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

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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
41 and multiple health outcomes, an umbrella review of the evidence across meta-analyses of observational
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
45 subjects, were identified. A robust evidence, supported by a p value < 0.001 , a large simple size, and not
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.

52
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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
67 the combination of foods which is linked to improved health. (2) This awareness shifted the research's
68 focus from the analysis of individual nutrients to the evaluation of the whole diet and the interaction
69 between its components.

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

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

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

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

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

91

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
100 health status “plasma lipids”, “cholesterol”, “triglycerides”, “glycaemia”, “hematic parameters”, “cancer”,
101 “circulatory diseases”, “cardiovascular disease”, “ischemic heart disease”, “cerebrovascular disease”,
102 “mortality”, “health effects”, “health status”, and their variants. The most updated or complete
103 publication was used when more than an article was present for a single study. In addition, separate meta-
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.

106

107 ***2.2. Eligibility criteria***

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

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

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

121

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
125 different study design may increase heterogeneity, wherever possible we considered summary results
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)
133 along with the corresponding 95% CI and quality of the included studies in each meta-analysis (when a
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 inflammatory
137 parameters.

138

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
146 evaluated using the I^2 statistic. (8) Where I^2 exceeded 50% or 75%, the heterogeneity was considered
147 substantial or considerable, respectively.

148 In order to detect any evidence for small-study effects, we performed the Egger's regression
149 asymmetry test (9) and we calculated the standard error (SE) of the effect size (under random effects) for
150 the largest study of each meta-analysis. The largest study was defined on the basis of the smallest SE. If
151 the p-value for Egger's test was <0.10 and the largest study had smaller effect size compared to the
152 summary effect size (more conservative) both criteria for existence of small-study effects were fulfilled.
153 (10)

154 Finally, according to previous umbrella reviews (11,12), we categorized the observed associations
155 as convincing or not, by using the following criteria: significance at $p \leq 0.05$ and $p \leq 0.001$, which is
156 considered to be a more appropriate threshold of statistical significance to reduce the number of false-
157 positive findings (13); inclusion of over than 500 or 1,000 cases for binary outcomes (more than 2,500
158 or 5,000 total participants if the metric was continuous); absence of considerable heterogeneity ($I^2 <$
159 75%); 95% PI excluding the null value and absence of small-study effects. Specifically, we identified 5
160 categories:

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

165 - *Highly suggestive evidence*: significance threshold reached at $p \leq 0.001$ 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 ($I^2 = 50-75\%$)

168 - *Suggestive evidence*: significance threshold reached at $p \leq 0.001$ 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 $p \leq 0.05$ for random-effects calculation

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

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

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

183

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.

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

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

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
217 the same study design existed, we retained the meta-analysis with the largest number of studies.
218 Furthermore, whether the overlapping meta-analyses had the same number of studies, we reported the
219 most recent.

220

221 ***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
223 intervention with the Mediterranean diet on 26 outcomes (Table 2), grouped as follows: overall mortality
224 (n=1), cardiovascular outcomes (n=26), metabolic disorders (n=41), and inflammatory parameters (n=3).
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
230 circumference, body mass index, total cholesterol, glucose, and C-reactive protein agreement existed
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.

238

239 ***3.3 Evaluation of bias, heterogeneity, and quality***

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

245 On the basis of the AMSTAR_{MedSD} assessment, meta-analyses achieved a medium-to-high quality
246 score (mean \pm SD: 16.36 \pm 2.36). As reported in Supplementary Table 6, 11 meta-analyses totalled >80%
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.

262

263 ***3.4. Strength of evidence***

264 Figure 4 shows the strength of the evidence estimated on the basis of the following criteria: level
265 of significance for both random- and fixed-effect calculations, sample size, heterogeneity, 95% PI, and
266 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
268 convincing/highly suggestive categories for 12 different health outcomes (overall mortality,
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
275 as anthropometrical, metabolic and inflammatory risk parameters, the grade of evidence resulted
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.

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

281

282 **4. Discussion**

283 The present is the first umbrella review estimating the association between the adherence to the
284 Mediterranean diet and 37 different health outcomes including overall mortality, cardiovascular
285 outcomes, cancer outcomes, cognitive disorders, metabolic disorders, as well as inflammatory parameters.
286 The overall analysis comprised 13 meta-analyses of observational studies and 16 meta-analyses of RCTs,
287 for a total population of over than 12,800,000 subjects. Most summary estimates supported the notion
288 that a greater adherence to the Mediterranean diet determines a reduction of the risk of chronic diseases
289 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 ≤ 0.001 , large sample
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

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

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

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

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_{MedSD}
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_{MedSD} 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
356 few studies exist for several outcomes like specific localizations of cancer or inflammatory parameters,
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 RCT's 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.

364 In conclusion, this umbrella review provides a comprehensive resume of the published meta-
365 analyses in relation to the Mediterranean diet and health outcomes, and maps the status of evidence. To
366 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.

374

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575 **Legend to figures**

576

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

578

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

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

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

Esophageal cancer	Schwingshackl 2015 ¹⁹	1 case-contr	high vs low	RR	304	743	0.26 (0.13; 0.52)	0.26 (0.13; 0.52)	0.0001	0.0001	NE	NE	Weak
Respiratory cancer	Schwingshackl 2015 ¹⁹	1 cohort	high vs low	RR	124	4 336	0.10 (0.01; 0.77)	0.10 (0.01; 0.77)	0.03	0.03	NE	NE	Weak
Head/neck cancer	Schwingshackl 2015 ¹⁹	3 case-contr	high vs low	RR	2 065	4 851	0.32 (0.26; 0.40)	0.32 (0.19; 0.55)	<0.0001	<0.001	(0.03; 2.95)	83%	Suggestive
Head/neck cancer	Schwingshackl 2015 ¹⁹	1 cohort	high vs low	RR	1 868	494 967	0.61 (0.33; 1.14)	0.61 (0.33; 1.14)	0.12	0.12	NE	NE	No evidence
Bladder cancer	Schwingshackl 2015 ¹⁹	1 cohort	high vs low	RR	1 425	477 312	0.84 (0.69; 1.02)	0.84 (0.69; 1.02)	0.08	0.08	NE	NE	No evidence
Endometrial cancer	Schwingshackl 2015 ¹⁹	1 cohort	high vs low	RR	1 392	84 415	0.98 (0.82; 1.17)	0.98 (0.82; 1.17)	0.82	0.82	NE	NE	No evidence
Endometrial cancer	Schwingshackl 2015 ¹⁹	2 case-contr	high vs low	RR	2 058	4 001	0.50 (0.41; 0.62)	0.61 (0.29; 1.29)	<0.0001	0.20	NE	89%	No evidence
Ovarian cancer	Schwingshackl 2015 ¹⁹	1 case-contr	high vs low	RR	696	82 948	0.91 (0.71; 1.17)	0.91 (0.71; 1.17)	0.46	0.46	NE	NE	No evidence

COGNITIVE DISORDERS

Neurodeg. diseases	Sofi 2014 ³	5 cohort	2-point increase	RR	1 074	136 235	0.87 (0.81; 0.94)	0.87 (0.81; 0.94)	0.0005	0.0005	(0.77; 0.98)	0%	Convincing
Neurodeg. diseases	Wu 2017 ²¹	9 cohort	high vs low	RR	3 627	34 168	0.81 (0.74; 0.89)	0.79 (0.70; 0.90)	<0.0001	0.0003	(0.60; 1.04)	22%	Highly suggestive
Cognit. impairment	Psaltopoulou 2013 ¹⁷	4 cohort	high vs low	RR	819	5 916	0.72 (0.58; 0.88)	0.72 (0.58; 0.88)	0.001	0.001	(0.45; 1.13)	0%	Suggestive
Cognit. impairment	Singh 2014 ²²	5 cohort	high vs low	HR	825	6 652	0.67 (0.55; 0.81)	0.67 (0.55; 0.81)	<0.0001	<0.0001	(0.49; 0.91)	0%	Suggestive
Cognit. impairment	Singh 2014 ²²	5 cohort	1-point increase	HR	709 [^]	6 878	0.92 (0.88; 0.97)	0.92 (0.88; 0.97)	0.0008	0.0008	(0.85; 1.00)	0%	Suggestive
Cognit. impairment	Psaltopoulou 2013 ¹⁷	1 case-contr	high vs low	RR	282	1 880	0.31 (0.16; 0.59)	0.31 (0.16; 0.59)	0.004	0.004	NE	NE	Weak
Cognit. impairment	Psaltopoulou 2013 ¹⁷	3 cross-sect	high vs low	RR	459	3 345	0.72 (0.58; 0.90)	0.52 (0.22; 1.22)	0.003	0.13	(0.01; 22.20)	88%	No evidence
Cognit. impairment	Wu 2017 ²¹	5 cohort	high vs low	RR	2 328	27 567	0.83 (0.75; 0.93)	0.83 (0.75; 0.93)	0.001	0.001	(0.66; 1.05)	0%	Highly suggestive
Alzheimer's disease	Wu 2017 ²¹	5 cohort	high vs low	RR	637	6 111	0.60 (0.48; 0.77)	0.60 (0.48; 0.77)	<0.0001	<0.0001	(0.44; 0.82)	0%	Convincing
Dementia	Cao 2015 ²³	5 cohort	high vs low	RR	1 081	8 174	0.69 (0.57; 0.84)	0.69 (0.57; 0.84)	0.0002	0.0002	(0.51; 0.95)	0%	Convincing
Dementia	Wu 2017 ²¹	3 cohort	high vs low	RR	662	8 873	1.07 (0.81; 1.42)	1.07 (0.81; 1.42)	0.63	0.63	(0.58; 1.97)	0%	No evidence
Depression	Psaltopoulou 2013 ¹⁷	1 cohort	high vs low	RR	480	10 094	0.58 (0.44; 0.77)	0.58 (0.44; 0.77)	0.002	0.002	NE	NE	Weak
Depression	Psaltopoulou 2013 ¹⁷	1 case-contr	high vs low	RR	111	345	0.21 (0.09; 0.48)	0.21 (0.09; 0.48)	0.0002	0.0002	NE	NE	Weak
Depression	Psaltopoulou 2013 ¹⁷	7 cross-sect	high vs low	RR	1 718	7 406	0.80 (0.69; 0.93)	0.80 (0.69; 0.93)	0.004	0.004	(0.67; 0.96)	0%	Weak

METABOLIC DISORDERS

WC (cm)	Kastorini 2011 ¹⁸	4 cross-sect	high vs low	MD	-	500 958 °	-1.34 (-1.42; -1.26)	-5.78 (-7.26; -4.31)	<0.0001	<0.0001	(-11.04; -0.52)	99%	Suggestive
WC (cm)	Godos 2017 ²⁴	4 cross-sect	high vs low	RR	-	11 868 °	0.83 (0.74; 0.93)	0.82 (0.70; 0.96)	0.002	0.01	(0.54; 1.23)	22%	Weak
HDL-C (mmol/L)	Kastorini 2011 ¹⁸	6 cross-sect	high vs low	MD	-	9 831 °	0.06 (0.05; 0.06)	0.06 (0.03; 0.09)	<0.0001	<0.0001	(-2.43; 2.55)	87%	Suggestive
HDL-C (mmol/L)	Godos 2017 ²⁴	4 cross-sect	high vs low	RR	-	11 868 °	0.92 (0.82; 1.02)	0.87 (0.77; 1.00)	0.10	0.04	(0.73; 1.04)	0%	Weak
TG (mmol/L)	Kastorini 2011 ¹⁸	6 cross-sect	high vs low	MD	-	9 831 °	-0.16 (-0.18; -0.14)	-0.11 (-0.18; -0.04)	<0.0001	<0.0001	(-15.06; 14.84)	82%	Suggestive
TG (mmol/L)	Godos 2017 ²⁴	4 cross-sect	high vs low	RR	-	11 868 °	0.88 (0.78; 0.98)	0.84 (0.70; 1.01)	0.02	0.06	(0.49; 1.44)	44%	No evidence
Glucose (mmol/L)	Kastorini 2011 ¹⁸	6 cross-sect	high vs low	MD	-	9 269 °	-0.32 (-0.34; -0.31)	-0.22 (-0.32; -0.11)	<0.0001	0.0009	(-7.01; 6.57)	89%	Suggestive
Glucose (mmol/L)	Godos 2017 ²⁴	4 cross-sect	high vs low	RR	-	11 868 °	1.03 (0.88; 1.21)	1.03 (0.87; 1.22)	0.73	0.72	(0.78; 1.35)	5%	No evidence
HOMA-Index	Kastorini 2011 ¹⁸	3 cross-sect	high vs low	MD	-	4 804 °	-0.41 (-0.43; -0.39)	-0.86 (-1.13; -0.59)	<0.0001	<0.0001	(-3.60; 3.08)	99%	Weak
Diabetes	Koloverou 2014 ²⁵	10 cohort	high vs low	RR	19 663	136 846	0.84 (0.79; 0.89)	0.83 (0.74; 0.93)	<0.0001	0.002	(0.58; 1.18)	58%	Weak
Diabetes	Schwingshackl 2014 ²⁶	8 cohort	high vs low	RR	19 463	111 269	0.83 (0.78; 0.89)	0.83 (0.74; 0.92)	<0.0001	0.0006	(0.62; 1.09)	56%	Highly suggestive
MetS	Kastorini 2011 ¹⁸	2 cohort	high vs low	RR	NA	4 495	0.80 (0.62; 1.03)	0.46 (0.11; 1.92)	0.08	0.30	NE	83%	No evidence

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

CVD = cardiovascular disease; CHD = coronary heart disease; MI = myocardial infarction; BP = blood pressure; CI = cognitive impairment; WC = waist circumference; HDL-C = high density lipoprotein cholesterol; TG = triglycerides; MetS = Metabolic Syndrome; RR = relative risk, MD = mean difference; OR = odds ratio; HR = hazard ratio; NA = not available; NE = not estimable because less than 3 studies were available for each meta-analysis

[°] number of total participants; [^] data from 1 study (Cherbuin 2011) was not available

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

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

Parameter	Description
Population	<p><u>Inclusion:</u> adults (>18 years)</p> <p><u>Exclusion:</u> children and pregnant women</p>
Intervention/correlate	<p><u>Inclusion:</u> Mediterranean diet</p> <p><u>Exclusion:</u> other diets</p>
Comparison	<p><u>Observational studies:</u> high adherence versus low adherence to the Mediterranean diet</p> <p><u>Randomized clinical trials:</u> Mediterranean diet versus other diets</p>
Outcome	<p><u>Inclusion:</u> 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)</p> <p><u>Exclusion:</u> not health-related outcomes</p>
Study design	<p><u>Inclusion:</u> systematic reviews including meta-analyses (quantitative analysis) of prospective studies, cross-sectional studies, case-control studies, or randomized clinical trials</p> <p><u>Exclusion:</u> studies not published as peer-reviewed meta-analyses in international scientific journals, systematic reviews without quantitative analysis</p>

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

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

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

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

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

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

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

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

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

INFLAMMATORY PARAMETERS

CRP (mg/L)	Nordmann 2011 ²⁸	<0.001	<0.001	<2500	Considerable	Including the null value	NA
CRP (mg/L)	Schwingshackl 2014 ³⁵	<0.001	<0.001	<2500	Considerable	Including the null value	NA
IL-6 (pg/mL)	Schwingshackl 2014 ³⁵	<0.05	<0.001	<2500	Considerable	Including the null value	NA

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

*These papers used as a threshold for high quality a NOS score = 6

° 1-point increase in adherence to the Mediterranean Diet

RCT = randomized controlled trials. Data not reported in the study by Godos et al, 2017²⁴

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

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

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

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

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

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

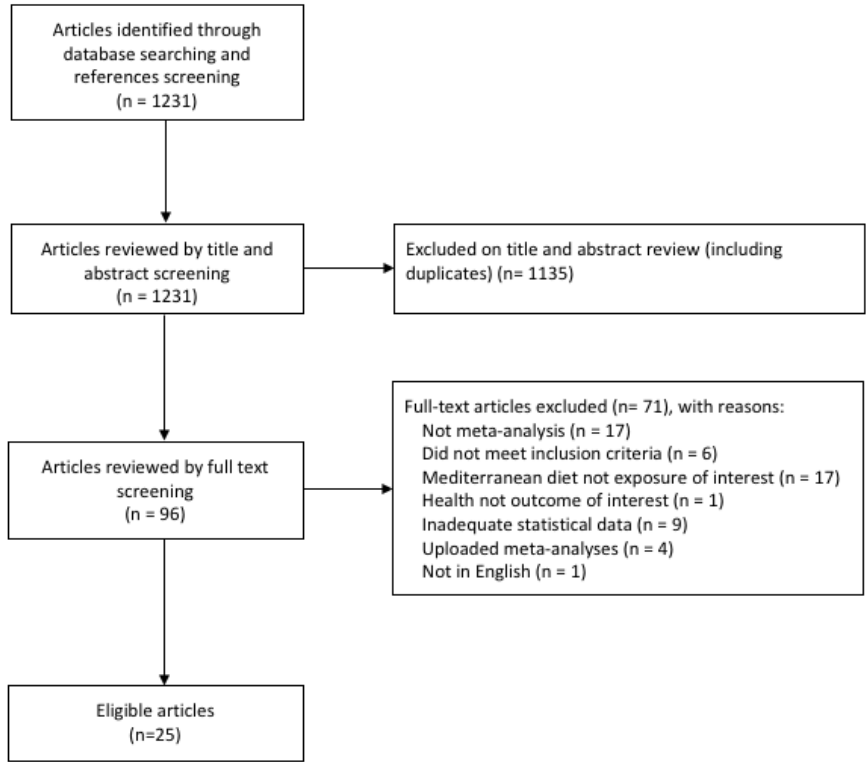
To convert mmol/L cholesterol to mg/dL, multiply mmol/L by 38.67. To convert mmol/L triglycerides to mg/dL, multiply mmol/L by 88.57. To convert mg/dL blood glucose to mmol/L, multiply mmol/L by 18.

Identification

Screening

Eligibility

Included



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

0.1 0.2 0.5 1 2

					Mean Difference (95% CI)	Mean Difference (95% CI)
HOMA-Index ¹⁸	3	cross-sectional	NA / 4 804	high vs low		-0.86 (-1.13, -0.59)
Systolic pressure ¹⁸	4	cross-sectional	NA / 14 734	high vs low		-1.81 (-4.83, 1.21)
Diastolic pressure ¹⁸	4	cross-sectional	NA / 14 734	high vs low		-2.36 (-6.12, 1.40)

-7 -4 -1 0 1 4

