal cancer **Respiratory cancer** Head/neck cancer Bladder cancer **Endometrial cancer Ovarian cancer** Neourodegenerative disease Cognitive impairment



Dementia Depression Weight BMI Waist circumference Total cholesterol LDL cholesterol HDL cholesterol Triglycerides Glucose HOMA-Index Insulin HbA1c Diabetes MetS MetS remission Systolic BP **Diastolic BP** FMD Adiponectin ICAM-1 CRP IL-6



Highly suggestive Convincing

Suggestive

Weak No evidence